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Corticospinal Excitability, Mental Rotation Task, Motor Performance and Disability in Subjects with Musculoskeletal Disorders of the Wrist and Hand

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Corticospinal Excitability, Mental Rotation Task, Motor Performance and Disability in Subjects with Musculoskeletal Disorders of the Wrist and Hand

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Résumé

L'objectif de cette thèse était de démontrer la présence de modifications des processus sensorimoteurs du système nerveux central (excitabilité corticospinale et schéma corporel tels que mesurés avec la Tâche de Reconnaissance de la Latéralité des Images droite gauche (TRLI)) chez des participants ayant des désordres musculosquelettiques au poignet et à la main. Un deuxième objectif était de déterminer la relation entre les changements de ces processus sensorimoteurs corticaux et des mesures sensorielles, de la fonction motrice, d'incapacité autodéclarée, de la douleur et des facteurs psychosociaux liés à la douleur.

Une étude observationnelle transversale a d'abord été menée pour mesurer l'excitabilité corticospinale des muscles de la main en utilisant la stimulation magnétique transcrânienne et la TRLI chez des participants en santé et des participants présentant des douleurs chroniques au poignet et à la main. L'excitabilité corticospinale du muscle court abducteur du pouce de la main affectée était augmentée chez les participants présentant une douleur chronique et ces changements étaient significativement corrélés avec l'intensité de la douleur, l'incapacité autodéclarée, et négativement corrélés avec l'excitabilité motoneuronale. Des différences de performances sur le TRLI, à la fois pour la précision et le temps de réaction, ont également été trouvées entre les participants du groupe contrôle et les participants avec douleur.

Dans une deuxième étude transversale, le TRLI, des mesures de motricité, sensibilité et des fonctions cognitives ont été administrées à soixante et un participants présentant des désordres musculosquelettiques du poignet ou de la main droite. Les modèles de régression linéaire multiple ont révélé que la prise de médicaments pour contrer la douleur, la participation à des activités (sociales, professionnelles, domestiques et récréatives), la discrimination tactile de deux points et le niveau de performance motrice expliquent les performances au TRLI. Les participants ayant pris des médicaments pour la douleur la journée de l'évaluation avaient une performance diminuée sur la précision et le temps de réaction sur le TRLI pour la main droite (affectée). Ces participants présentaient aussi une sévérité de douleur et d'incapacité plus élevée et une diminution de fonctions cognitives et motrices plus élevée que le reste des participants avec douleur qui ont été évalués.

Dans l’ensemble, ces résultats suggèrent que les participants présentant des désordres musculosquelettiques hétérogènes du poignet ou de la main montrent des changements des processus sensorimoteurs corticaux. Alors que l'excitabilité corticospinale semble être liée à l'intensité de la douleur et à l’incapacité autodéclarée, le TRLI peut être associé à une confluence de facteurs (sensoriels, moteurs, cognitifs-affectifs et comportementaux). Ces résultats suggèrent aussi que les changements sensorimoteurs corticaux ne sont pas simplement le résultat du désordre musculosquelettique, mais impliquent plutôt une interaction complexe entre la douleur, les processus sensorimoteurs et cognitivo-affectifs, et peut-être aussi des réponses comportementales à l’atteinte musculosquelettique. Les résultats fournissent également des informations précieuses à propos des personnes qui pourraient bénéficier d'interventions orientées vers le rétablissement des processus centraux en plus des traitements de réadaptation axés sur les structures périphériques.

Mots-clés: désordres musculosquelettiques, douleur, neuroplasticité, excitabilité corticospinale, stimulation magnétique transcrânienne, imagerie motrice, performance motrice, incapacité, schéma corporel, tâche de rotation mentale

Abstract

The objective of the thesis was to investigate for the presence of changes in cortical sensorimotor processes (corticospinal excitability and the body schema measured with the Left Right Judgment Task (LRJT) performance), in participants with Musculoskeletal Disorders (MSD) of the wrist/hand. A second objective was to determine the relationship between these cortical sensorimotor processes and measures of sensory and hand motor function, disability, pain and pain related psychosocial factors.

First, an observational cross-sectional study was conducted to explore corticospinal excitability of muscles in the hand and cortical sensorimotor processes, utilizing transcranial magnetic stimulation and the LRJT in healthy, pain-free participants and participants with chronic wrist/hand pain. Increased corticospinal excitability for the abductor pollicis brevis of the affected hand in participants with chronic MSD of the wrist/hand was found and these changes were significantly correlated with pain intensity, disability, and negatively correlated with spinal motoneuronal excitability. Differences in LRJT performance were also found between healthy control participants and participants with pain for both LRJT accuracy and reaction time.

In a second cross-sectional study, LRJT performance, motor, sensory and cognitive assessments were performed on sixty-one participants with MSD of the right dominant wrist/hand. The multiple linear regression model revealed that taking pain medication, participating in (social, work, household and leisure) activities, two-point discrimination, and motor performance explained performance on the LRJT of the right (affected) hand. Those participants that took pain medication on the day of the evaluation performed more poorly on both LRJT accuracy and reaction time of the right (affected) hand. These participants had higher pain severity and disability scores and decreased cognitive and motor function.

Collectively, these results suggest that participants with heterogeneous MSD of the wrist/hand display altered cortical sensorimotor processes. Whereas corticospinal excitability appears to be related to pain intensity and disability, the LRJT may be associated with a confluence of factors (sensory, motor, cognitive-affective, and behaviours). These findings suggest that cortical sensorimotor changes do not simply appear to be the result of the condition but involve a complex interaction between pain, sensorimotor and cognitive-affective processes, and possibly

behavioural responses to the condition. The findings also provide valuable insight as to those persons who may benefit from cognitively directed interventions in addition to peripherally driven rehabilitative treatments.

Keywords: musculoskeletal disorders, pain, neuroplasticity, corticospinal excitability, transcranial magnetic stimulation, motor imagery, motor performance, disability, body schema, sensorimotor integration, mental rotation task, implicit motor imagery

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Abbreviations

APB:	Abductor Pollicis Brevis
CNS:	Central Nervous System
CSP:	Cortical Silent Period
EMG:	Electromyography
FDI	First Dorsal Interossei
fMRI:	Functional Magnetic Resonance Imaging
I-O:	Input-Output
ISI:	Inter-Stimulus Interval
LBP:	Low Back Pain
LRJT:	Left Right Judgment Task
M1:	Primary Motor Cortex
MEP:	Motor Evoked Potential
MSD:	Musculoskeletal Disorders
MSO:	Maximum Stimulator Output
MT:	Motor Threshold
PPT:	Pressure Pain Thresholds
PPG:	Purdue Pegboard Test
rMT:	Resting Motor Threshold
RT:	Reaction Time
SI:	Primary Somatosensory Cortex
SII:	Secondary Somatosensory Cortex
SICF:	Short Interval Cortical Facilitation
SICI:	Short Interval Cortical Inhibition
TMS:	Transcranial Magnetic Stimulation
WHYMPI:	West Haven Yale Multidimensional Pain Inventory

Dedication

To the persons who consult with me for their confidence and involving me in one of the most important aspects of their lives - their health

To those who believed in me and gave me a chance

Most of all to my family

To my wife for her love, support, friendship, patience and understanding. I look forward to making up for lost time together.

To my children for their love, support, understanding, and helping me grow as a person and a father

Remerciements

This process was a labour of love mixed with a tinge of frustration, exhilaration, despair, stress, fatigue. I loved (almost) every moment.

Thank you to my research directors Johanne Higgins, PhD and Daniel Bourbonnais, PhD for sharing generously of their time, knowledge and expertise.

Although I had limited time to interact with other students, each encounter was a pleasure and rewarding.

Thank you to the support staff at l'Institut de réadpatation Gingras-Lindasy de Montréal. Your goodwill, time, patience, and work where not only helpful but essential.

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Thank you to my family who sacrificed evenings, weekends, and vacations to allow me to undertake such a challenge at this point of my life.

Avant propos

Twenty-five years ago, I graduated with a M.Sc. degree in Biomedical Sciences (option réadaptation) at the University of Montréal under the supervision of Robert Forget, Ph.D. and Daniel Bourbonnais, Ph.D. The study in which I participated involved reflex modulation between synergistic muscles of the lower extremity with conditioned H-reflexes. After the completion of the master's program, I had the full intention to pursue my doctoral studies. However, I was side-tracked for more than 20 years.

During the 20-year hiatus from research I taught as a part-time faculty member at Concordia University in the Exercise Science program and in osteopathic programs across Canada and Europe. However, most of my time was spent as a clinician working with individuals suffering from musculoskeletal conditions. Initially my practice was largely comprised of athletes and physically active individuals. The structural-pathology paradigm or biomedical model was the predominant model at the time of my undergraduate education and was an adequate conceptual and treatment model when working with acute musculoskeletal injuries in an athletic population. However, with time I began to see an ever-increasing number of persons suffering with chronic musculoskeletal injuries/conditions. Although treatment occasionally helps people to overcome their chronic musculoskeletal injuries/conditions, the biomedical model appears to be less efficacious and fails as a conceptual as well as a treatment model for these conditions. As a teacher and practitioner of a manual profession, given the heterogeneity in the application of interventions and poor intra- and inter-rater reliability of manual therapy diagnostic tests, I hypothesized that the much of what we do was related to neurophysiological, educational and behavioural changes associated with treatment more than biomechanical changes stemming from physical manipulation. Recently there has been an emergence of scientific literature of pain and of central neuroplastic changes associated with pain and musculoskeletal injuries across distributed areas of the nervous system that may provide additional insight into the neurophysiological underpinnings of both the clinical applications of treatment and manifestations of persons with chronic musculoskeletal injuries/conditions.

When I met with Daniel Bourbonnais and Johanne Higgins in 2012, I shared a review article, Boudreau et al (2010), *The role of motor learning and neuroplasticity in designing rehabilitation approaches for musculoskeletal pain disorders*. They were enthusiastic that

research investigating central neurophysiological changes, usually associated with neurological conditions such as stroke and traumatic brain injuries, also demonstrated changes associated with musculoskeletal conditions. We went about elaborating a study investigating neurophysiological changes associated with musculoskeletal disorders of the hand, tapping into the area of expertise of Dr Bourbonnais (dynamometric evaluation of the hand) and Dr Higgins (transcranial magnetic stimulation). We spent the next year and half reconstituting Dr Bourbonnais' lab at l'Institut de réadaptation Gingras Lindsay de Montréal, working with the biomedical engineer Michel Goyette at the research centre on the software, data acquisition and processing for the experiments. I enrolled in the Ph.D. in September 2013.

When I speak to friends, colleagues, patients, acquaintances I meet and tell them that I am pursuing my Ph.D. at the age of fifty, I am usually met with bemusement. I am inevitably asked why and what will I do with a Ph.D. My answer is usually somewhat long winded but involves three aspects: personal, professional and sociological. Personal motivations stem from an enjoyment of learning and belief that it is important for our health and well-being to undertake new challenges and live varied experiences. Professionally, I wished to gain increased knowledge of neurophysiological changes associated with pain and musculoskeletal disorders, and competencies to evaluate sensorimotor function. I believed these skills, knowledge and expertise would benefit my clinical practice and the comprehension of mechanisms that would hopefully result in better treatments for those persons suffering with chronic musculoskeletal disorders. Finally, the sociological motivation stems from my professional affiliation as an osteopath that is undergoing the process of regulation in the province of Quebec. I am motivated to augment my knowledge, expertise, and experience in the scientific process as well as sensorimotor processes associated with musculoskeletal disorders to contribute to the development of this profession. In areas of the world where the profession of osteopathy has been regulated there has been an evolution from private educational institutions to public/university programs. There will be a need for individuals with the knowledge and competencies for the scientific inquiry of physiological processes associated with osteopathic manual medicine, improved models resting upon current scientific knowledge and research principles, and proof of efficacy and the evolution of osteopathic concepts and interventions.

Chapter 1 Introduction

1.1 Epidemiology of Musculoskeletal Disorders (MSD)

Musculoskeletal Disorders (MSD) result from insult to muscles, tendons, tendon sheaths, ligaments, joints, cartilage and/or nerves (Barr et al. 2004). These injuries are associated with local and systemic inflammatory responses, cellular proliferative changes, altered sensorimotor processes and pain (Barr et al. 2004). MSD have a direct impact on a person's ability to work, their quality of life, and are associated with important socioeconomic costs (Statistics 1998) accounting for roughly 3.4% of the gross domestic product in Canada (Coyte et al. 1998). Direct medical costs and indirect productivity losses account for 29% and 71% respectively of the total costs associated with MSD (Coyte et al. 1998). In Québec, MSD are responsible for 38% of occupational injuries compensated by the Commission des normes, de l'équité, de la santé et de la sécurité du travail and generate more than 40% of the compensation costs (Lamarche et al. 2011).

In a review of articles related to the incidence and prevalence of upper extremity MSD, Huisstede et. al. (2006) found upper extremity (shoulder, elbow, wrist and hand) MSD have point prevalence rates in the general population between 1.6 and 53% (Huisstede et al. 2006). Injuries to the wrist and hand had population prevalence rates in men and women of working age of 17.7% for men and 26.9% with women in the United Kingdom (Walker-Bone et al. 2004). Hand and wrist injuries account for approximately 20% of hospital visits to the emergency room in the Netherlands (de Putter et al. 2012). Of the musculoskeletal injuries for which persons present themselves to the emergency room in the Netherlands, lower extremity fractures and hand injuries rank first in total cost (direct and indirect) associated with injury (de Putter et al. 2012).

MSD may become chronic conditions associated with pain and disability. A systematic review found prevalence estimates of chronic pain range between 11.5% to 55.2% (Ospina et al. 2002). In Canada prevalence of chronic pain was found to be 18.9% in persons over 18 years of age, with roughly 6% of those suffering with chronic pain where experiencing MSD of the wrist/hand (Schopflocher et al. 2011). Direct and indirect costs related to chronic pain are estimated to be between $560 to $635 billion a year in the United States, more than the annual cost for cancer, heart disease and diabetes combined (Gaskin et al. 2012).

Given the personal and societal burden of chronic MSD, it is important to understand the pathophysiology of MSD to aid in the development of more efficacious interventions. Recent evidence suggest that altered neurological mechanisms may contribute to chronic MSD and their clinical manifestation of altered sensorimotor functions.

1.2 Altered Sensorimotor Processes with MSD

MSD result in rapid neurochemical/molecular changes at the site of the injury and within the spinal cord, and resultant functional and structural changes in subcortical and cortical structures (Wall et al. 2002). As a result of these changes, MSD result in reorganizational changes throughout the somatosensory system from the peripheral sensory neurons to cortical areas (Wall et al. 2002). Although mechanisms remain poorly understood, motor control changes are also characteristic of MSD (Barr et al. 2004; Hodges et al. 2011).

1.2.1 Altered sensory processes

Subjects with MSD characteristically display changes in peripheral sensorimotor processes and function. With acute MSD, changes in sensory afferent output are present resulting from the inflammatory response and neurochemical changes locally at the site of the MSD (Wall et al. 2002). Damage to musculoskeletal structures affects receptor transduction of both nociceptive and non-nociceptive neural receptors (Voscopoulos et al. 2010; Ward et al. 2015). Subsequent changes in structures and function are found within the spinal cord, brain stem (cuneate and gracilis nuclei), and thalamus (Wall et al. 2002). Altered sensory function includes increased transduction and transmission of nociceptive and non-nociceptive stimuli (Fernandez-Carnero et al. 2009; Skou et al. 2013; Chiarotto et al. 2013; Lluch et al. 2014). Peripheral sensory function including two-point discrimination thresholds (Luomajoki et al. 2011; Stanton et al. 2013; Catley et al. 2014), and decreased joint position sense are often manifested in persons with MSD (Sharma et al. 1997; Valeriani, Restuccia, Di Lazzaro, Franceschi, et al. 1999).

1.2.2 Motor control changes with MSD

Altered motor control patterns are well documented with MSD (Hodges and Tucker 2011). Consistent experimental evidence demonstrates that experimentally induced acute pain, a model associated with acute MSD, is associated with decreased maximum voluntary contraction, decreased muscle endurance, delayed muscle activation, and altered EMG activity in agonist/synergist muscles during agonist (decreased) and antagonist (increased) phases of

muscle activity in painful muscles (Arendt-Nielsen et al. 2008; Graven-Nielsen et al. 2008; Schabrun and Hodges 2012; Bank et al. 2013). With chronic MSD, changes in motor control include changes in strength (Dominick et al. 2005; de Oliveira et al. 2011), impaired Electromyographic (EMG) muscle activation between and within muscles (Tucker and Hodges 2009; Tucker, Butler, et al. 2009), decreased central activation ratios where participants with MSD display a decreased ability to maximally recruit spinal motoneurons when performing maximal voluntary contractions compared to healthy control participants (Verbunt et al. 2005; Hart et al. 2010), and increased co-contraction of agonist and antagonist muscles (Falla et al. 2008). Changes in motor activation have been related to both pain intensity and measures of psychological distress (Verbunt et al. 2005). These changes along the entire somatosensory system, behavioural priorities, cognitive/psychological factors (such as fear avoidance and catastrophization) and associated forebrain mechanisms influence motor control (Field 2009). Specific mechanisms underlying these motor control changes are, however, not well understood.

1.2.2.1 Mechanisms responsible for motor control changes

The changes in motor control in subjects with MSD may be the result of local and central factors. Motor control changes found in persons with MSD may be the result of altered sensory input arising from altered mechanoreceptor, chemoreceptor and muscle spindle activity to cortical structures (Brumagne et al. 1999; Thunberg et al. 2001; Panjabi 2006). Alternatively, motor control changes may result from behavioural changes to protect the area of pain (Field 2009), or central neurophysiological processes to minimize functional loss and protect the injured area (Hodges and Tucker 2011). Changes in muscle activation may also be a direct consequence of nociception both from spinal (Bank et al. 2013) and cortical processes (Frot et al. 2013).

1.3 Changes in Sensorimotor Cortical Properties and Organization with MSD

The changes in peripheral sensory and motor processes appear to be associated with changes in cortical sensory and motor structure and function. Although it is generally believed that neuroplastic changes in the Primary Somatosensory (S1) and Primary Motor (M1) cortices associated with MSD are driven by pain (Moseley and Flor 2012) the specific relationship between pain, cortical sensorimotor processes and motor control is unclear. Animal models have demonstrated that peripheral tissue compromise results in neurochemical and molecular changes locally at the site of injury and concurrent neuroplastic changes in S1 and M1 in the development

of upper extremity overuse injuries of the wrist and hand (Barr 2006; Barbe et al. 2006; Coq et al. 2009). However, these models have difficulty in parcelling cortical changes driven by the learning of new motor tasks, the repetitive movements performed, and those associated with pain and inflammation associated with the MSD.

1.3.1 MSD and changes in the primary and secondary somatosensory cortices

Changes in sensory afferent output resulting with MSD are associated with changes in cortical properties and organization in S1 and the Secondary Somatosensory (SII) cortices. Evoked potential and Functional Magnetic Resonance Imaging (fMRI) studies have found changes in structure and function within S1 and SII in persons with chronic pain conditions such as complex regional pain syndrome (Maihofner et al. 2003), carpal tunnel syndrome (Tecchio et al. 2002), focal hand dystonia (Elbert et al. 2004), and Low Back Pain (LBP) (Flor et al. 1997; Giesecke et al. 2004; Lloyd et al. 2008; Hotz-Boendermaker et al. 2016). These changes in properties and organisation in S1 and SII may be associated with behavioural findings of altered sensory perception, tactile acuity, and proprioceptive acuity found in subjects with MSD including LBP (Goossens et al. 2018). Tactile acuity specifically has been correlated with S1 reorganisation in persons with complex regional pain syndrome (Pleger et al. 2006).

There is also indirect evidence of sensorimotor changes in persons with MSD. Persons with MSD display changes in performance of the Left Right Judgment Task (LRJT) that requires the participant to determine as accurately and as quickly as possible if images of body parts presented are of the left or right side (Coslett et al. 2010a; Coslett et al. 2010b; Stanton et al. 2012; Schmid et al. 2012). The LRJT is believed to implicate cortical sensory processes, an internal representation of the body in peri personal space in real time that is derived from sensory input (i.e sensory, vestibular, visual). This internal representation of the body is referred to as the body schema. The precise anatomical position of the body parts in peri personal space is necessary to efficiently engage motor control processes required for the planning and execution of movement (Bray et al. 2011). The LRJT implicates cortical areas in the parietal cortex associated with sensorimotor integration and in cortical areas involved in attention, movement planning and execution (Parsons et al. 1995; Kosslyn et al. 1998). Decreased performance on the LRJT has been associated with pain intensity in some studies (Moseley 2004b; Hudson et

al. 2006; Linder et al. 2016) but not others (Coslett et al. 2010b; Bray and Moseley 2011; Schmid and Coppieters 2012; Stanton et al. 2012).

1.3.2 Changes in the primary motor cortex associated with MSD

Peripheral and central somatosensory changes, psychological factors, as well as behavioural responses to pain and injury appear to affect motor control (Field 2009). Cortical changes in M1 have been demonstrated in models of acute pain and with chronic MSD.

1.3.2.1 Experimentally induced acute pain and the primary motor cortex

Evidence of changes within M1 associated with acute MSD is lacking. However, experimentally induced pain is utilized as an experimental model for acute pain associated with MSD. Research demonstrates that within M1, experimentally induced pain is associated with decreased corticospinal excitability (Cheong et al. 2003; Fierro et al. 2010; Dube et al. 2011; Bank et al. 2013). Decreased corticospinal excitability, other factors being equal, would result in decreased motor activation and weakness characteristic of acute MSD (Arendt-Nielsen and Graven-Nielsen 2008; Graven-Nielsen and Arendt-Nielsen 2008).

1.3.2.2 Chronic MSD and the primary motor cortex

Although chronic MSD are also characterized by changes in motor control, there appears to be more variability, specifically of spinal motoneuronal and corticospinal changes within and between subjects and conditions (Hodges et al. 2003; Hodges and Tucker 2011) compared with experimentally induced acute pain. However, a number of studies demonstrate changes in corticospinal properties and organization in M1 in subjects experiencing chronic MSD including measures of corticospinal excitability such as Motor Thresholds (MT), Motor Evoked Potential (MEP) amplitudes, and representational changes in M1 assessed with Transcranial Magnetic Stimulation (TMS) in participants with patellofemoral pain (On et al. 2004; Te et al. 2017), anterior cruciate ligament injury (Héroux et al. 2006; Lepley et al. 2015), LBP (Strutton et al. 2005; Tsao et al. 2008; Tsao, Danneels, et al. 2011; Masse-Alarie et al. 2012; Elgueta-Cancino et al. 2015; Massé-Alarie et al. 2017), sciatica (Strutton et al. 2003), rotator cuff tears (Ngomo et al. 2015) chronic shoulder pain (Bradnam et al. 2015), and lateral epicondylitis (Schabrun, Hodges, et al. 2014). These changes in corticospinal properties and organisation have been correlated with pain intensity (Elgueta-Cancino et al. 2015), symptom duration (Flor et al. 1997;

Ngomo et al. 2015), and the level of dysfunction (Ochi et al. 1999; Tsao et al. 2008; Kapreli et al. 2009; Tsao, Galea, et al. 2010). However, other studies have found no correlation between pain measures, function and changes in sensorimotor properties and organization (Bray and Moseley 2011; Ngomo et al. 2015; Bradnam et al. 2015; Te et al. 2017). Furthermore, altered cortical properties and representation in M1 may be present in the absence of pain and in the absence of peripheral nerve injury (Byl et al. 1996; Byl et al. 2000a; Byl et al. 2002).

1.4 MSD, Rehabilitation, Function and Disability

Conservative treatment for MSD is oriented to decreasing pain and restoration of motor and sensory function. Traditionally, rehabilitative care of MSD has been guided by a structural-pathology paradigm or biomedical model where local structural pathology is believed to be the source of pain and disability and the target of intervention (Foster et al. 2003). Inherent within the biomedical model is the belief that pain and disability will resolve with restoration of normalized structure and function of compromised musculoskeletal structures and the patient will return to pre-injury levels of function and activities (Burton et al. 2008). However, conservative treatment (pharmacological, medical, physical therapies, behavioural therapies and complementary and alternative medical practices) inspired from the biomedical model involving peripherally driven treatment at the site of the MSD has several failings (Burton et al. 2008) and has not consistently produced positive outcomes specifically with regard to chronic MSD such as LBP (Foster et al. 2003). These findings have led some researchers to hypothesize that other mechanisms, including neurophysiological changes in the Central Nervous System (CNS), may be implicated in the pathophysiology of chronic MSD (Barr et al. 2004; Langevin et al. 2007; Wand et al. 2008; Wand, Parkitny, et al. 2011; Moseley and Flor 2012). Increased comprehension of underlying processes involved in sensory and motor deficits should in theory yield more efficacious interventions.

1.5 Summary

There is a growing body of evidence in animals and humans that neuroplastic changes in S1 and M1 occur simultaneously with MSD. MSD are also associated with abnormal sensory and motor processes. Altered central sensorimotor processes have been hypothesized to contribute to the development and ongoing chronicity of MSD (Hodges and Moseley 2003; Barr et al. 2004; Langevin and Sherman 2007; Forget et al. 2008). Although studies often investigate the

relationship between neurophysiological sensorimotor changes with pain intensity and duration, few have directly related these changes with measures of motor function, psychosocial aspects related to pain, and disability. More clarity in the relationship between sensorimotor cortical changes in structure, organization, and function with sensory and motor functions is necessary (Elgueta-Cancino et al. 2017). For example, changes in motor cortical properties and organization can be driven by behavioural changes related to cognitive and psychological processes mediated in the forebrain (Field 2009; Simons et al. 2014), use-dependent plasticity and motor learning (Nudo et al. 1996; Ziemann et al. 2001), as the result of coupling between sensorimotor areas stemming from altered sensory output from the area of injury (Schabrun, Ridding, et al. 2012), or from direct nociceptive transduction (Frot et al. 2013). Results from studies on the impact of interventions specifically addressing neurophysiological changes, although preliminary, have been accompanied by the return to normal neural structure and function in S1 (Flor et al. 2001; Napadow et al. 2007; MacIver et al. 2008) and in M1 (Tsao, Galea, et al. 2010) and improved clinical outcomes (Dilek et al. 2018). This knowledge is clinically important as rehabilitation interventions target pain reduction and restoration of sensorimotor function.

1.6 Principal Objective/ Structure of the Thesis

The primary objective of this thesis was to determine if sensorimotor neurophysiological processes are affected in persons with heterogeneous MSD of the wrist/hand. Secondly, to determine if there is a relationship between changes in cortical sensorimotor processes and changes in pain and pain related measures (such as pain interference, life control and affective distress), motor performance, and self-reported disability in a heterogeneous sample of participants with chronic wrist/hand pain. The thesis begins with a review of literature of nociception, pain and cortical sensorimotor changes associated with MSD followed by an article arguing that the neurophysiological changes associated with chronic MSD may be part of the pathophysiological processes associated with these injuries/conditions and may help explain why current interventions, which do not specifically address these neuroplastic changes, yield consistently small effects (Chapter 2). Chapter 3 presents the objectives and hypothesis. Chapter 4 presents the methodology and methodological considerations. Chapter 5 presents the results and includes three articles. An article of the corticospinal properties of the Abductor Pollicis

Brevis (APB) muscle in participants with and without chronic wrist/hand pain and their relationship with measures of pain, motor performance and disability. A second article is presented of the Left Right Judgment Task and the relationship with measures of pain, motor function and disability. A third article presents results from a study investigating the role of sensory, motor, cognitive, and pain-related factors with LRJT performance in participants with heterogeneous MSD of the wrist/hand. A general discussion is presented in Chapter 6 and includes in the implications for rehabilitation section a review article of interventions that can be utilized to attempt to renormalize neuroplastic changes in the CNS in persons with MSD. Chapter 7 is the conclusion and future directions are found in Chapter 8.

Chapter 2 Review of Literature

The review of literature will present information regarding sensorimotor processes and function associated with MSD. As pain is invariably a consequence of MSD, it is often difficult to parcel neurophysiological changes in sensory and motor function associated with the MSD (and associated damage to anatomical structures and muscular, tendinous and articular afferents) from those attributed specifically to the transduction and transmission of nociceptors and the pain experience. The review of literature therefore includes sections related to nociception, pain, and sensory and motor processes associated with MSD.

The review of literature begins with a review of MSD, nociception and pain. These include sections related to nociception transduction and transmission to subcortical and cortical areas. The subcortical and cortical processing of nociceptive information is divided into the medial and lateral nociceptive systems. The medial nociceptive system includes areas of the brain implicated in cognition, affect and motivation. Psychological influences on the pain experience, brain structures associated with these psychological factors also mediated in similar brain regions as those of the medial nociceptive system, are reviewed. Finally, the lateral nociceptive system implicated in cortical areas involved in the sensory discriminative aspects related to pain, specifically S1 and SII is described.

The second portion of the review of literature presents evidence on sensory changes associated with MSD and of changes in cortical sensory processes and function in subjects experiencing MSD. Motor changes associated with experimentally induced pain and with chronic MSD are described. Studies involving the LRJT and MSD are presented. The evidence of changes in M1 associated with chronic MSD is also presented with a particular emphasis on studies involving TMS. Finally, an article arguing that the cortical changes associated with MSD are part of the pathophysiological process and that the integration of treatment oriented towards the restoration of sensorimotor cortical function may improve outcomes is presented.

2.1 Musculoskeletal Disorders, Nociception and Pain

2.1.1 Musculoskeletal Disorders (MSD)

MSD involve loss of structural integrity to muscles, tendons, tendon sheaths, ligaments, joints, cartilage and nerves (Barr et al. 2004). Injury to musculoskeletal structures results in a cascade

of interrelated events designed to combat infection, limit further damage, and initiate repair (Voscopoulos and Lema 2010). Musculoskeletal structures are richly innervated with mechanoreceptors, chemoreceptors and nociceptors, and MSD alters sensory output from these receptors (Barr et al. 2004; Langevin and Sherman 2007). These changes in sensory output concomitant with MSD arise from both injury to anatomical structures and the presence of neurochemical/molecular changes including inflammatory mediators (i.e. cytokines, chemokines and neurotrophins such as adenosine triphosphate, tumour necrosis factor α, bradykinin, prostogandins, substance P), nerve growth factors and hormones (i.e. adrenaline) impacting both the site of injury and neurophysiological processing of sensory information in the dorsal horn of the spinal cord (Wall et al. 2002; Langevin and Sherman 2007). Functional and structural changes in the nervous system, including the spinal cord, brain stem, thalamus and cortical sensory areas occur rapidly in association with peripheral injuries (Wall et al. 2002). These physiological changes associated with MSD result in changes in sensory output, including nociception transduction and transmission, and appear to be associated with other alterations in sensory function such as tactile acuity and proprioception as well as pain (Goossens et al. 2018). Restoration of sensory and motor function and alleviation of pain is at the core of rehabilitation efforts in persons with MSD.

2.1.2 Nociception and pain

One specific consequence of MSD is the transduction of nociceptors. Nociceptors are free nerve endings located in the skin, mucosa, connective tissues, ligaments and articular capsules, periosteum, muscles, tendons, and arterial vessels that are transduced by mechanical, thermal (hot and cold), and chemical stimuli as well as polymodal nociceptors that respond to all noxious stimuli (Almeida et al. 2004). Nociception is defined as "*the activity in the peripheral and central nervous system elicited by mechanical, thermal, or chemical stimuli having the potential to inflict tissue damage*" (Sherrington, 1906; Legrain et al. 2011). Nociceptive stimuli are propagated along high threshold, fast conducting myelinated Aδ fibers and unmyelinated slower conducting C fibers. Aδ and C nociceptive neurons synapse predominantly in lamina I, II and V of the dorsal horn of the spinal cord. There is a direct relationship between noxious stimuli, nociceptor transduction, nociceptor transmission and actual or potential tissue injury in first order neurons conveying nociceptive information from the periphery to the spinal cord (Woolf

2011). Nociceptive stimuli are subject to inhibitory and excitatory influences in the dorsal horn of the spinal cord that results from both local factors (i.e. inflammatory mediators, nerve growth factors) and descending pain modulatory influences that can alter (i.e. enhance or attenuate) nociceptive transmission along second order neurons to higher subcortical and cortical centers (Heinricher et al. 2009). The origin and type of nociceptor and the neurons conveying nociceptive information are subdivided within lamina I and II of the dorsal horn of the spinal cord with neurons from each subdivision synapsing on second order neurons that project to different areas of the CNS (Almeida et al. 2004; Zylka 2005).

Nociceptive transmission from the spinal cord to subcortical structures is carried along six different pathways (Almeida et al. 2004). They are the spinothalamic, spinomesencephalic, spinoreticular, spinoparabrachial, and spinohypothalamic and spinocervical tracts (Almeida et al. 2004). Direct nociceptive information to higher centres of the CNS includes projections to the reticular formation, mesencephalic area including the periaqueductal gray region, parabrachial area, hypothalamus, amygdala, limbic structures and the thalamus (Price 2002; Almeida et al. 2004). Nociceptive information is therefore conveyed to subcortical areas involved in arousal and regulation of bodily processes within the brain stem and limbic areas (Price 2002). Nociceptive information is also conveyed to sensory areas involved in sensory-discriminative functions including S1 and SII, which in turn convey processed nociceptive information to limbic and prefrontal structures as well as motor areas (Almeida et al. 2004). The cognitive areas in the prefrontal cortex receive nociceptive input indirectly from projections from the thalamus, via sensory discriminative networks, and brainstem and limbic structures as to establish the response to nociceptive stimuli influenced by behavioural priorities (Brooks et al. 2005).

The processing of nociceptive information can be described as involving two systems (Almeida et al. 2004; Brooks and Tracey 2005). The medial nociceptive system is comprised of limbic, meso-limbic and cortical regions involved in the cognitive-affective-motivational areas processing nociceptive stimuli. The lateral nociceptive system is comprised of S1 and SII, parts of the sensory-discriminative network of pain (Almeida et al. 2004). The direct pathways to the forebrain and indirect pathways via the thalamus converge in the cingulate cortex and

subcortical structures that yield emotional valence to the stimuli and help establish response priorities in association with prefrontal cortical areas (Price 2002).

Cortical and subcortical areas involved in the transmission and processing of nociceptive stimuli and the perception of pain therefore include the thalamus, S1 and SII cortices, insula, cingulate cortex, amygdala, prefrontal areas and the cerebellum (Tracey et al. 2007; Perini et al. 2013). It is important to note that these structures do not respond uniquely to nociceptive stimuli but are activated in response to behaviourally relevant salient sensory input (Mouraux et al. 2011; Legrain et al. 2011). Other areas consistently activated during nociceptive processing include subcortical structures: the hippocampus, basal ganglia and amygdala. Evidence suggests that it is the interaction between the different structures that dictates the pain experience and behavioural responses to pain and MSD (see Figure 2.1) (Iannetti et al. 2010; Legrain et al. 2011).

2.1.3 Pain and MSD

One possible consequence to the transduction, transmission, and processing of nociceptive information is pain. Pain is defined as a ``*Sensory and emotional experience associated with real or potential injuries, or described in terms of such injuries*`` (Merskey et al. 1994). It is possible to experience nociception in the absence of pain as it is possible to feel pain in the absence of nociception (Legrain et al. 2011).

Conservative treatment for pain associated with MSD has largely been guided with a biomedical focus and it is anticipated that resolution of pain *"will be achieved through reduction of important biological mechanisms such as spasms, inflammation, or restrictions in motion"* (Burton et al. 2008). However, pain is a conscious precept subject to modulation depending upon both the evoking stimulus and the context (Lee, Nassikas, et al. 2011; Bushnell et al. 2013; Carlino et al. 2016), including anxiety, attention, memories/past experiences and/or the emotional state (Ossipov et al. 2010). Pain is a strong motivator of behaviours and is mediated/influenced by forebrain processes associated with context, cognitive and psychological factors all of which drive behaviours that may influence motor processes (Wiech et al. 2013; Navratilova et al. 2014).

2.1.3.1 Medial nociceptive system – cognitive, affective, motivational areas of the brain

Nociceptive information is conveyed to subcortical and cortical structures in series and parallel (Price 2002). Several of the nociceptive pathways project to subcortical and cortical regions in the forebrain involved in arousal and homeostatic regulation, but also in areas related to cognition, affect and motivation. The medial nociceptive system involves cognitive-affective-motivational centres of the forebrain including the prefrontal cortex, limbic and mesolimbic (reward centre) areas. Pain is a perceptual experience that is affected by a confluence of factors several of which are mediated by structures and function in the forebrain areas (Simons et al. 2014; Carlino and Benedetti 2016).

Each of these forebrain structures contributes to the pain experience and ensuing behavioural responses. The prefrontal structures are involved in cognitive aspects related to pain, including executive functions, working memory, attentional resources, cognitive appraisal, risk assessment, decision-making, and self-referential thought (Tracey 2010; Wiech and Tracey 2013). Other subcortical structures involved in nociceptive processing include the amygdala (imprinting of emotional salience to incoming sensory input) (Veinante et al. 2013), insula (involved in homeostatic monitoring, valuation of intensity, salience) (Baliki et al. 2009; Nelson et al. 2010; Segerdahl et al. 2015), and cingulate cortex (attention, error prediction, emotional valence, motor functions) (Paus 2001; Milham et al. 2003; Shackman et al. 2011). The insula receives thalamic projections from the posterior nuclei and the posterior division of the ventromedial nucleus as well as SII (Almeida et al. 2004). The posterior portion of the ventromedial nuclear thalamic projections are largely comprised of nociceptive inputs and project to the mid and anterior insula (Craig 1995). The anterior portion of the insula appears to play a role in viscerosensory and autonomic control tasks as well as in general attention (Nelson et al. 2010). The posterior insula is activated in response to nociceptive input and appears to play a fundamental role in pain processing (Segerdahl et al. 2015). The insula is also believed to play a role in valuation of intensity of nociceptive stimuli (Baliki et al. 2009). The insula therefore appears to play a role in orienting attentional resources to nociceptive input, in the valuation of pain, contributing to the autonomic responses to the stimuli, and via connections with the amygdala and hippocampus any contribute to learning and memory associated with nociceptive stimuli (Schnitzler et al. 2000).

Recent evidence has also demonstrated changes in the motivational-dopaminergic areas of the brain (ventral tegmental area and the nucleus accumbens) (Baliki et al. 2010; Baliki et al. 2012) that are integral to the reward circuitry of the brain. In patients with chronic low back pain, functional magnetic imaging blood oxygen level dependent responses to acute thermal noxious stimuli was altered compared to healthy control subjects (Baliki et al. 2010). Healthy subjects demonstrated positive phasic activity in the nucleus accumbens at the onset of the noxious stimulus and a negative peak when the stimulus was withdrawn. In subjects with chronic pain, the second peak, at the time of stimulus withdrawal was reversed (positive rather than negative) and there was an increase in nucleus accumbens tonic activity. The positive signal in healthy subjects was consistent with reward associated with pain relief. In the subjects with chronic pain, the negative deflection is consistent with punishment associated with attention directed towards the chronic pain. Increased functional connectivity assessed with functional magnetic resonance imaging between the medial prefrontal cortex and the nucleus accumbens in subjects with back pain was also found to be predictive of those persons who would be experiencing back pain one year later (Baliki et al. 2012). A longitudinal study in rats in response to spared nerve injury demonstrated decrease connectivity between the nucleus accumbens and dorsal striatum, and decreased gene expression in the nucleus accumbens dopamine opioid receptors (Chang et al. 2014). The reward centres interact with other forebrain areas to affect motivational drive, influence cognitive appraisal, behavioural choices, and engage motor actions (Wiech and Tracey 2013; Navratilova and Porreca 2014). Activity within all these forebrain areas help to shape behavioural responses to the injury/condition (Wiech and Tracey 2013) and are implicated in self-regulatory and homeostatic processes involved in pain modulation (i.e. arousal, placebo response) (Benedetti et al. 2005).

2.1.3.2 Psychological factors associated with pain and disability

The response to nociceptive information in forebrain areas is dictated by psychological factors and associated neural processes that affect the interpretation, behavioural salience, and influence behavioural responses (Simons et al. 2014).

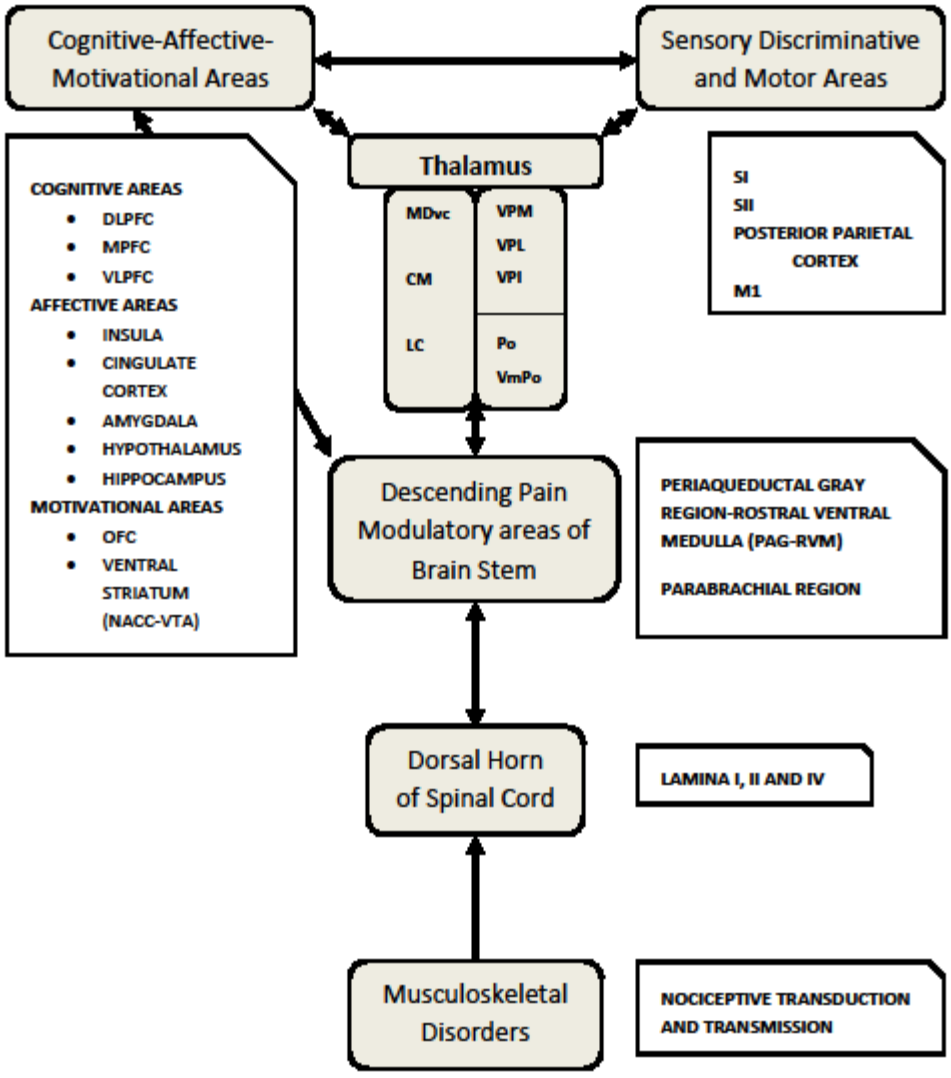

Figure 2.1: Nociception, central nervous system and musculoskeletal disorders

Nociception results from the chemical, mechanical and thermal stimulation and transduction of the nociceptors. Nociceptive information is processed in series and parallel within two brain areas. The lateral nociceptive system involves S1, SII involved in sensory discriminative aspects of the stimulus. The medial nociceptive system involves areas in the pre-frontal cortex, limbic and mesolimbic areas involved in the cognitive-affective and motivational aspects related to pain. Areas in the medial nociceptive system influence both descending modulatory systems and sensorimotor processes. DLPFC: Dorsolateral prefrontal cortex; VLPFC: Ventrolateral prefrontal cortex; MPFC: Medial Prefrontal Cortex; OFC: Orbital Prefrontal Cortex; NACC: Nucleus Accumbens; VTA: Ventral Tegmental Area: VPL: ventroposterolateral nucleus (VPL); VPM: ventroposteromedial nucleus; VPI: ventroposteroinferior nucleus; PO: posterior nuclei, VmPO: posterior division of the ventromedial nucleus; MDvc: ventral region of the dorsal medial nucleus; CM: centromedial nucleus: lateral central nucleus.

An extensive body of evidence supports the presence of psychosocial risk factors associated with pain and disability. Perceived pain intensity (Truchon 2001; Denison et al. 2004; Casey et al. 2008), depression (Creamer et al. 1999; Pincus et al. 2002; Casey et al. 2008; Vranceanu et al. 2009; Wideman et al. 2012; Ross et al. 2015), low self-efficacy (Creamer et al. 1999; Arnstein et al. 1999; Asghari et al. 2001; Denison et al. 2004; Meredith et al. 2006; Wright et al. 2008; Vranceanu et al. 2009; Lee et al. 2015), resilience (Wright et al. 2008; Vranceanu et al. 2009), somatosization (Pincus et al. 2002), catastrophization (Denison et al. 2004; Vranceanu et al. 2009; Wideman and Sullivan 2012), fear (Denison et al. 2004; Vranceanu et al. 2009; Wideman and Sullivan 2012; Lee et al. 2015), distress (Pincus et al. 2002; Vranceanu et al. 2009; Lee et al. 2015), anxiety (Creamer et al. 1999; Vranceanu et al. 2009), passive coping (Truchon 2001; Vranceanu et al. 2009), work dissatisfaction (Truchon 2001), monotonous work (Truchon 2001; Östergren et al. 2005) and pain related cognitions (Casey et al. 2008; Vranceanu et al. 2009) are all documented risk factors for pain and disability. Factors such as catastrophization (Wertli et al. 2014), self-efficacy (Arnstein et al. 1999; Denison et al. 2004; Meredith et al. 2006; Wright et al. 2008; Ross et al. 2015; Lee et al. 2015), fear (Denison et al. 2004; Lee et al. 2015), anxiety (Meredith et al. 2006) and psychological distress (Lee et al. 2015) appear to play important mediating roles between pain and disability and the literature suggests that these factors are part of the causal process. Collectively, these studies demonstrate that psychological factors influence the pain experience and are implicated in the disability that persons with MSD experience.

2.1.3.2.1 Psychological factors and forebrain cortical activity

Psychological factors are mediated by forebrain processes, which often involve many of the same forebrain regions involved in the pain experience (Price et al. 2012; Simons et al. 2014). Brain regions involved with depression include a network of structures equally implicated in chronic pain including the medial prefrontal cortex, limbic, striatal, thalamic, and basal forebrain structures (Price and Drevets 2012; Simons et al. 2014). Increased activity in the cingulate cortex and hippocampus as well as the prefrontal cortex is found when a negative mood is induced in healthy subjects (Berna et al. 2010). Neural mechanisms involving the association of external stimuli with fear (i.e. fear learning), for example the association of

movements with pain, also involves prefrontal and limbic areas including the hippocampus, dorsolateral and medial prefrontal cortex, and importantly the amygdala (Simons et al. 2014).

Some studies have demonstrated interactions between psychological factors related to pain and altered forebrain neural activity. Twenty-two healthy individuals were assessed for pain catastrophization and exposed to two intensities of noxious stimuli induced with electrical stimulation of the median nerve while blood oxygen level dependent changes was assessed utilizing fMRI (Seminowicz et al. 2006). There was a correlation between pain catastrophization and blood oxygen level dependent responses in the dorsolateral prefrontal, insula, rostral anterior cingulate, premotor, and parietal cortices. There was a negative correlation between activity in the prefrontal regions and pain catastrophization during the higher intensity noxious stimulation suggesting changes in cortical processes are associated with different psychological traits (Seminowicz and Davis 2006). The cerebral activation in response to manipulation of physical noxious stimuli or induced anxiety when exposed to noxious thermal stimuli was investigated in healthy participants (Ochsner et al. 2006). Anxiety sensitivity index scores correlated with activity in the medial pre-frontal cortex, a region associated with self-awareness/attention. Fear of pain questionnaire scores were associated with ventrolateral pre-frontal cortex areas and the cingulate cortex, regions associated with monitoring and assessment of affective responses (Ochsner et al. 2006).

Collectively, these findings suggest that psychological factors appear to implicate areas of the forebrain that also participate in the pain experience, and activity in these regions may be affected by these psychological factors and associated neural processes in response to nociceptive stimuli. Furthermore, evidence suggests that there is a relationship between the psychological states and motor control processes in subjects with MSD (see section 2.3).

2.1.3.3 Descending pain modulation system and sensitization

The cognitive, affective and motivational areas of the medial pain system communicate directly and indirectly with regions within the brain stem involved in modulation of nociceptive information. Descending modulation refers to supraspinal influences on the synapses between first and second order nociceptive neurons in the dorsal horn of the spinal cord altering the transmission of nociceptive input (Lee, Nassikas, et al. 2011). The brain stem areas involved in

descending pain modulation include the periaqueductal gray region and rostral ventral medulla, parabrachial region, and dorsal reticular nucleus (Heinricher et al. 2009; Ossipov et al. 2010). The study of connections of the best characterized descending modulatory pathway, the periaqueductal gray region and rostral ventral medulla, in vivo utilising diffusion tensor imaging demonstrate projections from several prefrontal and limbic structures including the anterior cingulate cortex, medial prefrontal cortex, insula, amygdala, thalamus, and dorsomedial hypothalamus (Hadjipavlou et al. 2006; Heinricher et al. 2009).

Descending modulation of nociceptive input involves a balance between inhibitory and facilitatory processes that is dictated by behavioural priorities and altered by emotional and pathological (i.e psychological) states (Heinricher et al. 2009). Sensitization is defined as an amplification of nociceptive transmission and processing (Latremoliere et al. 2009; Henry et al. 2011). Sensitization may be the result of peripheral and central factors. Peripheral sensitization refers to changes that result in increased responsiveness of the peripheral nerve endings. Central sensitization is the result of changes in the central nervous system. Peripheral sensitization result from the neuromolecular changes discussed in section 2.1.1. These include the presence of inflammatory mediators (i.e. cytokines, chemokines and neurotrophins such as adenosine triphosphate, tumour necrosis factor α, bradykinin, prostogandins, substance P), nerve growth factors and hormones (i.e. adrenaline) in the area of the MSD (Wall et al. 2002; Langevin and Sherman 2007).

Under pathological conditions, increased responsiveness of neural structures to nociceptive stimuli, mediated in part by mesolimbic and prefrontal areas and descending modulatory influences may become pathological resulting in maintenance and amplification of nociceptive transmission contributing to the phenomenon of sensitization (Zusman 2002; Zambreanu et al. 2005; Heinricher et al. 2009; Ossipov et al. 2010; Yarnitsky 2010; Bushnell et al. 2013). Central sensitization results in a change of the stimulus-response relationship to nociceptive stimuli as the result of activity in the CNS (Heinricher et al. 2009; Ossipov et al. 2010; Lee, Nassikas, et al. 2011; Staud 2012).

Sensitization is manifested clinically by hyperalgesia and allodynia. Hyperalgesia is the increased responsiveness to sub-threshold nociceptive stimuli (homosynaptic facilitation)

resulting in an increased pain response. Allodynia is manifested as the result of an enlargement of receptor fields in the dorsal horn of the spinal cord with second order neurons responding to both noxious and innocuous stimuli (heterosynaptic facilitation) where stimuli that does not usually elicit the perception of pain such as light touch is perceived as painful (Woolf 2011). Aβ fibers convey sensory information from mechanoreceptors found within the skin (contributing to the sense of touch) and secondary receptors for muscle spindles (contributing to proprioceptive sense) to the laminae in areas 3-5 of the dorsal horn of the spinal cord. Under pathological conditions Aβ input can be processed along nociceptive pathways contributing to the pain experience. The change in Aβ sensory information conveyed along nociceptive pathways results because of change in electrical properties and the neurotransmitter associated with their discharge within the spinal cord (Devor 2009). Changes in the spinal cord including the presence of neuromodulators and inflammatory mediators that increase synaptic transmission, decreased number of GABA inhibitory interneurons and changes in receptor function resulting in synaptic facilitation have all been proposed as mechanisms involved in increased Aβ transmission along nociceptive pathways (Latremoliere and Woolf 2009).

Central sensitization appears to be implicated in chronic pain states (Ji et al. 2003; Woolf 2011). Although sensitization is not manifested systematically across all persons with MSD, studies have demonstrated that central sensitization is manifested in some persons with MSD such as knee (Arendt-Nielsen et al. 2010; Skou et al. 2014; Lluch et al. 2014; Wylde et al. 2015) and thumb osteoarthritis (Chiarotto et al. 2013). The heightened response to nociceptive stimuli in chronic conditions, at least in part, is mediated by forebrain processes influencing descending modulatory pathways, affects the pain experience and may have behavioural implications.

The pain experience is therefore dictated by a confluence of factors. These include psychological factors, expectations, beliefs, cultural factors and context. Forebrain structures involved in cognition, affect, and motivation help to dictate the neurophysiological and behavioural responses to the MSD and pain. Activity within these forebrain regions influence descending modulatory systems in the brain stem that may amplify or attenuate the transmission and processing of nociceptive information which in turn may influence the pain experience, sensitization, behavioural responses and motor processes.

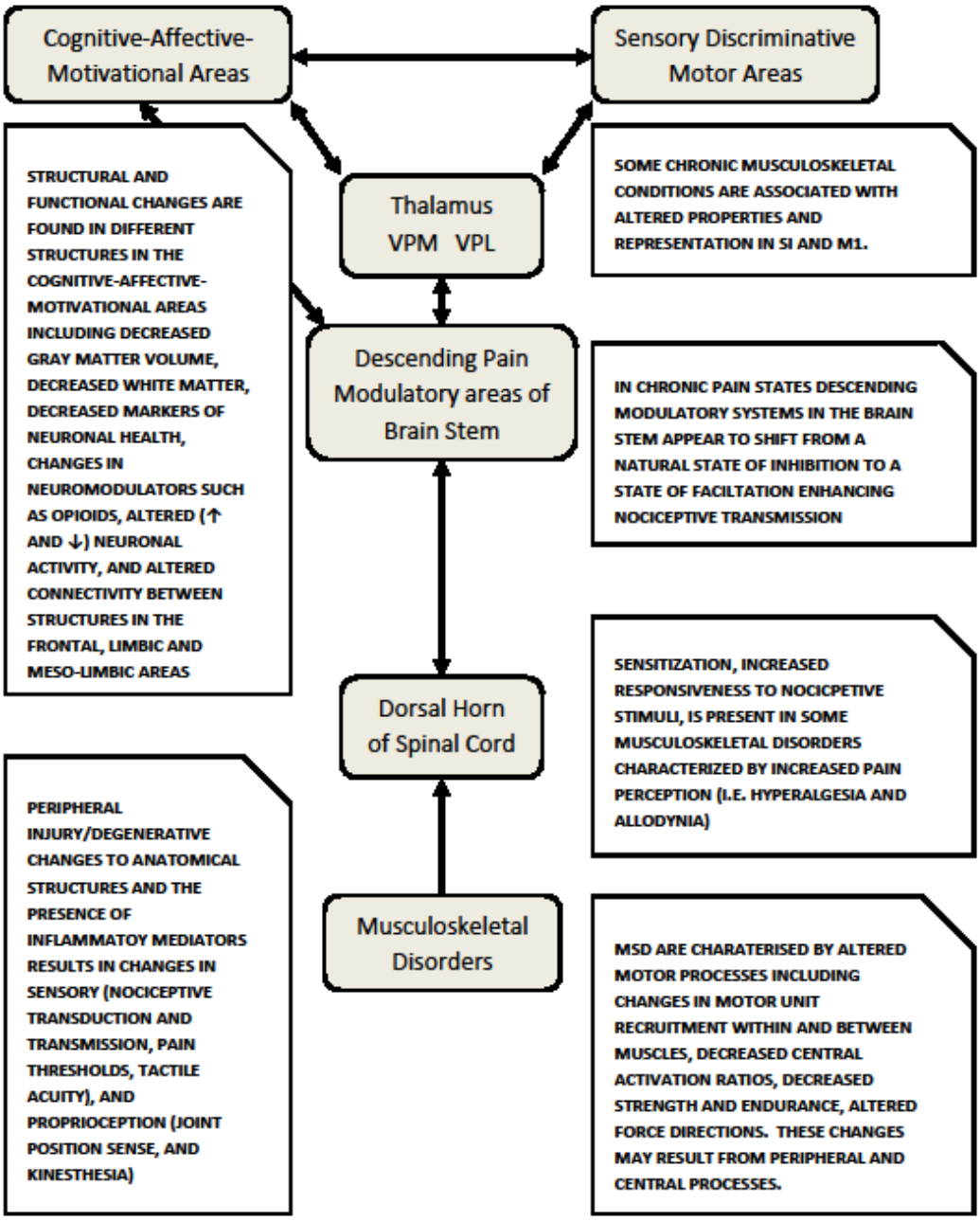

Figure 2.2: Changes in the central nervous system associated with pain and musculoskeletal disorders

Abbreviations: M1: Primary Motor Cortex; S1: Primary Somatosensory Cortex; VPL: Ventral Posterior Lateral; Ventral Posterior Medial

2.1.3.4 Constant vs intermittent pain in persons with MSD

Patients with osteoarthritis of the hip and pain often describe two types of pain (Hawker et al. 2008). For example, patients with osteoarthritis describe both constant aching pain and paroxysmal pain episodes that involve periodic, unexplainable intense sharp pain (Hawker et al. 2008). Although both of these types of pain were described as distressing, paroxysmal pain episodes were described as more distressing, having a greater negative impact on mood, and appear to have a negative influence on quality of life impacting their ability to participate in social and recreational activities (Hawker et al. 2008). In a study of participants with carpal tunnel syndrome, spontaneous fluctuations of intense pain where correlated negatively with decreases in nerve conduction velocity related to Aβ fibering of digits 1 and 3 (Truini et al. 2009). Nociceptive pain was induced with high intensity short duration impulses applied to the median nerve distribution in the hand resulting in a pin prick sensation. The Neuropathic Pain Symptom Inventory for pain and burning was correlated with laser evoked stimuli suggesting Ad fiber involvement (Truini et al. 2009).

2.1.3.5 Chronic pain

Changes in the medial nociceptive system, psychological factors, the descending modulatory systems in the brain stem and central sensitization have all been implicated with chronic pain and MSD. In the presence of chronic pain, imaging studies demonstrate a shift in activity from the lateral nociceptive structures (sensory discrimination) to areas of the medial nociceptive system, where different forebrain structures have demonstrated structural and functional changes including changes in grey matter volume, altered functional activity, decreased neuronal cell health, and alterations in white matter tracts interconnecting different structures (see Figure 2) (Apkarian et al. 2009; Apkarian et al. 2011; Bushnell et al. 2013; Mansour et al. 2013). These forebrain areas and associated neurochemical structural and functional neurophysiological changes are implicated in chronic pain states including chronic LBP and osteoarthritis (Apkarian et al. 2009).

The usual definition of chronic pain refers to a state of continued suffering that persists past what is generally considered the normal healing time of peripheral anatomical structures, usually 3-6 months after the initiating injury (Apkarian et al. 2009; Schopflocher et al. 2011). Chronic pain is associated with prolonged C fibre nociceptive transmission that is associated with

pathological and histochemical processes (Simons et al. 2014). The chronic dysregulation of physiological systems in response to chronic discharge of nociceptors and pain is associated with histochemical, structural and functional changes in the CNS (Apkarian et al. 2009; Apkarian et al. 2011; Wiech and Tracey 2013; Simons et al. 2014). Evidence suggests that chronic pain is associated with changes in structure, organization and function occurring within the CNS, including the spinal cord, cortical sensorimotor areas (i.e. S1 and M1) (Moseley and Flor 2012), forebrain areas, limbic and subcortical structures, and the brain stem (Heinricher et al. 2009; Apkarian et al. 2011). These changes are associated with altered cognitive (Berryman et al. 2013), affective and motivational states (Wiech and Tracey 2013). Neurophysiological changes in forebrain areas associated with pain has led Apkarian and his colleagues to offer an alternative definition of chronic pain as, *"a persistence of the memory of pain and/or the inability to extinguish the memory of pain evoked by an initial inciting injury"* (Apkarian et al. 2009) that incorporates the concept of engrained neuroplastic structural and functional changes across cognitive-affective-motivational areas as the neurophysiological reflection of chronic pain states. Pre-existing psychological states, associated with altered structure and function in the cognitive-affective-motivational areas of the brain, can increase the risk of development of chronic pain (Simons et al. 2014). Altered neuronal function and connectivity in forebrain areas have been strongly correlated with chronicity of LBP in prospective longitudinal studies (Baliki et al. 2012; Mutso et al. 2014).

The structure and function in the forebrain areas involved in nociceptive processing and the pain experience as well as psychological factors help to determine the behavioural responses to the MSD. As discussed in the previous sections, these forebrain processes can amplify or attenuate the pain experience with MSD will experience.

2.1.3.5 Lateral nociceptive system – sensory discrimination areas of the brain

Nociceptive information is not only conveyed to forebrain structures of the medial nociceptive system involved in the cognitive-affective-motivational aspects related to the MSD and pain, but also to somatosensory areas. The lateral nociceptive system involves SI and SII. These brain regions are implicated in the processing of unimodal sensory signals (S1) and the integration of bilateral multimodal sensory inputs (SII) (Goossens et al. 2018). SI and SII send processed sensory information to the associative areas found within the posterior parietal areas that are

involved in higher order sensorimotor integration and the body schema and are tightly interconnected with the premotor areas (Goossens et al. 2018).

Lesion studies in animals, fMRI and evoked potential studies in humans suggest that S1 is involved in the discrimination of sensory stimuli (type of modality and localization) and intensity of nociceptive stimulation (see (Bushnell et al. 1999)). Changes in sensory input can result in adaptation in the somatosensory representation within the brainstem, thalamic nuclei, and S1 (Wall et al. 2002).

2.2 Sensory Changes and MSD

Although sensory function is not altered systematically in all MSD, in some subjects with MSD, the altered sensory output appears to contribute to functional changes in sensory perception including tactile acuity, pain thresholds and joint position sense (Garn et al. 1988; Warner et al. 1996; Sharma and Pai 1997; Fischer-Rasmussen et al. 2000; Gill et al. 1998; Lysholm et al. 1998; Brumagne et al. 1999; Farrell et al. 2000; Kosek et al. 2000a; Newcomer et al. 2000; Brumagne et al. 2004; Giesecke et al. 2004; Small et al. 2006; Treleaven et al. 2006; Imamura et al. 2008; Jensen et al. 2008; Coombes et al. 2009; Fernandez-Carnero et al. 2009; Gwilym et al. 2009; Swart et al. 2009; Lee, Lu, et al. 2011; Wilgen et al. 2011; Georgy 2011). Although altered sensory function is believed to be driven by peripheral changes in sensory afference, it is possible that central processes may also contribute to sensory changes (Flor et al. 1995).

2.2.1 Cortical sensorimotor changes and MSD

Animal studies clearly demonstrate that altered sensory output results in cortical changes in the somatosensory system (Merzenich, Kaas, Wall, Sur, et al. 1983; Merzenich et al. 1984; Recanzone et al. 1992; Merzenich et al. 1993), and that these changes are affected by cognitive processes such as attention (Jenkins et al. 1990; Recanzone et al. 1992). Relatively few studies have investigated cortical sensory processes in the somatosensory areas in persons with chronic MSD. Evoked potentials to stimulation of digits 1 and 5 demonstrate a shrinking of the distance between the digits and shift of the hand area on the affected side in participants with complex regional pain syndrome (Juottonen et al. 2002; Maihofner et al. 2003). Magnetic source imaging in persons with focal hand dystonia demonstrates a smaller representation of the digits in the affected hand (Elbert et al. 1994; McKenzie et al. 2003). A study utilizing

magnetoencephalography found that persons with carpal tunnel syndrome display altered somatosensory representation that differed depending upon the nature of the symptoms (Tecchio et al. 2002). Persons suffering with carpal tunnel syndrome who complained of paraesthesia demonstrated an expansion of the representation, while persons who described pain as their principal symptom had a shrinking of the representation in S1.

In participants with a history of LBP peripheral stimulation of the lumbar region is associated with decreased evoked potentials (Zhu et al. 1993; Zhu et al. 2000). Evidence of changes in S1 includes altered evoked potentials from painful electrical stimulation applied to the back and finger in participants with chronic LBP (Flor et al. 1997; Lloyd et al. 2008) and changes in cortical representation in a subset of persons with LBP to vibration applied to the lumbar spine (Flor et al. 1997; Lloyd et al. 2008; Kong et al. 2013). Participants with LBP, but not healthy controls, demonstrated increased brain activation revealed with resting state fMRI in the contralateral S1 when pressure was applied to the thumbnail (Giesecke et al. 2004). Non-painful manually applied pressure to the spinous processes in the lumbar spine was associated with a hemodynamic response measured with fMRI in S1 in both healthy control participants and participants with chronic LBP (Hotz-Boendermaker et al. 2016). In SII, hemodynamic activation was somatotopically organized based on the vertebral level where the manually applied pressure was applied in healthy control participants. In participants with chronic LBP, there was a blurring of the representation of the three lumbar vertebrae in the right SII, suggestive of altered higher order processing of sensory information in participants with LBP related to sensory acuity and body representation (Hotz-Boendermaker et al. 2016). Changes in representation in S1 have been correlated with pain intensity (Flor et al. 1997; Maihofner et al. 2003).

2.2.2 Body schema and MSD

Changes in peripheral sensory output influence cortical sensory properties and organization and have clinical manifestations affecting both *body image* and the *body schema*. Body image has been defined as, *"the way one's body feels to it's owner"* (Lotze et al. 2007). Participants with chronic pain may complain of changes in the size of the injured area, which may feel larger, smaller or distorted (Tsay et al. 2015). Some participants with MSD and other pain conditions such as complex regional pain syndrome, including injuries of the wrist and hand, demonstrate

changes in the perception of the size of the injured body part where the region of injury feels to the subject to be larger or smaller than its actual size (Lewis et al. 2007; Lotze and Moseley 2007; Lewis et al. 2012).

Lotze and Moseley (2007) describe body image from a sensorimotor perspective as: *"the implicit maps that encode the position, movement, and anthropometric characteristics of the body that are the basis for motor commands."* This definition of body image from a sensorimotor perspective has also been referred to as the body schema, a real time internal representation of the body in peri-personal space derived from incoming sensory (proprioceptive, visual, vestibular and somatosensory) input (Schwoebel et al. 2001). The body schema is assessed indirectly utilizing the LRJT (Parsons 2001). The LRJT involves determining as quickly and as accurately as possible if an image of a body part is of the left or right side (for images of the trunk and neck the side of rotation is analyzed) and is assessed by performance accuracy (the percentage of correct responses), and Reaction Time (RT) (the average time in seconds for these responses).

The argument for linking the LRJT as a proxy measure of the body schema stems from several experimental observations. Performance of the LRJT is affected by the position of the subject's anatomical body part when the image is presented (Ionta et al. 2007). For example, studies have demonstrated that if the hand is positioned behind the back, or if the hands are positioned with the palm up, the time taken to indicate if the image of the hand is of the left or right side is increased, but not so for the feet (Ionta et al. 2007; Ionta et al. 2009; Coslett et al. 2010b). Studies have consistently demonstrated that more complex orientations of the anatomical part in the images is related to an increase in reaction time and also negatively affects accuracy when performing the task (Schwoebel et al. 2001; Schwoebel et al. 2002; Ionta et al. 2007; Ionta and Blanke 2009; Coslett et al. 2010a; Coslett et al. 2010b; Choisdealbha et al. 2011). Imaging studies have also demonstrated that the time to perform the LRJT is similar in length to the time required to physically execute the movement to position the body part in the same position as the image (Parsons 1994). The link between motor imagery time and motor execution time has previously been demonstrated (Decety and Michel 1989; Decety, Jeannerod, et al. 1989; Decety 1996a). It is therefore believed that the LRJT involves implicit motor imagery, where the subject mentally imagines positioning the body part congruent with the image to make the decision of

laterality (Parsons 2001; Nico et al. 2004; Ionta et al. 2007). To perform the motor action of positioning the body part in the same position as the image requires information as to the position of the body part in peri-personal space, the body schema. The body schema is believed to be tightly integrated with motor areas to establish motor control parameters to efficiently perform movements enabling efficient interaction with the environment.

It is, however, important to recognize that imaging studies have demonstrated that the LRJT is associated with activation of subcortical and cortical areas including frontal, pre-motor areas, basal ganglia, cerebellum and associative areas in the parietal cortex involving neural mechanisms associated with attention, sensorimotor integration, movement planning and execution (Hetu et al. 2013; Tomasino et al. 2015). TMS of the motor cortex after the presentation of an image affects LRJT reaction time (Ganis et al. 2000). The assessment of corticospinal excitability of the First Dorsal Interossei (FDI) while performing the LRJT was associated with an increase in corticospinal excitability, greatest 50ms after the presentation of the image of the hand, and when there were more complex transformations required to mentally rotate the hand (Hyde et al. 2017). Collectively these findings suggest distributed neural activity including modulation of M1 that is involved in the LRJT.

Studies have consistently found changes of LRJT performance in subjects with neuropathic pain conditions such as complex regional pain syndrome and carpal tunnel syndrome (Reinersmann et al. 2010; Reinersmann et al. 2012; Schmid and Coppieters 2012). In participants with MSD there has been variability in results of studies involving the LRJT both for MSD within the same anatomical regions (Bray and Moseley 2011; Linder et al. 2016) and across various regions when presented with images corresponding to their area of injury (Stanton et al. 2012). However, some studies in subjects with MSD have demonstrated changes in accuracy and/or reaction time to determine the laterality of the image suggestive of an altered body schema or other associated processes implicated in this task (Coslett et al. 2010a; Coslett et al. 2010b; Bray and Moseley 2011; Stanton et al. 2012; Botnmark et al. 2016). Although the LRJT is believed to be a proxy measure of the body schema, and the body schema is tightly integrated with motor processes, to our knowledge only one study to date has investigated the relationship between the LRJT and motor performance (Botnmark et al. 2016). The study in Botnmark et al (2016) was performed in healthy subjects and found LRJT RT to images of the shoulder to be negatively

correlated with two point discrimination, and positively associated with an upper extremity functional stability test (Botnmark et al. 2016). No correlations were found between LRJT accuracy with sensory and motor function (Botnmark et al. 2016). There have been only a few studies that have investigated LRJT performance to self-reported disability measures and these have found no associations (Schmid and Coppieters 2012; Linder et al. 2016). Conflicting results also exist in relation to the LRJT performance with measures of pain and sensory function such as pain intensity (Moseley 2004c; Coslett et al. 2010b; Bray and Moseley 2011; Reinersmann et al. 2012) and two-point discrimination (Stanton et al. 2013). The clinical and functional manifestations and the sensory, motor and even the cognitive and psychological factors associated with the body schema, and by extension the LRJT is poorly understood. Further investigation of the LRJT in subjects with MSD as to discern how LRJT relates to pain, sensory and motor performance and measures of disability is therefore warranted.

2.3 MSD, Motor Control and Pain

Changes in motor activation patterns are well documented in musculoskeletal pathology (Hodges and Tucker 2011). Studies have demonstrated plastic changes in the spinal cord, subcortical and cortical levels occurring with pain and appear to be associated with aberrant motor activation patterns seen with MSD (Roland 1986; Lund et al. 1991; Hodges and Tucker 2011). However, there is a lack of understanding of the mechanisms responsible for the changes in motor control (Field 2009; Hodges and Tucker 2011; Frot et al. 2013). As MSD and pain are inter-related, it is a challenge for researchers to decipher processes specifically related to nociception and pain, and those specific to consequences of the MSD and resultant damage to anatomical structures and changes in sensory afference due to damage to sensory and articular receptors.

Experimentally induced pain is utilized as a model for acute pain associated with MSD (Bank et al. 2013). Experimentally induced muscle pain results in motor control changes including a decrease in maximum voluntary contraction, decreased endurance time, and attenuated EMG activity of the painful agonist muscle (Graven-Nielsen et al. 1997). In a recent study, experimentally induced pain utilizing capsaicin applied to the volar aspect of the forearm resulted in group differences in a measure of corticospinal excitability in the FDI muscle (Martel, 2017). Two thirds of the subjects were found to have a decrease in corticospinal

excitability whereas one third had an increase in corticospinal excitability (Martel et al. 2017). Although there is some variability, the majority of studies, regardless of the modality utilized to elicit experimentally induced pain (i.e. capsaicin, laser, heat, hypertonic saline injection), observe a decrease in corticospinal excitability measured with TMS (Valeriani, Restuccia, Di Lazzaro, Oliviero, et al. 1999; Le Pera et al. 2001; Farina et al. 2001; Valeriani et al. 2001; Cheong et al. 2003; Svensson et al. 2003; Farina et al. 2009; Bank et al. 2013).

Whereas the motor control changes occurring with experimentally induced (acute) pain is characteristic and largely reproducible across studies resulting in inhibition of agonist and synergist muscles (Bank et al. 2013), chronic pain conditions display more variability and are not always stereotypical (Hodges and Tucker 2011). The motor control changes associated with chronic MSD include an array of facilitatory and inhibitory changes and the resultant behaviour appears to be unique to the individual and the task (Falla and Farina 2008; Hodges and Tucker 2011). The activity of spinal motoneurons in response to chronic pain conditions may be increased or decreased (Tucker and Hodges 2009) and units innervating a single muscle may be facilitated or inhibited (Tucker and Hodges 2009; Falla et al. 2009). In participants with chronic MSD maximum voluntary contraction of a single muscle is usually decreased although total force output of the muscles acting upon a joint may be stable, or only slightly affected, and appear to involve a reorganization of motor activation patterns to accomplish the task (Fadiga et al. 2004; Falla and Farina 2008; Tucker et al. 2010). Muscular endurance during sub-maximal tasks is decreased (for review see (Graven-Nielsen and Arendt-Nielsen 2008; Arendt-Nielsen and Graven-Nielsen 2008)), and there is evidence of increased co-contraction (van Dieen et al. 2003; Falla et al. 2009). Resultant changes in force direction and joint kinematics may be present (Tucker and Hodges 2010; Hodges and Tucker 2011; Mista et al. 2016).

The influence of pain on motor control processes may result from direct connections of nociceptive pathways to the motor cortex which appear to be excitatory (Frot et al. 2013). Altered sensory processes may also contribute to altered motor control. Reimann and Lephart (2002) state, *"Critical to effective motor control is accurate sensory information concerning both the external and internal environmental conditions of the body"* (Riemann et al. 2002). It has been hypothesized that altered mechanoreceptor, chemoreceptor and muscle spindle activity following musculoskeletal injury affects spatial and temporal coordination and activation of

muscles (Brumagne et al. 1999; Thunberg et al. 2001; Panjabi 2006). Altered sensory information may affect motor control through spinal and cortical processes. As previously discussed altered sensory input can modify structure and function in S1.

Projections conveying altered sensory input from cortical somatosensory areas to M1 may also result in altered motor control. M1 and S1 are co-modulated in response to peripheral electrical stimulation (Schabrun, Ridding, et al. 2012). Altered sensory input, including changes in S1 structure and function may affect the working body schema. The working body schema is related to areas involved in sensorimotor integration in the posterior parietal area (Machado et al. 2010). The somatosensory associative areas (SII and areas in the posterior parietal cortex) are strongly interconnected with the premotor areas which in turn project to the motor cortex. Altered motor control may also result in altered sensory feedback conveyed to spinal, subcortical and cortical structures influencing motor control (Bullock-Saxton 1994; Riemann and Lephart 2002; Panjabi 2006). Finally, the impact of neural activity in cognitive-affective and motivational areas that affects nociceptive processing and the pain experience influence behavioural responses to MSD, such as fear-avoidance, immobility and disuse (Field 2009).

In the study previously described by Martel et al (2017), between subject comparisons demonstrated that individuals that had decreased corticospinal excitability had increased β M1 – cuneus connectivity measured with electroencephalography where the opposite was true for individuals who had increased corticospinal excitability. The cuneus is involved in the integration of sensory information but also attention orienting behaviour (Corbetta et al. 2002). The cuneus may therefore play a role in helping to mobilize attentional resources in consideration of the context and incoming sensory information influencing motor cortical activity in function of the behavioral priorities (Martel et al. 2017). This study highlights that there is a great deal of inter subject variability in the TMS studies, and that differences in attentional resources may impact sensory information processing in turn possibly affecting sensorimotor integration and behavioural responses.

Preliminary evidence suggests that psychological factors are related to altered motor control processes in subjects with MSD. Subjects with LBP that display an increased expectancy of pain experienced decreased hand motor performance in a pain-provoking posture (Kusters et al.

2011). In 148 subjects with recurrent LBP, regression analysis revealed that greater psychological disturbance and catastrophizing, lower exercise self-efficacy, and more negative back beliefs were significant predictors of decreased performance in an endurance task (Mannion et al. 2011). Experimentally induced pain via the injection of hypertonic saline in sixteen healthy subjects without back pain results in different neuromuscular recruitment patterns between subjects expressing high catastrophization and kinesiphobia scores versus those with lower scores (Ross et al. 2017). These studies are cross-sectional and therefore do not provide information as to causality but suggest that psychological factors appear to be related to motor control disturbances.

It is apparent from the literature that pain, and motor control changes are tightly coupled together. It is generally assumed that the causal relationship runs from pain towards motor control changes. This is supported by the findings of studies utilizing experimentally induced pain as a model (Bank et al. 2013). However, persons with recurrent MSD may also display ongoing motor control changes even in the absence of pain (Tsao et al. 2008). Psychological and forebrain processes implicated in chronic pain and MSD also appear to influence motor control processes.

2.3.1 Changes in the primary motor cortex associated with MSD

Changes in motor control process may be mediated by peripheral and central factors, including changes in corticospinal properties and organization in M1. The majority of studies evaluating changes in corticospinal excitability and organization in M1 have utilised TMS.

2.3.1.1 Transcranial Magnetic Stimulation (TMS)

TMS consists of a transducing coil that is attached to a discharge system that emits high voltage (400V-3KV), high current (4-20 KA), but a short duration (100us) electrical pulse (Groppa et al. 2012). The electric current travelling through the induction coil produces a magnetic field (1.5-2.5 Tesla) that can traverse the skull painlessly (Groppa et al. 2012). When placed over the motor cortical region, the magnetic field in turn can induce an electric field within M1. The electrical current passing through the coil induces a magnetic field perpendicular to the direction of travel of the electrical current (Hallett 2007). The electric current induced in M1 occurs parallel to the scalp (Hallett 2007). When sufficient in intensity, the magnetic field can

depolarize neurons in M1 and result in muscular activity. At a neuronal level TMS depolarizes the neurons in the same manner as electrical current. It is believed that the TMS is able to activate cortical neurons at a depth between 1.5 to 3 cm depending upon the stimulation intensity and properties of the coil (Rossi et al. 2009). The magnetic current can depolarize the corticospinal neurons directly, but most corticospinal neurons are believed to be depolarized trans-synaptically by first depolarizing interneurons and polysnaptic neurons that synapse onto the corticospinal neurons (Di Lazzaro et al. 2004). These interneurons are depolarized as they transverse horizontally within M1, running perpendicular to the magnetic field and are identified as the result of longer latencies between stimulation with TMS and the EMG response within the muscle compared to those resulting from transcranial direct current stimulation (Hallett 2007). The EMG response in the muscle resulting from the TMS is described as the Motor Evoked Potential (MEP). MEPs represent not only the excitability of M1 neurons but represent the depolarization and transmission through the entire corticospinal system including excitatory and inhibitory interneurons in M1, corticospinal neurons, and spinal motoneurons (Groppa et al., 2012).

2.3.3.2 MSD and the primary motor cortex

M1 changes in corticospinal properties and organization in persons with MSD have been found. Changes in corticospinal properties and organization have been found in M1 in persons with anterior knee pain (On et al. 2004; Rio et al. 2016), knee osteoarthritis (Kittelson et al. 2014; Shanahan et al. 2015; Lepley et al. 2015), injury to the anterior cruciate ligament (Héroux and Tremblay 2006; Ward et al. 2016), lateral epicondylitis (Schabrun, Hodges, et al. 2014), hand injuries including arthritis (Parker et al. 2017), shoulder (Ngomo et al. 2015), cervical (Marker et al. 2014) and chronic LBP (Strutton et al. 2005; Tsao et al. 2008; Tsao, Danneels, et al. 2011; Masse-Alarie et al. 2012; Elgueta-Cancino et al. 2015; Elgueta-Cancino et al. 2017). TMS has been utilized to assess corticospinal excitability measures in persons with MSD including the motor threshold (the minimal TMS stimulation intensity to elicit an EMG response in the muscle), input-output curves (assessing EMG responses at increasing TMS stimulation intensities), inhibitory and facilitatory processes involving cortical interneurons (intracortical inhibition and facilitation using paired pulsed paradigms involving a subthreshold TMS conditioning stimulus followed by a TMS test stimulus), and mapping of motor cortex to assess

representational changes by eliciting EMG responses with TMS applied to a number of grid points over the motor cortex.

2.3.3.2.1 MSD and the motor threshold

All studies that utilize single pulse TMS involve determining the Motor Threshold (MT). The Resting Motor Threshold (rMT) is usually defined as the TMS stimulation intensity, expressed as a percentage of maximum stimulator output, which induces a MEP with a peak-to-peak amplitude of at least 50uv in 5/10 trials (Rossini et al. 1994). The location requiring the lowest stimulator intensity to induce the motor threshold is referred to as the Hotspot. Although most TMS studies in participants with MSD have not found differences in MT between healthy control participants and participants with MSD, some studies have found significant differences (Strutton et al. 2003; Strutton et al. 2005; Masse-Alarie et al. 2012; Bradnam et al. 2015; Lepley et al. 2015; McLeod et al. 2015; Maria da Graca et al. 2016). In studies that have found differences an increase in MT, indicative of a higher TMS intensity necessary to produce an MEP response, suggestive of decreased corticospinal or spinal motoneuronal excitability in the participants with MSD was found (Strutton et al. 2003; Strutton et al. 2005; Masse-Alarie et al. 2012; Bradnam et al. 2015; Maria da Graca et al. 2016) in all but one of the studies (McLeod et al. 2015). In the only prospective TMS study performed in participants with MSD, Lepley et al (2015) found in participants with anterior cruciate ligament injuries, changes in active MT at different time points. Active MT of the quadriceps muscle was decreased pre-surgery and increased post-surgery suggesting that changes in MT (and therefore corticospinal excitability) may be variable over time (Lepley et al. 2015). Studies with participants with MSD have found the MT to be correlated with pain severity (Strutton et al. 2005; Kittelson et al. 2014), pain duration (Ngomo et al. 2015), with self-reported disability questionnaires (Strutton et al. 2003; Strutton et al. 2005), and with abnormal muscle activation (Masse-Alarie et al. 2012).

2.3.3.2.2 MSD and intracortical inhibition and facilitation

Studies of M1 inhibitory and facilitatory processes within M1 utilizing TMS may involve two methods: paired pulse paradigms to study intracortical inhibition and facilitation and the cortical silent period (see 2.3.3.2.3). The paired pulse paradigms involve a test pulse (usually eliciting a MEP of approximately 1 mv to a test stimulus delivered in isolation) proceeded by a conditioning stimulus (80-90% of MT) at the same location in M1 at different Inter-Stimulus

Intervals (ISI). The intensity of the conditioning stimulus is sufficient to depolarize cortical interneurons but insufficient to depolarize corticospinal neurons and produce a MEP. The responses of the conditioning+test stimuli are compared to the responses of the test stimuli alone and traditionally presented as a ratio ((conditioned+test MEP)/ (test MEP alone)).

Short Interval Cortical Inhibition involve ISI between the conditioning and test stimuli of 1-4 ms (Hallett 2007; Groppa et al. 2012). At these inter-stimulus intervals, the conditioned MEP will be depressed compared to the values when the test stimulus is administered in isolation. Pharmacological studies suggest that these inhibitory effects are mediated by $GABA_A$ secreting inhibitory interneurons (Di Lazzaro et al. 2004). Intracortical facilitation involves the application of TMS at conditioning and test stimuli at interstimulus intervals of between 7-20 ms (Groppa et al. 2012). With Long Interval Cortical Inhibition (LICI) the conditioning stimulus, applied to the same location as the Test stimulus, will be applied at percentage of rMT at interstimulus intervals of 50-200 ms.

Studies of intracortical inhibition and facilitation have been performed in participants with experimentally induced pain and in participants with MSD. Hypertonic saline injection in the FDI muscle in healthy control participants resulted in a decrease in the EMG response in the FDI and the non-injected abductor digiti minimi assessed with TMS (Schabrun and Hodges 2012). Intracortical inhibition was increased after the injection, while intracortical facilitation was decreased during and after the painful injection. Studies in participants with MSD have found decreased intracortical inhibition (Masse-Alarie et al. 2012; Massé-Alarie et al. 2016; Parker et al. 2017) while other studies have found no differences (Kittelson et al. 2014; Maria da Graca et al. 2016; Ward et al. 2016). Two studies, one in persons with chronic LBP and the other in persons with osteoarthritis of the hands found decreased short interval cortical inhibition (Masse-Alarie et al. 2012; Parker et al. 2017), and the later also found an increase in short interval cortical facilitation (Parker et al. 2017) suggestive of increased corticospinal excitability. In the study by Parker et al (2017), short interval cortical inhibition and short interval cortical facilitation was correlated with pain duration (Parker et al. 2017). However, other studies that have investigated intracortical inhibition and intracortical facilitation in persons with MSD have not found differences compared with healthy controls (Schwenkreis et al. 2010; Kittelson et al. 2014; Maria da Graca et al. 2016; Ward et al. 2016). Interestingly, a

study in persons with chronic neck pain did not find that short interval cortical inhibition was altered in comparison with healthy control subjects, but found different modulation of short interval cortical inhibition under high and low mental stress conditions between groups (Marker et al. 2014) reflecting possible influences between forebrain processes, psychological factors, and corticospinal excitability.

2.3.3.2.3 MSD and the cortical silent period

TMS applied to the motor cortex over the hotspot of a muscle when that muscle is contracting results in a period of EMG absence within the muscle for a period lasting usually between 100-300ms. This interruption of EMG activity is called the Cortical Silent Period (CSP). CSP is believed to be reflective of inhibitory mechanisms impacting motor cortical activity (Rossini et al. 1994; Clark et al. 2008). This inhibition is believed to be mediated by spinal refractoriness (first 50ms) and by cortical inhibitory mechanisms (Groppa et al. 2012). This inhibitory period is inhibited by pharmacological interventions that affect the $GABA_B$ function (Groppa et al. 2012; Wernham 1999).

The threshold for inducing the CSP was found to be higher in participants with LBP and sciatica that was correlated with self-reported disability scores (Strutton et al. 2003; Strutton et al. 2005). Increased (Bradnam et al. 2015; Ward et al. 2016), decreased (Maria da Graca et al. 2016), or no changes (Héroux and Tremblay 2006; Masse-Alarie et al. 2012; Parker et al. 2017) in CSP duration have been found in studies in participants with various MSD. CSP duration in participants with MSD has been negatively correlated with both pain and disability suggestive that increased corticospinal excitability is associated with increased pain/disability (Maria da Graca et al. 2016) or contrarily no association was found (Bradnam et al. 2015; Ward et al. 2016).

2.3.3.2.4 MSD and corticospinal excitability measured with input-output curves

Corticospinal excitability has also been assessed with Input-Output (I-O) curves and MEP peak-to-peak amplitudes at single intensities of stimulation (i.e. 120-130 % of MT). I-O curves involve determining MEP amplitudes at increasing TMS intensities. Studies involving participants with MSD and controls have found no differences in I-O curves between groups (Héroux and Tremblay 2006; Ngomo et al. 2015; Parker et al. 2017), although others have found

an increase in slope of the curve in participants with MSD (Berth et al. 2009; Rio et al. 2016). The Heroux and Tremblay study (2006) found a relationship between slope parameters and quadriceps torque in the injured leg in participants with anterior cruciate ligament injuries. Studies utilizing single measures of MEP amplitudes at 120-130% of MT have also found no differences (Strutton et al. 2003; Strutton et al. 2005; Bradnam et al. 2015; Maria da Graca et al. 2016; Ward et al. 2016) or increased corticospinal excitability (On et al. 2004; Schabrun, Hodges, et al. 2014). One study found that peak MEP amplitudes were increased in both the extensor digitorum and extensor carpi radialis brevis muscles in participants with lateral epicondylagia compared to healthy control participants that was correlated with worst pain score in the previous six months (Schabrun, Hodges, et al. 2014).

2.3.3.2.5 MSD and TMS mapping

Several studies have performed TMS mapping in persons with MSD. TMS mapping involves stimulation around grid points centred about the hotspot and provide information of corticospinal excitability (map area and volume) and representation of corticospinal projections to a muscle(s). These studies all involved a comparison between the experimental and control groups. There was no difference in the age of participants in the control and experimental groups in any of the TMS mapping studies. These studies have found a decrease in the number of peaks (Schabrun, Hodges, et al. 2014; Elgueta-Cancino et al. 2015; Elgueta-Cancino et al. 2017; Te et al. 2017), an overlapping of muscle representations that are usually distinct (Tsao, Danneels, et al. 2011; Schabrun, Hodges, et al. 2014; Te et al. 2017), and changes in the position of greatest corticospinal excitability, the centre of gravity, of muscle activations in M1 (Tsao et al. 2008; Tsao, Danneels, et al. 2011; Schabrun, Hodges, et al. 2014; Elgueta-Cancino et al. 2015; Te et al. 2017). These representational changes have been associated with changes in muscle activation (Tsao et al. 2008; Masse-Alarie et al. 2012). Map volume changes in participants with MSD are variable with studies finding both increased (Tsao et al. 2008; Schabrun, Hodges, et al. 2014), decreased (Tsao, Danneels, et al. 2011; Elgueta-Cancino et al. 2017; Te et al. 2017) or no difference (Elgueta-Cancino et al. 2015; Ngomo et al. 2015) between participants with and without MSD. Map parameters have been associated with pain severity (Schabrun, Hodges, et al. 2014; Elgueta-Cancino et al. 2015; Elgueta-Cancino et al. 2017) or neither pain severity

or duration (Tsao, Danneels, et al. 2011; Te et al. 2017) suggesting that factors other than pain may be related to M1 changes in corticospinal properties and organization.

2.3.3.2.6 Summary of TMS changes and MSD

Studies in persons with MSD have demonstrated changes in inhibitory processes, corticospinal excitability, and an overlapping of the corticospinal projections within M1 of the muscles innervating the area of the MSD. However, these changes in corticospinal excitability that have been demonstrated in persons with MSD would be best characterized as variable. Whereas several studies have found changes in the motor thresholds, the majority of studies have not. Some studies have found changes in inhibitory processes such as short interval cortical inhibition and CSP while others have not. In the same anatomical regions, differences in study results have been found. Although the assessment of corticospinal excitability with TMS assesses the depolarization and transmission through the entire corticospinal system, including excitability of spinal motoneurons, only a few studies have evaluated spinal motoneuronal excitability (Lepley et al. 2015; McLeod et al. 2015). The Lepley and al. (2015) study, the only prospective study assessing corticospinal excitability in a sample population with MSD, also included an assessment of spinal motoneuronal excitability. Subjects with anterior cruciate ligament injury were assessed at three-time points, pre-surgery and 1 and 6-month post-surgery. Motor thresholds varied across time points as did spinal motoneuronal excitability. Interestingly, the decrease in MT post-surgery, indicative of increased corticospinal excitability corresponded with a decrease in spinal motoneuronal excitability observed at the same time points (Lepley et al. 2015). These findings are suggestive of an interrelationship between cortical and spinal measures of excitability. Therefore, changes in measures of corticospinal excitability found across various studies involving MSD may be reflective of altered spinal excitability and not simply excitability changes within M1.

2.3.3.2.7 MSD, corticospinal changes and motor function

Most of the TMS studies in persons with MSD have investigated the relationship between measures of corticospinal excitability and pain severity, symptom duration, and to a lesser extent self-reported disability. The relationship between the changes in corticospinal excitability and measures of pain and symptom duration are variable. Studies have found positive correlations with pain intensity (Kittelson et al. 2014; Schabrun, Hodges, et al. 2014; Bradnam et al. 2015;

Elgueta-Cancino et al. 2015; Shanahan et al. 2015; Maria da Graca et al. 2016; Elgueta-Cancino et al. 2017), others with symptom duration (Ngomo et al. 2015; Parker et al. 2017), and others with neither (Tsao, Danneels, et al. 2011; Ward et al. 2016; Te et al. 2017). Relatively few studies have looked at the relationship between measures of corticospinal excitability and motor function. Changes in corticospinal representations have been associated with muscle activation changes related to a postural perturbation task (Tsao et al. 2008; Masse-Alarie et al. 2012). Only one study has looked at the relationship between corticospinal excitability and measures of sensory function and found that no significant correlations between map parameters and measures of two point discrimination and pressure pain thresholds in participants with chronic non-specific LBP (Elgueta-Cancino et al. 2017). Due to the variability of study results it is therefore presently difficult to understand the underlying processes involved in modulation of corticospinal excitability and even the functional relevance of these changes.

Collectively these findings appear to suggest that corticospinal excitability changes are not a simple function of pain. Sensorimotor integration, defined by Machado et al (2010), *"as the capability of the central nervous system to integrate different sources of stimuli, and parallelly, to transform such inputs in motor actions"* is affected in persons suffering with MSD (Machado et al. 2010). Altered sensory processes and sensorimotor integration, forebrain influences (directly or via alterations of behaviour), spinal and cortical interrelationships, conflicting behavioural priorities in response to pain may all be factors influencing corticospinal excitability (see Figure 2.3). Furthermore, the majority of studies that have looked into associations between changes in corticospinal excitability and function have relied on self-reported measures of disability. There is a lack of understanding in how the changes in the different measures of corticospinal excitability that were found relate to clinical measures of sensory and motor function as well as disability.

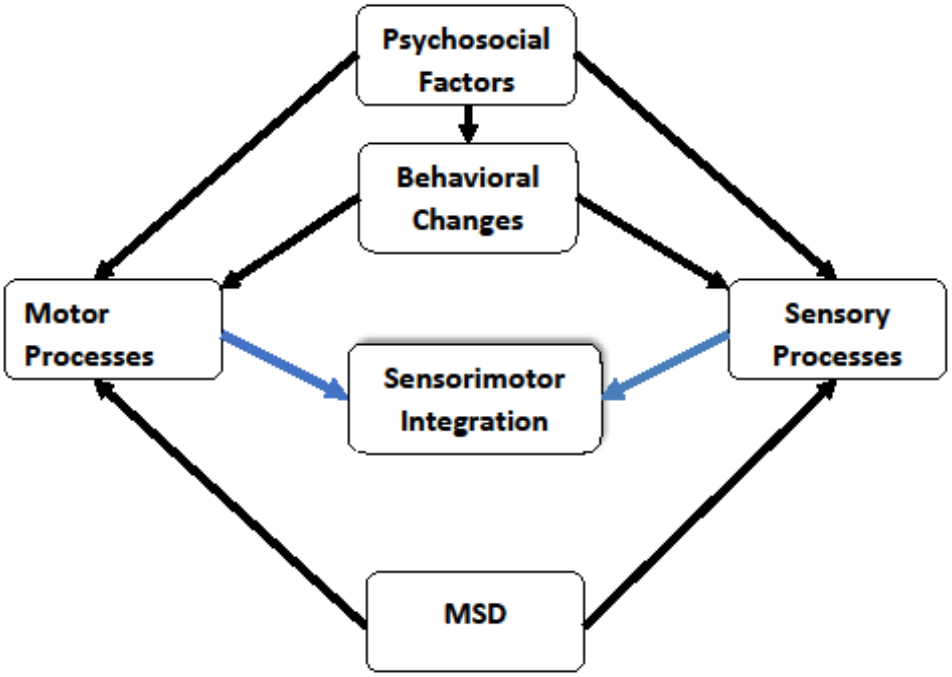

Figure 2.3: Musculoskeletal disorders and sensorimotor integration

Musculoskeletal Disorders (MSD) are characterised by altered sensory and motor processes. These changes and motor and sensory processes are the result of peripheral and central factors. Peripheral factors include localized insult to anatomical structures and the neurochemical changes resulting from the inflammatory mediators and nociceptor stimulation (i.e. bradykinins, prostaglandins, nerve growths factors, substance P) that influence local sensory output and the processing and transmission of sensory information in the spinal cord. These changes in sensory (i.e. pain) transduction and transmission in turn influence cortical sensory areas including the primary and secondary somatosensory areas and appear to affect the body schema. The body schema is an internal online representation of the body in peri-personal space derived from sensory, proprioceptive and visual input. Motor processes are affected by changes in the spinal cord affecting spinal motoneuronal excitability, but also from changes in sensory input as the result of the MSD and changes in sensory output related to behavioural changes and altered movement patterns. Central factors, such as psychological factors including catastrophization, pain related cognitions such as fear-avoidance, pain-related anxiety appears to affect sensory and motor processes directly through neural pathways and indirectly through behavioural changes. Collectively, altered sensory and motor processes appear to affect processes involved in sensorimotor integration.

2.4 Article 1: Is neuroplasticity in the central nervous system the missing link to our understanding of chronic musculoskeletal disorders?

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As the principal author of this manuscript, I confirm that I was responsible for performing the literature review in regard to this article and the writing of the manuscript. Dr Higgins and Dr Bourbonnais provided supervision and revision of the manuscript.

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2.4.1 Abstract

2.4.1.1 Background

Musculoskeletal rehabilitative care and research have traditionally been guided by a structural pathology paradigm and directed their resources towards the structural, functional, and biological abnormalities located locally within the musculoskeletal system to understand and treat Musculoskeletal Disorders (MSD). However, this structural pathology model does not adequately explain many of the clinical and experimental findings in subjects with chronic MSD and more importantly treatment guided by this paradigm fails to effectively treat many of these conditions.

2.4.1.2 Discussion

Increasing evidence reveals structural and functional changes within the Central Nervous System (CNS) of people with chronic MSD that appear to play a prominent role in the pathophysiology of these disorders. These neuroplastic changes are reflective of adaptive neurophysiological processes occurring as the result of altered afferent stimuli including nociceptive and neuropathic transmission to spinal, subcortical and cortical areas with MSD that are initially beneficial but may persist in a chronic state and may be part and parcel in the pathophysiology of the condition and the development and maintenance of chronic signs and symptoms. Neuroplastic changes within different areas of the CNS may help to explain the transition from acute to chronic conditions, sensory-motor and perceptual disturbances, and why some individuals continue to experience pain when no structural cause can be discerned. Furthermore, neuroplastic changes may help to explain why some persons fail to respond to conservative interventions and the persistent sensory motor findings in subjects with chronic MSD. We argue that a change in paradigm is necessary that integrates CNS changes associated with chronic MSD and that these findings are highly relevant for the design and implementation of rehabilitative interventions for this population.

2.4.1.3 Summary

Recent findings suggest that a change in model and approach is required in the rehabilitation of chronic MSD that integrate the findings of neuroplastic changes across the CNS and are targeted by rehabilitative interventions. Effects of current interventions may be mediated through peripheral and central changes but may not specifically address all underlying neuroplastic changes in the CNS potentially associated with chronic MSD. Novel approaches to address these

neuroplastic changes show promise and require further investigation to improve efficacy of currents approaches.

2.4.2 Keywords

Musculoskeletal disorders, chronic low back pain, osteoarthritis, neuroplasticity, periaqueductal grey, rostral ventromedial medulla, rehabilitation, primary somatosensory cortex, primary motor cortex, limbic, pre-frontal, pain.

2.4.3 Background

The treatment of Musculoskeletal Disorders (MSD) has been guided by a structural-pathology paradigm where the source of dysfunctions associated with the injury are to be found locally at the site of injury, the premise of "end organ dysfunction" (Wand, Parkitny, et al. 2011). The structural-pathology paradigm helps to comprehend and guide treatment effectively in acute MSD. There are however many unanswered questions and discrepant findings with chronic MSD where the structural-pathology paradigm fails as a working model for comprehension, research and in treatment. These include allusive questions such as why diagnostic imaging findings correlate poorly with pain and dysfunction, the presence of bilateral sensorimotor findings, why a large proportion of persons with damage to musculoskeletal structures are asymptomatic, why some persons heal and others develop chronic MSD, and persisting sensory motor abnormalities (Teresi et al. 1987; Stadnik et al. 1998; Tempelhof et al. 1999; Mazanec et al. 2005; Finan et al. 2013). In an attempt to better understand the clinical and experimental manifestations of these disorders researchers have expanded their scope of inquiry to include neurophysiological processes and plasticity within the Central Nervous System (CNS) associated with MSD.

Neuroplasticity is an intrinsic fundamental neurophysiological feature that refers to changes in structure, function and organisation within the nervous system that occurs continuously throughout a person's lifetime (Sanes et al. 2000; Kleim et al. 2008; Boudreau, Farina, et al. 2010; Pascual-Leone et al. 2011). Recent studies have revealed structural and functional changes within the CNS of people with chronic MSD. These changes are believed to be reflective of adaptive neurophysiological processes occurring with MSD that are initially beneficial and aid in the healing process by protecting the injured structures from further insult. In a chronic state, the structural pathology paradigm dictates that that these neuroplastic changes associated with chronic MSD are secondary to the injury and result from ongoing altered sensory transmission arising from the area of the musculoskeletal injury. Clinical and experiment findings however challenge this belief and demonstrate that neurophysiological adaptations may persist and be implicated in the development and maintenance of chronic signs and symptoms, possibly in lieu of healing to the peripheral musculoskeletal structures or co-existing with peripheral mechanisms (Coombes et al. 2009; Wand, Parkitny, et al. 2011). It has recently been

proposed that chronic pain associated with MSD is the result of imprinting, an implicit and/or explicit learned response that has formed a maladaptive memory sustaining the persistence of chronic pain (Apkarian et al. 2011; Moseley and Flor 2012; Davis et al. 2013; Mansour et al. 2014). According to this hypothesis, associative learning resulting from the initial trauma and subsequent events that reinforces the concurrent pairing between movement and pain results in an aversive association that is reflected and maintained by plastic changes in the meso-limbic and prefrontal areas (Mansour et al. 2014).

This article will argue that neuroplastic adaptations and their effects may initially result from structural injury, but in chronic conditions contribute to the pathophysiology of the condition possibly even in the absence of any continued anatomical/structural insult to musculoskeletal structures. These neuroplastic changes explain many of the experimental and clinical findings present in subjects with chronic MSD. These changes result in sensory amplification (Latremoliere and Woolf 2009), changes in sensory and motor representations (Flor et al. 1997; Tsao et al. 2008; Tsao, Danneels, et al. 2011) resulting in perceptual changes in body image (Bray and Moseley 2011; Lotze and Moseley 2007), changes in motor control (Hodges and Tucker 2011), bilateral diagnostic findings (Koltzenburg et al. 1999; Forget et al. 2008; Heales et al. 2013), the persistence and amplification of pain (Latremoliere and Woolf 2009; Woolf 2011), and why some individuals transit from acute to chronic disorders (Baliki et al. 2012; Mansour et al. 2013). Further evidence arguing to the importance of these neurophysiological adaptations are recent studies targeting neuronal processes appear to restore function and decrease pain (Moseley 2004b; Bowering et al. 2012; Moseley and Flor 2012; Bowering et al. 2013). These findings are highly relevant for the design and implementation of rehabilitative interventions for MSD which when guided by the structural-pathology paradigm have limited success in the treatment of many of these chronic conditions (Wand and O'Connell 2008). If neuroplastic changes in the CNS are not simply an epiphenomenon but are part and parcel to the pathophysiological process in chronic MSD, interventions that target these underlying pathophysiological mechanisms have the greatest chance of success (Snodgrass et al. 2014). Current conventional interventions in rehabilitation do not usually address underlying neuroplastic changes in the CNS associated with MSD (Snodgrass et al. 2014) and the incapacity to effectively treat these chronic MSD may stem as they are incomplete and/or misdirected (Barr

et al. 2004; Barr 2006; Wand and O'Connell 2008; Kapreli et al. 2009; Wand, Parkitny, et al. 2011).

2.4.4 Discussion

The structural pathology paradigm is guided by the inherent belief that pain and other neurophysiological changes are secondary to local structural insult to musculoskeletal structures. Both in animal and human studies, it is apparent that local and systemic inflammatory responses, cellular and vascular proliferative changes as well as degeneration and fibrosis are all hallmarks of chronic and overuse MSD (Barr et al. 2000; Barbe et al. 2003; Barr et al. 2004; Barr 2006; Barbe and Barr 2006). Injury to musculoskeletal structures, inflammatory mediators, and subsequent fibrosis change the mechanics of muscles and connective tissues affecting their physical properties and these in turn impacting sensory receptor activity and transmission (Petersen-Felix et al. 2002; Wilder-Smith et al. 2002; Barr et al. 2004; Costigan et al. 2009; Phillips et al. 2011; Coombes et al. 2009; Langevin and Sherman 2007). Under the structural-pathology paradigm neurophysiological consequences, with the exception of damage to the nerve(s), are secondary and should disappear when normal tissue properties are restored, and receptor activity, sensory transmission, and perception should renormalize to reflect the state of the healed structure(s). Within this paradigm pain is simply a symptom and reflects the degree of damage to the musculoskeletal structure and associated biological responses locally in the area of injury. This viewpoint is supported by the findings that demonstrates the reversal of some, but not all Central Nervous System (CNS) changes when anatomical insult to musculoskeletal structures and pain disappears (Rodriguez-Raecke et al. 2009; Seminowicz et al. 2011).

This paradigm however fails to explain many of the experimental findings with chronic MSD. For example, on a population level anatomical insult to musculoskeletal structures correlates poorly with findings from diagnostic imaging and these across a wide range of musculoskeletal disorders (Teresi et al. 1987; Stadnik et al. 1998; Tempelhof et al. 1999; Mazanec and Benzel 2005; Finan et al. 2013). Therefore, structural damage to musculoskeletal structures alone cannot always fully explain the presence of signs and symptoms in chronic MSD. Cognitive based interventions that involve education of pain processing and faulty beliefs regarding pain and movement yield better outcomes, between 10-20% improvement in disability and

performance scales (Moseley et al. 2004), than interventions involving education of anatomical and structural basis of injury (Koes et al. 1994; Moseley et al. 2004; Nijs, Meeus, et al. 2014; Louw et al. 2011) suggesting that central rather than peripheral influences play a key role in the clinical and experimental manifestation of at least some chronic MSD (Nijs, Meeus, et al. 2014), and that clinical interventions aimed to modify the central processing of pain should be further evaluated and compared to clinical interventions targeting peripheral mechanisms.

2.4.4.1 Principles of experience dependent plasticity

Neuroplasticity refers to changes in neuronal properties, structure and organization and is the manner in which the nervous system encodes new experiences. Neuroplastic changes has been demonstrated in response to experience and behaviour (Recanzone et al. 1992; Pascual-Leone et al. 1995; Tyc et al. 2005; Hasenkamp et al. 2012), motor learning (Nudo et al. 1996; Kleim et al. 1998; Plautz et al. 2000; Kleim et al. 2002; Bayona et al. 2005; Adkins et al. 2006), pain (Flor et al. 1997; Flor 2002; Mercier et al. 2010; Bank et al. 2013), injury (Hamilton et al. 1998; Elbert and Rockstroh 2004), sensory stimuli (Merzenich, Kaas, Wall, Nelson, et al. 1983; Merzenich et al. 1984; Merzenich and Jenkins 1993; Hamdy et al. 1998), and cognitive processes (Pascual-Leone et al. 1995; Schwartz 1999; Fourkas et al. 2008; Hasenkamp and Barsalou 2012). Changes can be transient, reflecting the adaptability of the sensorimotor system to respond to internal and environmental demands and can occur over short training periods (Classen et al. 1998; Hayashi et al. 2002). Neuroplastic changes are stimulus driven and result in lasting neuroplastic changes when the internal and external pressures are repetitive, salient, involve learning and require sustained attention (Jenkins et al. 1990; Pascual-Leone et al. 1995; Byl et al. 1997; Remple et al. 2001; Tyc et al. 2005; Kleim and Jones 2008). Neuroplastic changes have been observed in different areas of the CNS including the spinal cord, subcortical and cortical areas.

2.4.4.2 Plasticity in the spinal cord and brain stem with chronic MSD

Sensory testing has demonstrated changes in sensory transmission and processing across a number of MSD including osteoarthritis (OA) (Stanton et al. 2013; Sofat et al. 2013), Patella-Femoral Pain Syndrome (PFPS) (Jensen et al. 2008), tendinitis (Wilgen et al. 2011), Lateral Epicondylitis (LE) (Fernandez-Carnero et al. 2009), Carpal Tunnel Syndrome (CTS) (Fernandez-de-las-Penas, de la Llave-Rincon, et al. 2009), lumbar (Giesecke et al. 2004) and

cervical injuries including whiplash (Giesecke et al. 2004). These studies include findings of changes in perception threshold to noxious and innocuous stimuli, but also other sensory alterations including stimuli being processed more slowly, incorrect localization, and decreased accuracy in recognition of tactile stimulation (Sharma and Pai 1997; Tinazzi et al. 2000; Wilder-Smith et al. 2002; Brumagne et al. 2004; Giesecke et al. 2004; Jensen et al. 2008; Fernandez-Carnero et al. 2009; Fernandez-de-las-Penas, de la Llave-Rincon, et al. 2009; Wand et al. 2010; Luomajoki and Moseley 2011; Wilgen et al. 2011; Moseley, Gallagher, et al. 2012; Stanton et al. 2013). These changes have been demonstrated bilaterally and in sites remote to the initial injury (Smeulders et al. 2002; Jensen et al. 2008; Fernandez-Carnero et al. 2009). Proprioceptive deficits include increased errors in repositioning (Brumagne et al. 1999; O'Sullivan et al. 2003; Huysmans et al. 2010), decreased position sense and ability to detect joint motion (Gill and Callaghan 1998; Field 2009), difficulty to adopt postures seen on a photograph (Luomajoki and Moseley 2011; Moseley, Gallagher, et al. 2012) across a number of MSD.

Although not all studies involving subjects with chronic MSD demonstrate altered sensory transmission (Baliki et al. 2010) many studies with chronic MSD demonstrate augmented nociceptive transmission involving responsiveness to normally sub threshold nociceptive stimuli that results in hyperlagesia, an increase in nociceptive transmission and pain perception, indicative of an altered stimulus-response relationship to nociceptive stimuli, a process called Central Sensitization (Sterling et al. 2002; Giesecke et al. 2004; Latremoliere and Woolf 2009; Fernandez-Carnero et al. 2009; Fernandez-de-las-Penas, de la Llave-Rincon, et al. 2009; Woolf 2011; Lee, Lu, et al. 2011; Arendt-Nielsen et al. 2010). This is a normal, adaptive and reversible process that is biologically advantageous to protect the injured structure from further insult and is a consistent notion within the structural-pathology paradigm (Woolf 2011).

Neurophysiological changes also result in the amplification of noxious and innocuous stimuli within the dorsal horn of the spinal cord that persist in chronic pain states. These changes are reflective of processes similar to experience dependent plasticity and result from segmental, spinal and supraspinal processes that modulate membrane excitability and affect inhibitory and facilitatory processes within the spinal cord (see(Latremoliere and Woolf 2009)). Some dorsal horn nociceptive neurons develop increased receptor field size (wide-dynamic range neurons) responding to nociceptive and cutaneous stimuli that results in secondary hyperalgesia and

allodynia (spread and perception of pain with innocuous stimulation) (Latremoliere and Woolf 2009).

The supraspinal influences on dorsal horn nociceptive transmission include descending pain modulatory systems including the Periaqueductal grey (PAG)-Rostral Ventromedial (RVM) pathway. Under normal circumstances these systems inhibit the transmission of nociceptive stimuli in the dorsal horn of the spinal cord (Heinricher et al. 2009). There exists convincing evidence in animal models that these descending modulatory systems are disrupted in chronic pain subjects shifting from a state of inhibition to a mal-adaptive state of facilitation amplifying the transmission of nociceptive stimuli, contributing to the process of central sensitization, and perpetuating the augmented transmission of neuropathic stimuli (Heinricher et al. 2009; Phillips and Clauw 2011). For example, an increase in activity of cells that project to the dorsal horn of the spinal cord from the RVM that facilitate the transmission of noxious stimuli is present only in animals with neuropathic pain behaviours (De Felice et al. 2011). The microinjection of lidocaine into the RVM, causing a temporary cessation of neuronal activity, and an ipsilateral lesion of the dorsal lateral funiculus that house neuronal projections from the RVM towards the dorsal horn both decrease the threshold to elicit withdrawal reflexes, indicative of increased pain perception and that neuronal activity of the RVM is facilitating the transmission of nociceptive/neuropathic stimuli (Wang et al. 2013). Electrical stimulation of the RVM paired with cutaneous stimulation recorded from second order spinal nociceptive neurons results in a 130% increase in neuronal activity (Porreca et al. 2002). In CLBP patients there is a decrease in PAG cerebral blood flow not seen in healthy control subjects suggestive of decreased neuronal activity (Giesecke et al. 2006). In humans there is evidence that the a test noxious stimulus, under normal circumstances, is inhibited by a preceding noxious conditioning stimulus, a process called Conditioned Pain Modulation (Yarnitsky 2010), and is disturbed in subjects in some MSD and chronic pain states (Kosek et al. 2000b; Yarnitsky 2010). Collectively the results from these studies demonstrate that the PAG-RVM pathway not only facilitates nociceptive transmission in the dorsal horn of the spinal cord but actually perpetuates the transmission of pain. This argues against a peripherally driven source of augmented nociceptive/neuropathic transmission and for a centrally mediated mechanism perpetuating the transmission of afferent stimuli that is inconsistent with the structural-pathology paradigm.

Neuroplastic changes amplifying sensory transmission have functional implications. Subjects demonstrating central sensitization (hypersensitivity and allodynia) have a poorer prognosis to treatment including surgical interventions for varied MSD (Farrell et al. 2000; Sterling et al. 2002; Gwilym et al. 2011; Davis and Moayedi 2013). Furthermore, studies in both animals and humans demonstrate that altered sensory transmission may result in changes in neuronal properties and organization within different subcortical and cortical areas including the thalamus, primary somatosensory cortex (S1) and the primary motor cortex (M1) implicated in sensory transmission, perception and motor control (Jones et al. 1998; Kambi et al. 2014).

2.4.4.3 Neuroplastic changes in the primary somatosensory cortex and perceptual changes with MSD

Studies of cortical properties and organisation within the sensorimotor areas have been performed with subjects with anterior knee pain (On et al. 2004), anterior cruciate ligament (ACL) deficiency and reconstruction (Ochi et al. 1999; Ochi et al. 2002; Héroux and Tremblay 2006; Kapreli et al. 2009), CLBP (Flor et al. 1997; Strutton et al. 2003; Strutton et al. 2005; Lloyd et al. 2008; Tsao et al. 2008; Tsao, Druitt, et al. 2010; Tsao, Danneels, et al. 2011), cervical pain and whiplash injury (Tinazzi et al. 2000; Falla and Farina 2008), rotator cuff tears (Berth et al. 2009; Berth et al. 2010), dystonia (Byl et al. 1996; Byl et al. 1997; Byl et al. 2000b; Byl et al. 2002; Butterworth et al. 2003; Byl et al. 2000a) and CTS (Tinazzi, Zanette, Volpato, and al 1998; Druschky et al. 2000; Tecchio et al. 2002; Maeda et al. 2013). These studies suggest that neuronal properties, organization, and morphometric changes are present in subjects with chronic MSD. For example subjects with CLBP demonstrate a 2.5 cm shift of the somatotopic representation in S1 (Flor et al. 1997; Lloyd et al. 2008) and grey matter volume changes that correlate with chronicity of symptoms (Apkarian et al. 2004; Schmidt-Wilcke et al. 2006). Studies in subjects with CTS reveal changes along the afferent pathway in the spinal cord, brain stem and S1 (Tinazzi, Zanette, Volpato, Testoni, et al. 1998), a decrease in grey matter volume (Maeda et al. 2013) and a loss of spatially segregated representations of digits 2 (D2) and digits 3 (D3) in the contralateral S1 that correlate with changes in nerve conduction velocity (Tinazzi, Zanette, Volpato, Testoni, et al. 1998; Napadow et al. 2006; Maeda et al. 2013). Somatotopic re-organisation in CTS subjects are specific to the nature of sensory stimuli as the representation of the digits in S1 is decreased with pain and increased with paraesthesia (Tecchio et al. 2002).

In the perspective of the structural-pathology paradigm, these changes in S1 associated with MSD may simply be reflective of altered peripheral sensory transmission reflective of altered afferent peripheral sensory stimuli and transmission occurring as the result of insult to musculoskeletal structures and inflammation. Studies in non-human primates with peripheral de-afferentation and spinal cord injury demonstrate degeneration in the cuneate nucleus of the brainstem, an area that contains axons from the dorsal root ganglion transmitting cutaneous and proprioceptive stimuli, as well as somatotopic reorganization in an area of the thalamus (ventral posterior lateral nucleus) that transmits sensory afferent stimuli to S1. The changes in S1 in these studies mirror the changes found in the thalamus suggesting that the changes in sensory afferents including noxious, cutaneous, and possibly proprioceptive afferent transmission are implicated in S1 reorganization (Jones and Pons 1998; Kambi et al. 2014). However, should altered afferent transmission persist, potentiated by functional changes in the brain stem and the spinal cord, neurophysiological changes appear to result in behavioural and functional implications that are not simply a reflection of altered sensory afference.

There is growing evidence that pain associated with MSD such as osteoarthritis and CLBP may be, at least in part, the result of the plasticity of the sensory representation of the body and perceptual disturbances (Preston et al. 2011; McCabe 2011; Wand et al. 2013). Distortions in body image have been found in a range of conditions where cortical reorganization in S1 are present including Phantom Limb Pain (PLP), Complex Regional Pain Syndrome (CRPS) and in CLBP (Buchner et al. 2000; Moseley, Parsons, et al. 2008; Mancini et al. 2011; Bray and Moseley 2011; Moseley and Flor 2012). These changes include the sensation of abnormal size, shape, swelling, and position (Moseley 2004b). Perceptual changes may also arise from abnormal or conflicting sensory and /or motor inputs (Swart et al. 2009; Bailey et al. 2012). Perceptual changes also have functional implications. Incongruence and manipulation between sensory and motor input has been shown to cause sensory disturbances, aggravate symptoms, and pain (McCabe et al. 2005). Modulation of the shape and size of a limb can impact tactile acuity and pain (Osumi et al. 2014). Visual distortion of the hands in subjects with osteoarthritis help to decrease pain (Preston and Newport 2011). Interventions targeting changes in somatotopic reorganization through the use of sensory discriminative training and visual distortion can renormalize S1 representation and decrease pain (Moseley 2004b; Napadow et al.

2007; Lewis et al. 2011; Wand, O'Connell, et al. 2011; Wand et al. 2013). The modulation of the size of the limb can alter subjective feelings of pain and motor imagery can cause an increase in pain and swelling that cannot be attributed to increased peripheral sensory afference arising from nociceptors or peripheral neural injury (Moseley, Zalucki, Birklein, et al. 2008; Moseley, Parsons, et al. 2008). The persistence of abnormal motor imagery in recurrent low back subjects is also believed to be reflective of ongoing disruption of cortical maps even in the absence of pain (Moseley 2014). These findings support the belief that structural injury to musculoskeletal structures are not the only driver of pain and dysfunction, CNS changes play an active role in the pathophysiology of chronic pain conditions, and interventions that target these CNS changes may decrease pain, improve function, and even affect mechanisms involved in the local biological response to injured structures such as swelling.

2.4.4.4 Changes in primary motor cortex associated with MSD

Studies that investigate changes in the properties, function and organisation within the primary motor cortex (M1) of subjects with different MSD have been performed, of which the majority utilise Transcranial Magnetic Stimulation (TMS). TMS produces a high intensity electrical pulse resulting in a magnetic field perpendicular to the stimulating coil. The magnetic pulse traverses the skull and when applied over the motor cortex with sufficient intensity, can depolarize corticospinal neurons directly or indirectly. This stimulation results in the depolarization of different motoneuron pools within the spinal cord and an electromyographic response, the Motor Evoked Potential (MEP) can be recorded. Utilising different parameters of stimulation and experimental protocols, TMS allows for the appreciation of corticospinal excitability, inhibitory and facilitatory processes, and somatotopic organization of corticospinal neurons. Studies of corticospinal excitability have been performed in subjects with various MSD including PFPS (On et al. 2004) , ACL deficiency (Héroux and Tremblay 2006) , CLBP (Strutton et al. 2003; Strutton et al. 2005; Tsao et al. 2008; Tsao, Tucker, et al. 2011; Tsao, Danneels, et al. 2011), and Rotator Cuff Tears (Berth et al. 2009; Berth et al. 2010). Collectively these studies demonstrate changes in corticospinal excitability that correlate with pain and disability scores. Changes in motor behaviour that are present in subjects with CMSD appear to be largely mediated by changes in the cortical areas including M1. Inhibition of corticospinal output is increased in experimentally induced muscle pain resulting in decreased motor

responses to transcranial magnetic stimulation at rest (Schabrun and Hodges 2012) and increased corticospinal output during forceful muscle contractions (Del Santo et al. 2007; Martin et al. 2008). Findings from these studies appear to be consistent with the experimental findings that demonstrate variable motor control changes including reorganization of motor unit recruitment both within and between muscles in an attempt to minimize the motor consequences associated with chronic MSD (see(Coombes et al. 2009; Hodges and Tucker 2011; Bank et al. 2013)), co-activation of muscles and overlapping of muscle/movement representations in M1 (Tsao, Danneels, et al. 2011; Hodges and Tucker 2011), and variations in corticospinal output in an attempt to maintain constant force under painful conditions and compensate for increased inhibition (Del Santo et al. 2007).

In a series of experiments Tsao and his colleagues investigated the properties and organization of the representation of muscles in the lumbar spine within M1. They demonstrated that the area of corticospinal recruitment of muscles of the lumbar spine in M1 are altered in CLBP subjects (Tsao et al. 2008). These changes correlate with changes in motor recruitment (Tsao et al. 2008; Tsao, Danneels, et al. 2011). Motor skill learning involving exercises to specifically recruit the transverse abdominus muscle, but not a walking exercise, could restore the representation within M1 and EMG activation pattern in CLBP subjects to that seen in healthy controls (Tsao, Druitt, et al. 2010). The changes in the representation of the movements elicited by the trunk muscles in M1 are associated with the impaired activation of these muscles and may underpin changes in motor activation, specifically the inability to selectively recruit these muscles. This, in turn is consistent with the increased activation of superficial muscles in this population when performing movements (Hodges and Moseley 2003) and the altered activation of the multifidus that has been demonstrated in patients with recurrent LBP (Sihvonen et al. 1997; Danneels et al. 2002). These studies demonstrate that neuronal properties and organisation within M1 are modified in CLBP subjects and that intervention specifically targeting these representational changes improve function and decrease pain.

The relationship between the plastic changes in the spinal cord, brain stem and cortical sensori-motor areas are complex. Experimental findings suggest the possibility of two-way causality, where altered sensory input including enhanced nociceptive/neuropathic stimuli, altered cutaneous and proprioceptive input affects sensorimotor organisation and processes within the

CNS, and these changes in turn affect perception, pain, and motor control processes contributing to the pathophysiology of the condition (Preston and Newport 2011; McCabe 2011). If these processes remain present for a substantial period of time they may result in lasting neurophysiological adaptations that may become imprinted and can outlive the insult to peripheral musculoskeletal structures (Moseley and Flor 2012; Mansour et al. 2014). It is important to note that a return to before injury sensory transmission and the performance of repetitive strengthening exercises may not be sufficient to return the neuronal properties and organization within the sensorimotor areas to a pre-injury state (Lundbye Jensen et al. 2005). Specific interventions addressing these neuroplastic changes in sensorimotor areas appear to be required. Repetitive unskilled movements do not result in neuroplastic changes in M1 (Remple et al. 2001; Bayona et al. 2005). Motor skill training however has proven successful in the treatment of some musculoskeletal conditions, improves task performance and helps promote neuroplastic changes in M1 (Karni et al. 1995; Pascual-Leone et al. 1995; Svensson et al. 2006; Koeneke et al. 2006; Jull et al. 2009; O'Leary et al. 2009; Tsao, Druitt, et al. 2010). These findings are suggestive that the neuroplastic changes in the sensory-motor areas are implicated in the pathophysiology of some chronic MSD and should impact rehabilitative treatments.

2.4.4.5 Role of Pain in Central Nervous System (CNS) plasticity

Findings from experimental studies do provide convincing evidence that pain provides an impetus for CNS changes with MSD. Experimentally induced pain impacts neuronal properties and organisation in S1 and M1 (Soros et al. 2001; Tsao, Tucker, et al. 2011) and subjects with chronic pain associated with unilateral herpes simplex virus have a decreased representation between digits 1-5 in the contralateral S1 (Vartiainen et al. 2009). Although the causal relationship between pain and cortical reorganization has not been definitively established with MSD, the evidence suggests that pain is a driver of cortical re-organization. In other conditions where re-organisation in S1 is present there is a renormalisation with the attenuation of pain (Birbaumer et al. 1997; Huse et al. 2001) and some, but not all, of the morphological changes in brain grey matter volume and changes in cortical somatotopy return to those seen in normal healthy subjects when pain is eliminated (Birbaumer et al. 1997; Huse et al. 2001; Rodriguez-Raecke et al. 2009; Seminowicz et al. 2011).

However, pain alone is neither necessary nor sufficient to drive neuroplastic changes. Dystonia and CTS are both conditions where researchers have demonstrated neuroplastic changes in M1 and S1 in the absence of pain. Focal hand dystonia involves a loss of individual control of the digits of the hand that results from rapid repetitive motor actions of the fingers. These movements result in blurring of the representation of the digits with loss of spatial segregation (Byl et al. 2000a; Byl et al. 2002; Butterworth et al. 2003). Subjects with recurrent low back pain continue to demonstrate abnormal motor control in the absence of pain possibly reflecting continued reorganisation of neuronal properties and organisation in M1 (Brumagne et al. 2008; D'hooge, Cagnie, et al. 2013; D'hooge, Hodges, et al. 2013). Behavioural interventions that help to restore somatotopic organisation also improve function and decreases pain suggesting the possibility of two way causality between pain and sensorimotor representations (Tsao, Danneels, et al. 2011).

Although pain provides an impetus for neuroplastic changes in the CNS, other forms of stimuli, cognitive processes and behaviours can induce plastic changes. Studies in animals, healthy human and neurologically compromised human subjects have demonstrated that repetition and attention/salience are important factors inducing neuroplastic changes in S1 and M1 (Jenkins et al. 1990; Braun et al. 2002; Stefan et al. 2004; Kleim and Jones 2008). The limbic and prefrontal structures are the cortical areas responsible for these aspects of behaviour and findings have demonstrated important changes in these areas in chronic pain states including some MSD (Mansour et al. 2014; Apkarian et al. 2011).

2.4.4.6 Neuroplastic changes in meso-limbic and prefrontal structures in chronic pain states

Of all the areas of the CNS with documented changes occurring in association with chronic MSD, the meso-limbic and prefrontal structures are the most impressive and possibly the most important as changes in these areas demonstrate strong correlations with chronicity (Apkarian et al. 2011), and furthermore can be predictive and possibly even determine who will transit from acute to chronic pain (Baliki et al. 2012; Mansour et al. 2013; Mansour et al. 2014). In a recent systematic review article of fMRI studies in persons with chronic pain by Kumbhare et al. (2017) and a summary of the results of this review presented by Davis and Semenowicz (2018), it is argued that there are general disruption of anatomical and functional brain networks that are associated with chronic pain conditions, however these is a great deal of variability

between studies (Kumbhare et al. 2017; Davis et al. 2017). The systematic review found that are the important intersubject variability including gender differences in brain circuitry and connectivity (Davis and Seminowicz 2017). Experimentally induced pain results in the activation of characteristic cortical regions including S1, S2, insula, cingulate cortex, amygdala, and prefrontal cortex in what is commonly referred to as the pain matrix, but is possibly more reflective of a salience network as these structures are not only active with painful stimuli but also in conditions involving increased attention/salience (Legrain et al. 2011; Henry et al. 2011).

Experimental findings suggest that the structure and function of the brains of subjects with chronic pain including CLBP and OA are different from healthy controls and this is most important in the meso-limbic and prefrontal areas (see(Apkarian et al. 2011)). When experimentally induced pain is applied to subjects with CLBP and osteoarthritis (OA) while performing a fMRI, both CLBP and OA subjects demonstrate spontaneous fluctuations of pain that is not time locked to the experimental noxious stimuli and are not present in healthy control subjects (Baliki et al. 2006; Parksl et al. 2011). Spontaneous pain engages pre-frontal and limbic areas important for the processing and cognitive response to incoming stimuli (Apkarian et al. 2011; Parksl et al. 2011; Bushnell et al. 2013). FMRI studies have demonstrated that subjects with chronic MSD, specifically CLBP and OA, demonstrate abnormal activity in the cingulate cortex, the amygdala, the insula, nucleus accumbens (NAc) and pre-frontal areas including the medial prefrontal cortex (mPFC) and the dorsolateral prefrontal cortex (dlPFC) (Apkarian et al. 2004; Apkarian et al. 2011; Parksl et al. 2011). These mesolimbic-prefrontal areas are involved in the cognitive affective aspects of pain and injury including the behavioural response to these, the processing of fear, emotions, negative conditioning and attention (Kulkarni et al. 2007; Pereira et al. 2010). One result of the abnormal activity in these areas is increased vigilance and a decreased ability to disengage from pain (Davis and Moayedi 2013). These limbic structures have direct and indirect connections with both the sensorimotor areas and the brain stem and provide the substrate of attention and salience necessary for the induction of neuroplastic changes in these areas (Paus 2001; Bushnell et al. 2013). Furthermore, these structures influence descending pain modulatory systems including the PAG-RVM pathway where, as discussed earlier, compelling evidence suggests is disrupted in chronic pain subjects and perpetuate the ongoing abnormal augmented pain transmission originating from nociceptive and non-

nociceptive peripheral receptors in the dorsal horn of the spinal cord (Apkarian et al. 2009; Heinricher et al. 2009).

The brain derived biomarkers from abnormal activity in the mesolimbic and prefrontal areas correlate strongly with clinical measures in patients with CLBP and correlate better with clinical findings than do structural and psychosocial findings (Apkarian et al. 2009; Apkarian et al. 2011). Increased insular activation is correlated with pain duration, while mPFC activation is correlated with pain intensity in CLBP subjects (Apkarian et al. 2011). Abnormal increased connectivity between the mPFC and the NAc is highly predictive (90%) of who will go on to develop CLBP suggesting that there may be pre-disposing biomarkers for the development of chronicity (Mansour et al. 2013; Baliki et al. 2006). For a more thorough overview of changes in the meso-limbic and prefrontal areas associated with CMSD excellent reviews have been published (Apkarian et al. 2009; Apkarian et al. 2011; Mansour et al. 2014).

The complex interrelationship between pain, cortical reorganization, disability, and abnormal motor behaviour is compounded by the implication of psychological factors associated with chronic pain and injury. Catastrophization ("tendency to focus and magnify pain sensation, and to feel helpless in the face of pain") and fear play a role in the etiology and prognosis of chronic pain conditions (Denison et al. 2004; Somers et al. 2009; Linton et al. 2011; Wertli et al. 2014). Psychosocial factors predict variance in pain, gait velocity, and psychological disability in OA subjects, appear to increase pain and disability (see(Somers et al. 2009; Linton and Shaw 2011)), impact pain perception in healthy controls (Weissman-Fogel et al. 2008; Somers et al. 2009), and may result in a learned avoidance behaviour perpetuating the disability (Turk et al. 2010; Linton and Shaw 2011). These changes in the pre-frontal cortex activation are also consistent with fMRI studies that have correlated changes in prefrontal activity with psychosocial variables involved in CLBP and OA, including dlPFC activity being negatively correlated with Pain Catastrophizing Scores and mPFC activity correlated with fear-avoidance/anxiety (Seminowicz and Davis 2006; Ochsner et al. 2006; Davis and Moayedi 2013). Pain catastrophizing and fear-avoidance cause behavioural changes and may be responsible for changes in neuronal properties and somatotopic reorganization because of disuse similar to learned non-use in stroke patients (Taub et al. 1999; Takeuchi et al. 2012). Neural circuits not actively engaged in task performance for an extended period of time begin to degrade (Kleim and Jones 2008; Lissek et

al. 2009). Prolonged non-use of the affected limb may lead to a vicious cycle whereby immobility, changes in cortical representation, and atrophic changes re-enforce each other.

2.4.4.7 Integrating CNS changes into a more comprehensive model of chronic MSD

It would appear that behavioural changes and psychological processes in chronic pain subjects involve activity in the meso-limbic and pre-frontal areas that influence pain perception and behaviour. Although speculative the behavioural changes associated with these changes in meso-limbic and pre-frontal areas may therefore be reflective of salience and increased attention directed towards the injury and associated pain. The meso-limbic and prefrontal structures influence descending modulatory pathways and facilitate the transmission of noxious stimuli which perpetuates the altered transmission of sensory stimuli and appear to influence sensorimotor representations and neuronal properties. It is possible that these changes collectively result in a vicious cycle where injury, pain, altered sensory transmission, sensorimotor changes, behavioural changes, salience, attention, and fear-avoidance may feed off one another perpetuating the disability. It has been hypothesized that the neuroplastic cortical changes in the meso-limbic pre frontal areas associated with chronic pain states are reflective of learned operant and classic conditioning resulting in the formation of a "pain" memory (Flor 2003; Apkarian et al. 2011; Davis and Moayedi 2013; Moseley and Flor 2012). Providing support for this hypothesis are findings where imagery affects pain, swelling, and cortical excitability (Moseley, Zalucki, Birklein, et al. 2008). Consistent with the implication of altered neuronal activity in the meso-limbic and prefrontal areas in the pathophysiology of chronic MSD are the findings from educational and cognitive based interventions. Educational programs explaining the neurophysiological mechanisms of pain have proven more effective than back schools (which emphasize end organ dysfunction and behavioural changes to decrease loading of anatomical structures) in CLBP patients (Koes et al. 1994; Moseley et al. 2004; Moseley 2004a; Nijs, Meeus, et al. 2014). These educational programs attack faulty pain beliefs which leads to fear-avoidance often present with chronic MSD (Leeuw et al. 2007). The findings that altered functional connectivity in these areas are the best predictors of chronicity in the transition from acute to CLBP further supports the argument as to the importance of the changes in these areas in the pathophysiology of MSD (Mansour et al. 2013). These findings are inconsistent with a structural- pathology paradigm of a solely peripherally driven source of dysfunction in

chronic MSD. Chronic MSD such as OA and CLBP, and possibly other MSD may have prominent CNS contributions with peripheral and central factors, cortical and limbic areas, all playing a role in the pain and dysfunction they produce (Phillips and Clauw 2011; Coombes et al. 2009). Collectively these findings of changes in meso-limbic and pre-frontal structures provide compelling evidence that CNS changes contribute to the pathophysiology of at least some chronic MSD and conversely, that the structural-pathology paradigm of local tissue compromise being solely at the root of chronic MSD is at the very least incomplete and insufficient. A model integrating central neurophysiological modifications must be integrated into the present paradigm to broaden its scope and be further investigated.

2.4.4.8 Impact of CNS plasticity in the rehabilitation of chronic MSD

Restoration of motor activity and function are integral to current practice in rehabilitation (Hodges 2011; Nijs, Meeus, et al. 2014). The notion of addressing neuroplastic changes is well established in neurological rehabilitation (Snodgrass et al. 2014). Outcomes of interventions presently utilized in conventional rehabilitative care may result from peripheral and central mechanisms and it remains a challenge to distinguish their relative contribution. For example, resistance training in subjects with non-specific shoulder and neck pain increased local and distal pressure pain thresholds suggestive a central mechanism underlying these effects (Andersen et al. 2012). However studies also demonstrate that specific types of interventions may be better suited at inducing neuroplastic changes (Remple et al. 2001; Lundbye Jensen et al. 2005; Adkins et al. 2006; Boudreau, Farina, et al. 2010). Rehabilitative interventions specifically addressing neurophysiological changes, in addition to peripheral end organ dysfunction, may prove to be an important avenue of investigation in the hope to improve treatment success in the rehabilitation of musculoskeletal injuries (Boudreau, Farina, et al. 2010; Snodgrass et al. 2014). Studies in animal models have demonstrated that the neuroplastic changes in S1 and M1 occur concurrently with tissue damage, inflammation, and motor impairment and therefore would need to be addressed early on in the rehabilitation process (Barr et al. 2004; Coq et al. 2009). Addressing neurophysiological changes would involve interventions in an attempt to minimize and/or normalize structure, function and organization to that found in uninjured healthy controls by explicitly targeting and priming neuronal structures and processes including those in the sensorimotor, meso-limbic and pre-frontal areas. These

could include incorporating approaches to present conventional care such as education of neuronal and pain processes (Moseley 2004a; Nijs, Meeus, et al. 2014), cognitive based interventions such as Cognitive Behavioural Therapy (Bernardy et al. 2010; Lamb et al. 2010) and Mindfulness Based Stress Reduction (Grossman et al. 2004; van Hooff et al. 2012) which have been associated with changes in pre-frontal and meso-limbic structures (Zeidan et al. 2011; Jensen et al. 2012; Zeidan et al. 2012; Seminowicz et al. 2013; Shpaner et al. 2014; Ehde et al. 2014), mental imagery (Bowering et al. 2013), peripheral sensory and electrical stimulation (Flor 2002; Wand, O'Connell, et al. 2011), visual distortion and the use of non-invasive brain stimulation such as Transcranial Direct Current Stimulation and TMS for example to alter neuronal processes (Chipchase et al. 2011a; Schabrun and Chipchase 2012; Schabrun, Jones, et al. 2014). Effect sizes of rehabilitation approaches are consistently small regardless of intervention in many MSD and therefore multiple and progressive interventions may be warranted (Nijs, Meeus, et al. 2014).

2.4.4.9 Research

Research investigating changes in S1 and M1 across a large range of MSD, including changes in responsiveness, inhibitory processes, and somatotopic organization would help elucidate the mechanisms and their presence in MSD. Subsequent studies evaluating novel treatment approaches such as motor skill training, mental imagery, action observation, mirror therapy, peripheral sensory stimulation and cortical stimulation as adjuncts to traditional rehabilitative care for MSD to impact neuronal responsiveness and reorganization are needed. Research in changes in neuronal processes and organization of techniques presently utilized in rehabilitation, such as manual therapies, may help elucidate the physiological mechanisms of action and lead to more effective application and outcomes. Further research of the plastic changes occurring in meso-limbic and prefrontal areas and the complex interrelationship between structures and connections on these areas, cortical sensorimotor areas, descending modulatory processes, and psychological traits and behaviours associated with CMSD will not only increase our comprehension, but help guide the development of more effective pharmacological, behavioural and rehabilitative interventions.

2.4.5 Summary

In our opinion the present structural-pathology paradigm guiding treatment for MSD is at the very least incomplete as it fails to integrate recent findings of important neurophysiological changes associated with chronic MSD and that appear to be involved in the pathophysiology of these conditions either in isolation or co-existing with peripheral mechanisms. Musculoskeletal injury, in addition to the local damage to anatomical structures and inflammation, results in changes in sensory stimuli, transmission and processing including neuroplastic changes along the neuroaxis of pain within the spinal cord and brain stem, in the properties and functions of neurons within S1 and M1. There are associated changes also found in the meso-limbic pre-frontal areas in subjects with chronic MSD some which may pre-dispose the injury. The neuroplastic changes may occur rapidly in response to injury causing adaptive changes that may help in the protection and healing response. However, these changes may persist and no longer perform their intended function contributing to the development of chronic disability and dysfunctional pain with enduring neuroplastic changes along the neuroaxis of pain resulting in peripheral and central sensitization, in the sensorimotor areas affecting perception and motor behavior, and in the meso-limbic prefrontal areas influencing emotional, attentional and cognitive processes (Wand and O'Connell 2008; Costigan et al. 2009; Coombes et al. 2009). In some musculoskeletal conditions the responsiveness and somatotopic organization in S1 and M1, including changes in excitability, the blurring of the representation of anatomical structures and a shift in the representation of muscles within somatotopic representations are present. These changes in properties, function and organization within the CNS often correlate with the severity and duration of pain, functional changes including aspects of motor control, psychological traits associated with the chronic pain states, and can be predictive of prognosis. These findings have important implications in the rehabilitation of MSD. Many questions remain to be answered including the specific nature of the contribution of these neuroplastic changes to the clinical condition specifically in relation to causation and how widespread these changes are with different MSD. In this respect, we are in agreement with the hypothesis that failure of rehabilitative and medical interventions to treat these chronic musculoskeletal conditions effectively may stem from failure to address these neuroplastic cortical changes and are of the opinion that the elaboration and evaluation of rehabilitative interventions, some

presently utilised in neurological rehabilitation, in the prevention and treatment of chronic MSD are desirable (Wand and O'Connell 2008; Snodgrass et al. 2014).

2.4.6 Abbreviations

MSD, Musculoskeletal disorders; CNS, Central nervous system; SEP, Somatosensory evoked potentials; CLBP, Chronic low back pain; OA, Osteoarthritis; PFPS, Patella-femoral pain syndrome; LA, Lateral epicondylitis; CTS, Carpal tunnel syndrome; PAG, Periaqueductal gray; RVM, Rostral ventromedial; S1, Primary somatosensory cortex; M1, Primary motor cortex; ACL, Anterior cruciate ligament; fMRI, Functional magnetic resonance imaging; SEP, Somatosensory evoked potentials; PLP, Phantom limb pain; CRPS, Complex regional pain syndrome; TMS, Transcranial magnetic stimulation; MEP, Motor evoked potential; NAc, Nucleus accumbens; mPFC, Medial prefrontal cortex; dlPFC, Dorsolateral prefrontal cortex

2.4.7 Competing Interests

The authors declare that they have no competing interests.

2.4.8 Author's Contributions

RP was the principal author for the manuscript. JH and DB participated in the elaboration, content and drafting of the manuscript. All authors read and approved the final manuscript.

2.4.9 References

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Chapter 3: Objectives and Hypothesis

There is an emergence of studies that have investigated changes in central sensorimotor processes associated with various MSD. However, the literature demonstrates variability of results in measures of central sensorimotor processes, both for changes in corticospinal excitability and in a proxy measure of the body schema, the LRJT. The relationship between measures of corticospinal excitability and the LRJT with pain and symptom duration are unclear. The relationship between cortical sensorimotor changes and clinical measures of function are often neglected and therefore the relevance of these cortical sensorimotor changes is also not well understood. Finally, although psychosocial factors are known risk factors for chronicity and disability, their relationship with sensorimotor processes has not been well characterized and therefore poorly explained.

3.1 General Objectives and Hypothesis

The main objective of the thesis was to investigate for the presence of altered cortical sensorimotor processes in participants with MSD and to determine if these changes are related to pain, motor function, disability, and psychosocial factors related to pain. Based on the literature, we hypothesized that cortical sensorimotor processes would be altered in participants with chronic MSD of the wrist and hand. We also hypothesized that changes in cortical sensorimotor processes in persons with MSD of the wrist/hand would be related to motor function, self-reported disability, pain and pain related psychosocial factors.

3.2 Specific Objectives of the Thesis

Specific objectives of the thesis presented in the subsequent chapters are:

1. To determine if participants with heterogeneous MSD of the wrist/hand, sufficient to interfere with their activities of daily living, demonstrated changes in corticospinal excitability compared to healthy control participants.
2. To determine the relationship between changes in corticospinal excitability in participants with and without MSD of the wrist/hand with clinical measures of pain, motor function (strength and dexterity), self-reported disability, and pain related psychosocial factors.

3. To determine if participants with heterogeneous MSD of the wrist/hand demonstrated changes in the body schema as measured by the LRJT compared to healthy control participants.
4. To determine the relationship between changes in the LRJT performance in participants with MSD of the wrist/hand pain with clinical measures of pain, sensory and motor function, self-reported disability, and psychosocial factors related to pain.

Chapter 4: Methodology and Methodological Considerations

The research articles presented are the result of two separate studies. The first study involved an assessment of corticospinal excitability, LRJT performance, pain, motor performance and self-reported disability in persons with and without MSD of the wrist/hand. The second study involved assessment of the LRJT, cognitive, sensory, motor, self-reported disability and pain related psychosocial factors related to pain in participants with MSD of the wrist/hand.

4.1 Corticospinal Excitability, Left Right Judgment Task, Pain, Disability and Motor Performance

An observational cross-sectional study was performed at the Centre intégré universitaire de santé et de services sociaux centre-sud-de-l'île-de-Montréal, l'Institut de réadaptation Gingras Lindsay de Montréal. Ethical approval was obtained from the institutional review board. Participants were recruited from web-based advertising, social media, word of mouth and publicity distributed to private physiotherapy, occupational therapy and osteopathic clinics in the greater Montreal area. Inclusion criteria for the experimental group included experiencing pain in the wrist/hand for greater than 3 months and the participants indicated interfered with activities of daily living. Participants were screened for contraindications to TMS (Rossi et al. 2009; Rossi et al. 2011). They had to be capable of communicating in English or French, not suffering from any neurological disorder or condition that interfered with their ability to understand the nature of the study and follow instructions, other MSD or conditions affecting the cervical spine or upper extremity over the previous three years, and not experiencing any radicular symptoms in the upper extremity. All participants provided verbal and written informed consent. Policies and procedures conformed to the Declaration of Helsinki.

4.1.1 Measures

The measures administered in the study of corticospinal excitability, LRJT, pain, disability and motor performance are found in Table 4.1 and are described in the following sections.

4.1.1.1 Demographic and baseline information

The patient intake form included age, gender, diagnosis for the attending physician, and symptom onset. Handedness was verified utilizing the Edinburgh Handedness Inventory (Oldfield 1971).

Table 1: Measures performed in study of corticospinal excitability in persons with MSD of the wrist/hand

Measures	Specific Measures	
Descriptive information		Age, gender, diagnosis, symptom duration, localization of pain
Self reported Disability	**AUSCAN™**	Includes three sections: Part 1: is comprised of 5 items related to pain at rest and performing movements involving the hand. Part 2: 1 item in relation to stiffness Part 3: 9 items related to ability to perform different hand functions.
	Disability of Arm, Shoulder and Hand questionnaire (DASH)	Has 30 items with 21 questions specifically related to the difficulty in performing activities, 4 questions related to sensory symptoms, 1 question related to psychological aspects, and 4 questions related to social participation.
Pain and pain related aspects	**Visual Analog Scale**	Pain at beginning of evaluation on a 0-10 cm line anchored with no pain (0) and worst imaginable pain (10)
	West Haven Yale Multidimensional Pain Inventory (WHYMPI)	Pain and pain related aspects from a cognitive behavioural/ biopsychosocial construct. Includes 12 subscales including Pain severity, Pain Interference, Life Control, Affective Distress, Support, Negative responses, Solicitous Responses, Attentional Responses, Participation in household, work and leisure activities and General activities (all)
Strength	**Isometric ABD**	Dynamometric evaluation of strength for the APB (abduction of the thumb) and FDI (abduction of the second digit)
	Key Pinch Grip	Dynamometric evaluation of the strength between the thumb and the medial aspect of the proximal interphalangeal joint of the second digit.
Motor Performance	**Purdue pegboard test**	Manual dexterity and fine motor control. Involves five scores: right hand, left hand, both hands, a total score of the three previous measures, and a score for the building of small assemblies.
Electrophysiological measures	**Mmax**	Maximum compound action potential from peripheral stimulation of the medium and ulnar nerves proximal to the wrist.
	Fwave	A test of spinal motoneuronal excitability resulting from the antidromic activation of motoneurons from supramaximal (1.3 x Mmax) stimulation of the median and ulnar nerves proximal to the wrist. Fwaves are a measure of spinal motoneuronal excitability.
	Resting motor Threshold (rMT)	Intensity of stimulation expressed as a percentage of maximum TMS output requiring the lowest intensity of stimulation (i.e. area of greatest excitability) for the muscles investigated in the motor cortex (i.e. Abductor Pollicis Brevis and First Dorsal Interossei)
	Input-Output curves	Measure of corticospinal excitability that involves an increase in recruitment of corticospinal neurons with higher stimulation intensities as a function of the resting motor threshold (0.95 – 1.5 x rMT).
	Cortical Silent Period (CSP)	Period of electromyographic absence after TMS at 1.2xrMT induced MEP in a contracting muscle. The CSP is a measure of inhibition mediated by spinal and cortical mechanisms.
Sensorimotor Integration/Body schema	**Left Right Judgment Task (LRJT)**	50 images of the hands where presented. Participants were required to answer as quickly and as accurately as possible if the image was of the right or left side. Assesses the ability to recognise the side of the anatomical image (accuracy) displayed and the time taken to answer (reaction time)

4.1.1.2 Pain related disability

Pain was assessed with a visual analog scale (0-10 cm) with the extremities anchored at no pain and worst imaginable pain (Jensen et al. 1989). Pain related disability was also assessed with Part 1 of the AUSCAN™ questionnaire. Part 1 is comprised of 5 items specifically related to pain at rest and during four activities of the previous 48 hours (no pain – extreme pain) (Bellamy, Campbell, Haraoui, Gerecz-Simon, et al. 2002; Bellamy, Campbell, Haraoui, Buchbinder, et al. 2002; Bellamy et al. 2010). Higher scores indicate more pain related disability.

4.1.1.3 Pain related psychosocial factors

The West Haven Yale Multidimensional Pain Inventory (WHYMPI) is valid and reliable questionnaire commonly utilized in research (Kerns et al. 1985; Riley III et al. 1999). It is derived from a cognitive behavioural perspective stemming from a biopsychosocial model. The WHYMPI questionnaire consists of 51 items that are grouped into three sections (Pain and pain related aspects, Spousal Responses, and Activities and Participations) and twelve subscales. The WHYMPI meets standards of reliability and convergent validity (Bernstein et al. 1995) and the factor analysis demonstrates a good fit (Riley III et al. 1999).

4.1.1.4 Motor performance

4.1.*1.4.1* Isometric strength

Figure 1.1: Isometric strength testing of the Abductor Pollicis Brevis

Maximum voluntary isometric contractions for the First Dorsal Interossei (FDI) and the Abductor Pollicis Brevis (APB) muscles were performed. These measurements of force were performed utilizing a custom-built dynamometer previously utilized in research (Bourbonnais et al. 1991; Bourbonnais et al. 1993) (see Figure 4.1). Participants performed three contractions in abduction at the distal interphalangeal joint of the index for the FDI and interphalangeal joint of the thumb for the APB. Three contractions were performed with rest periods of 20-30 seconds. A visual display indicating direction of force output and verbal encouragement was provided. Maximum key pinch grip was also assessed utilizing a custom-built strain gauge.

4.1.*1.4.2* Purdue pegboard test

Fine and gross motor function was assessed with the Purdue pegboard test (Lafayette Instruments, Lafayette IN, USA, Model #32020A) a standard test to assess fine motor control and manual dexterity commonly utilized in research and clinical settings that involves placing pins in slots with their right hand, left hand and both hands in 30 second time epochs (Tiffin et al. 1948). There is also a total score consisting of the aggregate sum of these three measures. Finally, participants perform the building of small assemblies involving pins, washers and collars in a one-minute epoch. Studies have been performed to assess reliability and validity (Tiffin and Asher 1948; Buddenberg et al. 2000).

4.1.1.5 Disability

Disability of Arm, Shoulder, and Hand questionnaire (DASH) assesses both symptoms and functional status in patients with upper extremity MSD. It is a self-rated assessment with documented construct validity and reliability (Hudak et al. 1996; Gummesson et al. 2003). It consists of 30 items, with 5 items related to sensory symptoms (pain, tingling, weakness and stiffness), 21 items related to the difficulty performing specific tasks (daily activities, household chores, yardwork, shopping and errands, recreational activities, eating, self-care and sexual activities), and 4 items related to social activities (including work, family care and socializing with friends and family), and one question regarding psychological function (self-image). The DASH therefore provides information of symptoms and physical function of the hand, the impact of the upper extremity disability on health, and to a lesser extent measures related to the health status. Items are scored on a 5-point Likert scale. Maximum scores are 100 with higher scores indicating greater disability. The DASH is psychometric questionnaire most utilized in patients with wrist and hand injuries (Hoang-Kim et al. 2011).

The AUSCAN™ is a self-report questionnaire developed to measure hand function and pain related disability. It is comprised of 15 items divided into three sections (Bellamy, Campbell, Haraoui, Gerecz-Simon, et al. 2002; Bellamy, Campbell, Haraoui, Buchbinder, et al. 2002; Bellamy et al. 2010). Part 1 is comprised of 5 items specifically related to pain at rest and during 4 activities in the previous 48 hours (no pain – extreme pain), Part 2 has one item specifically related to morning stiffness, and Part 3 has 9 items related to the level of difficulty in performing 9 activities of daily living (no difficulty to extreme difficulty). The visual analog scale version

was utilized so responses for each of the items ranged from 0-100, with section maximum scores of 500, 100, and 900 respectively. Higher scores indicate greater pain and disability. The psychometric properties have been studied and demonstrate acceptable reliability, construct validity, and responsiveness (Bellamy, Campbell, Haraoui, Buchbinder, et al. 2002; Bellamy, Campbell, Haraoui, Gerecz-Simon, et al. 2002; Allen et al. 2006; Allen et al. 2007; Bellamy et al. 2010).

4.1.1.6 Assessment of corticospinal excitability

TMS allows for probing corticospinal properties and organization by different measures.

4.1.1.6.1 The hotspot and Resting Motor Threshold (rMT)

The rMT is the minimal TMS output intensity required to depolarize the corticospinal cells at the hotspot (the location requiring the lowest TMS intensity to evoke a MEP), expressed as a percentage of the Maximum Stimulator Output (MSO). The rMT is usually defined as the lowest stimulator output intensity that produces a MEP with peak-to-peak amplitude of at least 50uv in at least 5 of 10 consecutive trails at rest (Rossi et al. 2009). The MT is a global measure of membrane excitability (Clark et al. 2008). The MT is believed to reflect the intrinsic neuronal excitability of the most excitable central core of neurons (Hallett 2007; Groppa et al. 2012). The MT is influenced by pharmacological interventions that affect Na-Ca channels that increase the MT threshold (Ziemann 2004). The MT is a function of many variables including the technical setup, patient positioning, age and target muscle (Hallett 2007). The motor threshold in the FDI has found to be reliable across sessions (Carroll et al. 2001).

*4.1.*1.6.*2* Input-Output curves

The I-O curves reflect the growth of MEP peak-to-peak amplitudes with increasing TMS intensities. I-O curves are constructed by applying TMS stimulations at increasing intensities as of function of the MT or alternatively, as was performed in the present experiment, at fixed intervals of the maximum stimulator output. To minimize the possibility of serial order effects, randomized TMS stimulation, a minimum of 10 per stimulator intensity at inter-pulse intervals varying between 4 and 10 seconds, were performed at multiples of the rMT ranging from 95% rMT to 150% of the rMT. I-O curves were constructed, and the slope determined for analysis. The I-O curve is believed to be a very sensitive measure of corticospinal excitability and allow for the manifestation of changes that occur in excitability as larger motorneurons are recruited

(Ridding et al. 1997). The increase in MEP size with increasing stimulus intensities is believed to be a function of recruitment of corticospinal neurons surrounding the central core of excitability in M1 of the muscle under study. These neurons, surrounding the core of most excitable neurons, are believed to be intrinsically less excitable or recruited as the result of an increase in the area of influence of the TMS within the cortex at rising intensities (Hallett 2007; Groppa et al. 2012). The slope of the I-O curve provides information as to the excitability of the motor cortical neurons that influence EMG activity in the recorded muscle (Devanne et al. 1997). Increasing MEP amplitudes with increasing stimulation intensities allow for the manifestation of changes that occur in excitability as progressively larger motor neurones are recruited and providing information about the spatial distribution of excitable elements under the TMS coil (Ridding and Rothwell 1997). Reliability of I-O curves have been documented (Carroll et al. 2001; Malcolm et al. 2006; Cacchio et al. 2009; Pearce et al. 2013).

4.1.1.6.3 Cortical Silent Period (CSP)

The CSP is an interruption of the EMG activity in the contracting muscle subsequent to a MEP induced when a single TMS pulse is applied to the hotspot of the contralateral M1. The duration of the CSP is defined as the first defection (positive or negative) of the MEP until the initial deflection (positive or negative) of the EMG signal associated with the resumption of voluntary EMG activity. This method of analysis has previously been demonstrated to have high inter-rater reliability (Damron et al. 2008). The CSP was determined by applying TMS stimulation at an intensity of stimulation of 120% rMT at an inter-pulse interval of greater than 5 seconds while the participant performed an isometric contraction at 50% of MVC (see Figure 4.2). The signal was recorded for 400ms, 100ms prior to the TMS stimulation and 300ms subsequent. CSP is believed to be reflective of inhibitory mechanisms impacting motor cortical activity (Clark et al. 2008). This inhibition is believed to be mediated by spinal

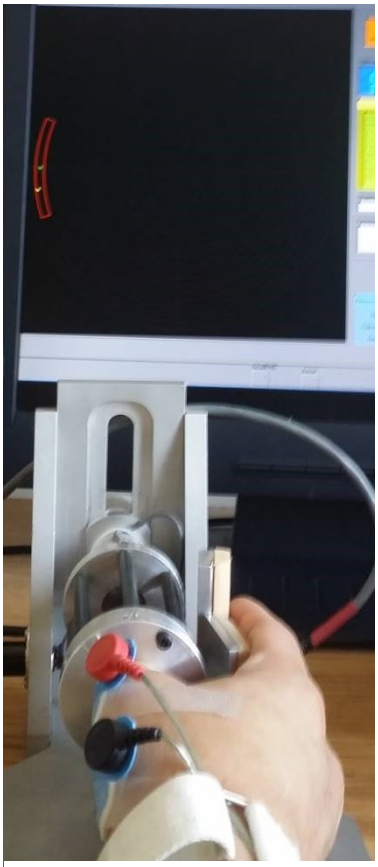

Figure 4.2: Cortical silent period for the abductor pollicis brevis

refractoriness (first 50ms) and by cortical inhibitory mechanisms (Groppa et al. 2012). These inhibitory mechanisms are suppressed by pharmacological interventions that affect the gamma-aminobutyric acid B receptor function (Groppa et al. 2012). Intra-rater reliability for the assessment of the CSP has found to be good (Intraclass coefficients = 0.98) (Fritz et al. 1997; Kimberley et al. 2009)

4.1.1.6.4 Spinal motoneuronal excitability

Single pulse TMS was utilized to assess the entire corticospinal pathway and therefore assess both corticospinal and spinal motoneuronal excitability. Therefore, it is necessary to assess changes in spinal motoneuronal excitability before attributing any changes in MEP amplitudes as the result of TMS to cortical mechanisms alone. Spinal motoneuron excitability in humans can be assessed indirectly by three methods: Cervicomedullary stimulation, H-reflexes and Fwaves.

Cervicomedullary stimulation of the corticospinal tract with TMS is the most direct measurement of spinal motoneuronal excitability to synaptic input in humans. Contrary to the H-reflex, this tract is not influenced by pre-synaptic inhibition. The corticospinal tract depolarized by the stimulation is largely monosynaptic in the upper extremity (Lemon 2008). However, this form of stimulation is painful when performed in relaxed subjects and may result in guarding and involuntary muscle contraction that may negatively impact results. Furthermore, in some muscles it is difficult to elicit evoked potentials of sufficient intensity. For these reasons, studies generally perform assessment of spinal motoneuronal excitability utilizing cervicomedullary stimulation in a small segment of the sample that may also influence interpretation. There were no persons in our laboratory who felt qualified in applying this procedure.

The elicitation of Fwaves involves supramaximal stimulation of a motor nerve. The Fwave response is the result of antidromic (backfiring) stimulation. Fwaves involve the recruitment of a small number of spinal motoneurons of varied sizes throughout the motoneuron pool. However, Fwaves predominantly involve larger spinal motoneurons and therefore differ from the recruitment of spinal motoneurons resulting from descending voluntary drive and reflex responses. Although believed to be a direct measure of spinal motoneuronal excitability (Fischer

1992), the sensitivity of Fwaves to changes in spinal motoneuronal excitability has been questioned (Espiritu et al. 2003). Although H-reflexes and Fwaves are sensitive to changes in spinal motoneuronal excitability, Fwaves appear to be a magnitude less sensitive than H-reflexes (Hultborn et al. 1995). However, Fwaves do appear to reflect motoneuron excitability in a *"general way but do not allow for accurate measures of short term changes in excitability*" (Lin et al. 2004) such as when a change in excitability in response to an experimental manipulation is being investigated (Burke 2014). Several parameters of Fwaves are measured including peak to peak amplitudes, Fwave area, Fwave latency, chrondrodispersion (differences between the shortest and longest latency responses), and persistence (number of Fwave responses in a given number of stimuli presented). Of the different Fwave parameters, persistence appears to be the most conservative Fwave measure of spinal motoneuronal excitability (Lin and Floeter 2004; Rivner 2008). Fwave persistence refers to the number of measurable Fwave responses in a series of stimuli. Fwave persistence provides information as to the antidromic excitability within the motor neuron pool (Fischer 1992). H-reflexes were not utilized as they are difficult to produce in the intrinsic hand muscles at rest.

Maximum compound motor action potentials and Fwaves for the APB and FDI were elicited by stimulating the median and ulnar nerve respectively, proximal to the wrist, with a 1ms rectangular pulse with a monopolar electrode. The stimulus intensities were increased until the maximum compound motor response was determined (Mmax) at an inter-pulse interval of 5 seconds. Fwaves were obtained from 32 supra-maximal consecutive stimuli with a square wave pulse of 0.2ms at a frequency of 0.5Hz and amplified using a band-pass filter of 1-1000Hz at a stimulation intensity of 1.3xMmax (Fischer 1992; Panayiotopoulos et al. 1996).

4.1.1.6.5 Data acquisition and processing

MEPs were recorded for 200ms including 100ms prior to stimulation with TMS. Signals with EMG bursts in the 50ms prior to stimulation were discarded. For the CSP, data acquisition was for a 400ms window including 100ms prior to stimulation with the TMS. EMG signals were amplified (x1000), band pass filtered (1Hz-1KHz) using a second order Butterworth filter, sampled (10 KHz) with a laboratory A/D conversion system (PCI-MIO-16E-4, National Instruments, Texas, USA), displayed, and recorded. Electrophysiological analysis of EMG responses was performed off-line (see Figure 4.3).

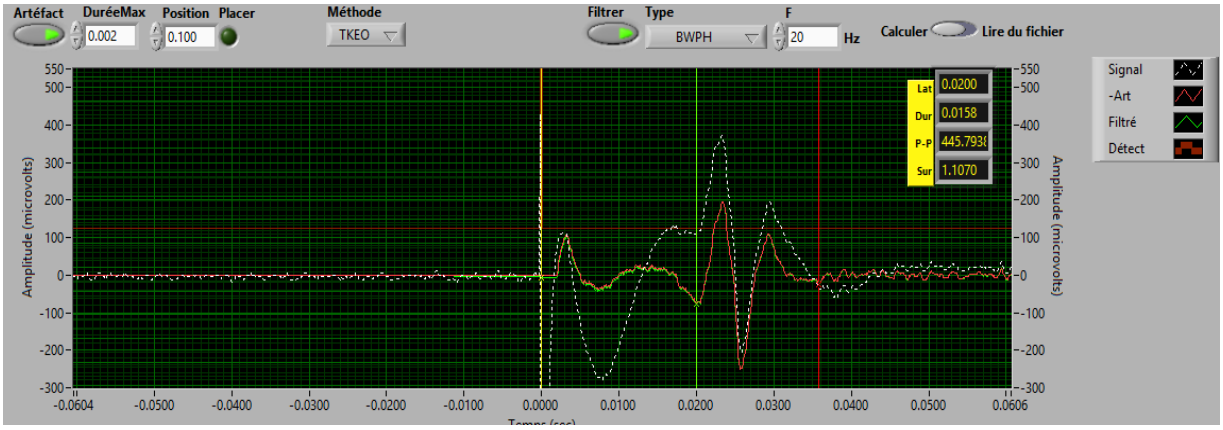

Figure 4.3: Example of motor evoked potential in abductor pollicis brevis

The analysis of MEP, Mmax and Fwave was performed offline utilizing custom-built software (see Figure 4.4 for representational traces). The TMS stimulation artefact was removed as it often interfered with the MEP. The artefact in the EMG signal was detected (Solnik et al. 2010) and the EMG signal following the stimulus artefact was filtered using a 50 Hz low-pass filter. The low pass signal and the stimulus artefact were subtracted from the original EMG signal to remove low frequency effects of the artefact. In a second pass, the EMG response was filtered using a fourth order high pass Butterworth filter at 20Hz. There was no removal of the stimulus artefact for the Mmax and Fwave signals. Mmax was processed with a 20 Hz whereas the Fwave signals with a 100 Hz fourth order Butterworth high pass filter (Eisen et al. 1999; Espiritu et al. 2003).

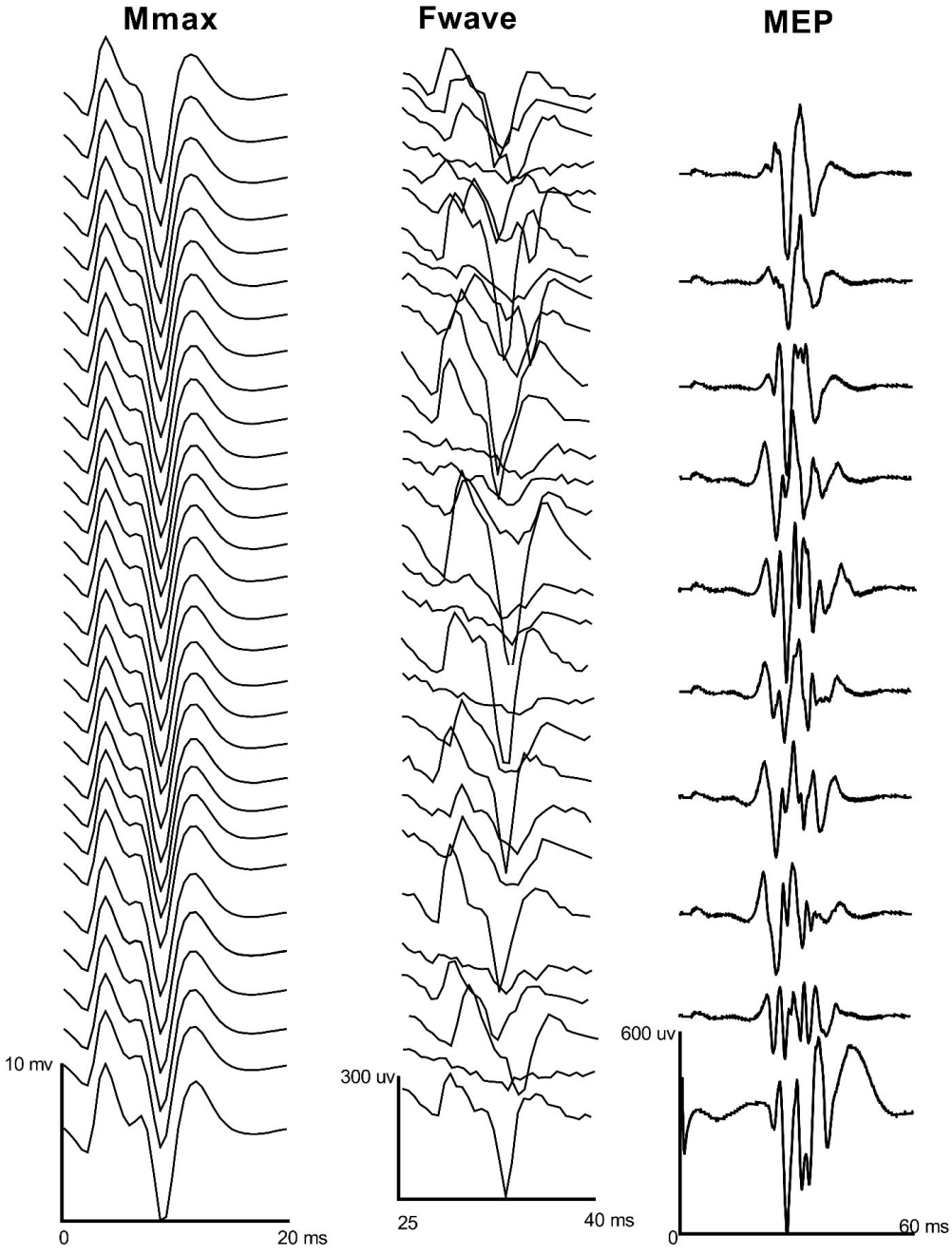

Figure 4.4: Representational traces of Mmax, Fwave and motor evoked potentials in one participant in the abductor pollicis brevis

4.1.1.7 Body schema

The LRJT involved determining if images of hands were of the left or right side. The task involved a block of 50 images of hands presented on a plain (vanilla) background with a maximum duration per image of 5 seconds on an 8-inch computer tablet. Participants were instructed to answer, "as quickly and accurately as possible". Participants were given the chance to practice on 10 images before proceeding with the actual task. The order of the block of images for the hands was randomized across participants. The LRJT was performed utilizing the Recognise^{TM} (Neuro-orthopedic Institute, Adelaide, South Australia) software (Wallwork et al. 2013; Linder et al. 2016; Breckenridge et al. 2017). The participants provided a verbal response to indicate laterality (Fiorio et al. 2005; Cocksworth et al. 2013). Results were displayed for accuracy (percentage of correct responses) and RT (seconds). The validity and reliability of the LRJT for the shoulder (Breckenridge et al. 2017) and reliability for the hand has been demonstrated (Zimney et al. 2018).

4.2 Assessment of Left Right Judgment Task, Cognitive, Sensory, Motor, Disability and Psychosocial Factors in Participants with Wrist/Hand Pain

The second experiment was conducted at the hand clinic of the Centre intégré universitaire de santé et de services sociaux centre hospitalier de l'Université de Montréal Notre Dame hand clinic. Ethical approval was obtained from the institutional review board (CÉR-CHUM 16.372). Right-handed individuals with MSD of the right wrist/hand were recruited when attending the hand clinic for an appointment with a plastic surgeon. Persons were initially screened at the reception. While in the waiting area participants were further screened for eligibility and explained the nature of the study. To be eligible participants were required to be 18 years and older and suffering with MSD of the wrist/hand that impacted their activities of daily living in their right dominate hand. Participants had to be capable of following instructions and completing questionnaires in English or French, had no known neurological condition that impacted cognitive function, and were not suffering from lower extremity pain and injuries. If they agreed to participate, verbal and written informed consent was obtained prior to the commencement of the evaluation.

4.2.1 Measures

Several measures were identical to those performed in the previous study. These included the LRJT (body schema), DASH questionnaire (self-rated disability), the West Haven Yale Multidimensional Pain Inventory (pain severity and psychosocial aspects related to pain), and Purdue pegboard test (motor performance). In addition, several other measures were performed. The measures performed in this evaluation are found in Table 4.2.

4.2.1.1 Sensation

4.2.1.1.1 Tactile acuity

Tactile acuity was assessed with a two-point discrimination task utilizing a hand-held caliper (Fowler, Model # 54-101-150-2, Newton, MA, USA). The method proposed by Tong et al (2013) involving vertical and horizontal discrimination was utilized (Tong et al. 2013). The participants were blindfolded and asked to determine if they felt one or two points of contact of the caliper performed over the thenar and hypothenar eminences. When two points of contact were indicated by participants they were required to indicate if the points were oriented horizontally or vertically (Tong et al. 2013). For standardization, the caliper was held at the end and only the weight of the caliper head was utilized to apply pressure. Assessment was performed by beginning at 10 mm and increasing or decreasing separation distance. Two vertical and horizontal trials were performed at each site, randomly interspersed with contact with only one point, applied for each distance of separation. The distance at which the participant consistently had 75% correct responses for the thenar and hypothenar eminences were recorded. Assessment of intra-rater reliability (Dellon et al. 1987; Catley et al. 2013) is good but interrater reliability of tactile for the hand is variable (Catley et al. 2013). Validity of the two-point discrimination task has been performed for the hand in healthy subjects (Tong et al. 2013).

4.2.1.1.2 Pressure pain threshold

Pressure pain threshold was assessed with a hand-held algometer (Wagner Instruments, Greenwich, CT, USA, model# Wagner FPX25). Pressure was applied on the palmar surface of the first carpal metacarpal joint and medial to the pisiform in both hands. A conscious attempt was made to apply a gradual and constant increase in pressure. Three measurements were taken at each location in both hands. The average of the three measures was recorded (Nussbaum et al. 1998; Chiarotto et al. 2013). The order of assessment for the site and hand was randomized

Table 4.2: Measures performed in study of the Left Right Judgment Task, sensory, motor and cognitive assessment in participants with wrist/hand pain

Measures	Specific Measures	
Descriptive information		Age, gender, diagnosis, symptom duration, localization of pain, pain medication
Sensorimotor integration/body schema	**Left Right Judgment Task (LRJT)**	40 images of the Hands and Feet where participants were required to answer as quickly and as accurately as possible if the image was of the right or left side. Assesses the ability to recognise the side of the anatomical image (accuracy) displayed and the time taken to answer (reaction time)
Self-Reported Disability	**Disability of Arm, Shoulder and Hand questionnaire (DASH)**	Has 30 items with 21 questions specifically related to the difficulty in performing activities, 4 questions related to sensory symptoms, 1 question related to psychological aspect, and 4 questions related to social participation.
Pain and pain related aspects	**Visual Analog Scale**	Pain at beginning of evaluation on a 0-10 cm line anchored on no pain (0) and worst imaginable pain (10)
	West Haven Yale Multidimensional Pain Inventory (WHYMPI)	Pain and related to pain related aspects from a cognitive behavioral/ biopsychosocial construct. Includes 12 subscales including Pain severity, Pain Interference, Life Control, Affective Distress, Support, Negative responses, Solicitous Responses, Attentional Responses, Participation in household, work and leisure activities and General activities (all)
Strength	**Grip Strength**	Dynamometric evaluation of strength was performed utilizing the JAMAR hand held dynamometer utilizing the standardized protocol three times in each hand. Maximum values were recorded.
Motor Performance	**Purdue pegboard test**	Evaluates manual dexterity and fine motor control. Involves five scores: right hand, left hand, both hands, a total score of the three previous measures, and a score for the building of small assemblies.
Sensory	**Tactile Acuity**	Two Point Discrimination (TPD) was performed with a hand-held caliper with distances between points between 2 and 14mm on the thenar and hypothenar areas of the hand bilaterally. Participants were required to indicate if they felt one or two points of contact and if the points were oriented vertically or horizontally. The distance where the participant consistently indicated correctly ¾ responses was recorded.
	Pressure Pain Threshold (PPT)	Pressure pain thresholds were assessed on the palmar surface over the first carpal-metacarpal joint and lateral to the pisiform with a hand-held algometer. Three readings were taken at each site in each hand and the average value was recorded.
	Joint Position Sense (JPS)	JPS was assessed by asking the person to indicate if the polystyrene balls placed in each hand were of the same or different sizes. The participant was required to indicate if the ball (seven different sizes) in their right (affected) hand was smaller, the same size or larger than the reference ball in the left hand (3 different sizes). The number of errors of the 21 comparisons performed was recorded.
Cognitive function	**Stroop Test**	Selective attention was assessed utilizing software downloaded on an 8-inch computer tablet. The task required the participants to indicate the colour in which the words or neutral stimulus was written (blue, red or green and a neutral stimulus (####)) written in different colours for 2 series of 10 words without error. The total time taken to perform the task was recorded.
	Motor Imagery Ability (MIQ-RS)	Motor Imagery Ability was assessed utilizing a valid and reliable questionnaire that required that participants reporting their ability to see themselves performing 7 different actions vividly (visual motor imagery) and feel that they were performing the action (kinesthetic motor imagery). Each action was scored on a 7-point Likert scale. Higher values indicate better motor imagery ability with maximum scores of 49 for each of the Visual and Kinesthetic Imagery ability and a total possible score of 98.

across subjects. Hand held assessment of pressure pain thresholds has positive evidence of intra-rater reliability, agreement, and responsiveness (Alqarni et al. 2018).

4.2.1.2 Proprioception

Joint Position Sense (JPS) was assessed by the same method previously described by Kalisch et al. (2012). Participants were blindfolded with the palm of their hands positioned palm up. Three different diameter polystyrene reference balls (7.0, 8.0, 9.6 cm diameter) were placed in the participant's left hand. A second polystyrene ball, of seven possible different diameters (6.6, 7.0,7.3, 8.0,9,.0, 9.6, 10 cm diameter), were placed in the right (affected) hand. Participants were instructed to squeeze the polystyrene balls and then relax the tension to control for thixotrophy effects influencing JPS (Tsay et al. 2015). They were not permitted to manipulate or turn the balls. The participants were required to verbalize if the polystyrene ball in the right hand was smaller, larger or the same size as the reference ball placed in the left hand within 5 seconds (Kalisch et al. 2012). The number of errors were recorded. This method of assessing joint position sense has not been evaluated for validity however reliability was found to be acceptable (Cronbach $\alpha = 0.8$) (Kalisch et al. 2012)

4.2.1.3 Motor performance

4.2.1.3.1 Grip strength

Dynamometric evaluation of grip strength was performed utilizing a hand-held Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA) following the recommended protocol (Mathiowetz et al. 1984). Participants performed three isometric contractions for each hand and the maximum value was recorded. Subjects were given 20-30 second rest periods between contractions and verbal encouragement was provided. The maximum value was recorded. The reliability and validity of this task has previously been documented (Mathiowetz et al. 1984; Peolsson et al. 2001; Mathiowetz 2002).

4.2.1.4 Cognition/attention

4.2.1.4.1 Stroop test

Selective attention has also been proposed as a reason for the variability in LRJT performance. Therefore, attention was evaluated utilizing a modified Stroop test (Stroop 1935) with the Encephalapp application installed on an 8 inch computer tablet (Bajaj et al. 2015). This task involves determining as quickly and accurately as possible the colour in which the word is

presented and not the reading of the word (red, green, blue). Therefore, if the word blue is presented in the colour red, the participant must depress the red button. The time taken to perform 2 successful trials of 10 words without making an error was recorded. The test is considered a test for selective attention capacity and processing speed ability (Lamers et al. 2010). Imaging studies demonstrate that the Stroop test involves activation in the dorsolateral prefrontal cortex and anterior cingulate cortex, areas involved in working memory, executive function, decision-making and error monitoring (Milham et al. 2003). This measure is included to account for possible differences in attention level mediating changes in LRJT performance (Roelofs et al. 2002; Dick et al. 2007). The validity, reliability and sensitivity of the Stroop test has been documented (see (Homack et al. 2004)).

4.2.1.4.2 Motor imagery ability

The LRJT appears to involve implicit motor imagery and therefore differences in motor imagery ability has been proposed as a reason behind variability in LRJT performance (Stanton et al. 2012). Motor imagery was assessed by the Movement Imagery Questionnaire – Revised Second version (MIQ-RS) (Gregg et al. 2010). The reliability, factorial structure and validity of this instrument are documented (see (McAvinue et al. 2008)).

Chapter 5 Results

The results of the present thesis are presented in three articles in which two are published and one article has been submitted. At the end of the first article there is supplementary material that has been added. The research articles presented are the following:

Article 2:

Pelletier, R., Higgins, J., & Bourbonnais, D. (2017). The relationship of corticospinal excitability with pain, motor performance and disability in subjects with chronic wrist/hand pain. *Journal of Electromyography and Kinesiology*, *34*, 65-71.

Article 3:

Pelletier, R., Higgins, J., & Bourbonnais, D. (2018). Laterality recognition of images, motor performance, and aspects related to pain in participants with and without wrist/hand disorders: An observational cross-sectional study. *Musculoskeletal Science and Practice*, *35*, 18-24.

Article 4:

Pelletier, R., Bourbonnais, D., Higgins, J., Mireault, M., Danino, A.M., Harris, P. (2018). Left Right Judgement Task and sensory, motor, cognitive and psychosocial assessment in participants with musculoskeletal disorders of the wrist/hand.

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5.1 The relationship of corticospinal excitability with pain, motor performance and disability in subjects with chronic wrist/hand pain

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As the principal author of this manuscript, I confirm that I was responsible for subject recruitment, participated in all the experimentation, data processing, statistical analysis and writing of the manuscript. Dr Higgins participated in the experimentation. Dr Higgins and Dr Bourbonnais provided supervision and revision of the manuscript.

Article reference:

Pelletier, R., Higgins, J., & Bourbonnais, D. (2017). The relationship of corticospinal excitability with pain, motor performance and disability in subjects with chronic wrist/hand pain. *Journal of Electromyography and Kinesiology*, *34*, 65-71.

5.1.1 Preface

The literature suggests that persons with MSD often demonstrate changes in measures of corticospinal excitability measured with TMS. However, most of these studies have not investigated spinal motoneuronal excitability therefore, even when differences in corticospinal excitability are present, these often cannot be attributed to properties and organisation of corticospinal neurons in the primary motor cortex. The literature also has not associated the changes along the corticospinal pathway in participants with MSD with measures of function and therefore the relevance of these changes in corticospinal excitability in relation to motor performance is not well understood. When changes in corticospinal excitability are present, they sometimes correlate with pain intensity, symptom duration or neither. An association is sometimes found with measures of self-reported disability.

The general objective of the thesis is to determine if participants with MSD demonstrate changes in altered cortical sensorimotor processes and the relationship of any changes with measures of motor function/performance, pain and disability. The present article addresses the first specific objective of the thesis as to determine if participants with heterogeneous MSD of the wrist/hand demonstrated differences in corticospinal excitability compared to healthy control participants. A heterogeneous sample was utilized as to provide some indication if corticospinal excitability changes were specifically related to the MSD or possibly as the result of behavioural changes as the result of the MSD. The present study also measured spinal motoneuronal excitability to control for excitability changes in the spinal cord when interpreting any changes in corticospinal excitability measured with the use of TMS. The second specific objective was to determine the relationship between corticospinal changes in measures of motor function and self reported disability measures. Therefore, the study also measured gross motor function (dynamometric measure of isometric strength) and motor performance (Purdue pegboard test).

We hypothesized that corticospinal excitability would be affected in the participants with MSD of the wrist/hand. We also hypothesized that these changes in corticospinal excitability would result in different correlations between the corticospinal measures and measures of motor function/performance.

5.1.2 Keywords Musculoskeletal, Input-Output Curve, Transcranial Magnetic Stimulation, Motor Evoked Potentials, Motor function, Disability, Strength

5.1.3 Abstract

There is a growing body of evidence of changes in corticospinal excitability associated with musculoskeletal disorders, however there is a lack of knowledge of how these changes relate to measures of pain, motor performance and disability. An exploratory study was performed utilizing Transcranial Magnetic Stimulation to investigate differences in corticospinal excitability in the Abductor Pollicis Brevis (APB) between 15 pain-free subjects and 15 subjects with chronic wrist/hand pain and to determine how corticospinal excitability was associated with measures of pain (visual analog scale), hand motor performance (isometric and key pinch strength, Purdue pegboard test), pain related disability (AUSCAN^{TM}), and spinal motoneuronal excitability. Input–output curves demonstrated increased corticospinal excitability of the APB in the affected hand of subjects with chronic pain ($p<0.01$). Changes in corticospinal excitability were significantly correlated with pain intensity ($r=0.77$), disability ($r=0.58$), and negatively correlated with spinal motoneuronal excitability ($r= -0.57$). Corticospinal excitability in subjects with heterogeneous injuries of the wrist/hand was associated with disability and pain.

5.1.4 Abbreviations

AH:	Affected Hand
APB:	Abductor Pollicis Brevis
AUSCAN^{TM}:	Australian Canadian Osteoarthritis Hand Index
CMSD:	Chronic Musculoskeletal Disorders
CNS:	Central Nervous System
EMG:	Electromyography
I-O:	Input-Output curve
M1:	Primary Motor Cortex
MEP:	Motor Evoked Potential
Mmax:	Maximum Compound Motor Action Potential
NAH:	Non-Affected Hand
PPG:	Purdue Pegboard Test
RH:	Right Hand
rMT:	Resting Motor Threshold
S1:	Primary Somatosensory Cortex
TMS:	Transcranial Magnetic Stimulation
VAS:	Visual Analog Scale

5.1.5 Introduction

Changes in the properties and organisation of the primary motor (M1) cortex have been found in clinical conditions involving the hand such as complex regional pain syndrome, focal hand dystonia and carpal tunnel syndrome (McKenzie et al. 2003; Krause et al. 2006). There is a growing interest in determining if similar neurophysiological changes may also be associated with Musculoskeletal Disorders (MSD) as these may provide a target for rehabilitative interventions (Snodgrass et al. 2014; Pelletier et al. 2015).

The evaluation of properties and organisation of corticospinal outputs from M1 have been investigated in subjects with MSD. Tsao and colleagues found changes in map representation of corticospinal neurons innervating the multifidus and longissimus muscles in subjects with back pain (Tsao et al. 2008; Tsao, Galea, et al. 2010; Tsao, Danneels, et al. 2011). In subjects with lateral epicondylitis, there were increased Motor Evoked Potential (MEP) amplitudes and an increase in the number of active sites eliciting MEP with Transcranial Magnetic Stimulation (TMS), indicative of increased corticospinal excitability (Schabrun, Hodges, et al. 2014). Changes in motor thresholds elicited by TMS of the quadriceps motor area have also been found in subjects with anterior cruciate ligament injury (Héroux and Tremblay 2006), and increased MEP amplitude values of the quadriceps muscles have been found in subjects with patellofemoral pain (On et al. 2004). Increased neuronal activity was also demonstrated in brain areas, including M1, in persons with MSD such as knee osteoarthritis (Shanahan et al. 2015). Although study results of measures of corticospinal excitability are variable in subjects with MSD, studies tend to suggest that altered M1 properties and organisation are associated with increased corticospinal excitability and this for diverse MSD affecting different joints.

Since M1 is implicated in both motor control and motor learning, one would expect changes in corticospinal properties to impact motor function. Although corticospinal changes have been associated with measures of pain (Schabrun, Hodges, et al. 2014; Bradnam et al. 2015; Shanahan et al. 2015; Elgueta-Cancino et al. 2015) and symptom duration (Ngomo et al. 2015), few studies have investigated changes in corticospinal properties and their relationship with measures of motor performance, disability and pain (Tsao et al. 2008).

The aim of this study was to determine if subjects with pain associated with varied MSD of the wrist and hand demonstrate increased corticospinal excitability compared to pain-free individuals, and if so, how these changes relate to measures of motor function, disability and pain. The importance of the information arising from this exploratory study is to provide a clearer understanding of the relationship between pain, altered motor function, disability and corticospinal changes which may prove important in rehabilitation of MSD.

5.1.6 Methods

5.1.6.1 Subjects

Fifteen pain-free subjects (10F, 14 RH dominant) and fifteen subjects with wrist/hand pain (7F, 14 RH dominant) participated in the experiment. Subjects with wrist/hand pain were recruited from advertising and social media and had to be 18 years of age or older, experiencing unilateral pain in the wrist/hand for greater than 3 months that impacted activities of daily living. Pain-free participants were a convenience sample from the community, free of previous injury to the wrist and hand.

Subjects were excluded if presenting with any contraindications for TMS procedures, neurological conditions known to affect corticospinal or wrist/hand function, symptoms of radiculopathy or neuropathic pain, or previous injury to the hand (Rossi et al. 2009; Rossi et al. 2011). Dominance was assessed using the Edinburgh Handedness Inventory (Oldfield 1971). The study received ethics approval from the institutional review board and experiments were performed at the Institut de réadaptation Gingras-Lindsay of the Centre intégré universitaire de santé et de services sociaux centre-ud-de-île-de-Montréal (CRIR-793-1113). All subjects provided written informed consent and the study was performed in accordance with the Declaration of Helsinki.

5.1.6.2 Measures of pain intensity, hand motor performance and disability

5.1.6.2.1 Pain intensity and pain related disability

Pain was assessed with a Visual Analog Pain Scale (VAS) (Jensen et al. 1989) and pain related disability with part 1 of the Australian Canadian Osteoarthritis Hand Index (AUSCAN^{TM}) questionnaire for pain levels during the performance of daily functional activities in the previous 48 hours (Bellamy, Campbell, Haraoui, Buchbinder, et al. 2002). Date of pain onset was recorded to determine symptom duration.

5.1.6.2.2 Hand motor performance

Pinch strength was assessed using a U-shaped aluminum structure equipped with strain gauges. Isometric maximal abduction force of the thumb was measured utilizing a force transducer (Bourbonnais and Duval 1991; Bourbonnais et al. 1993). Subjects were provided with 30-second rest periods between trials and a visual display indicating direction and force displacement. The maximum force produced over three trials was retained. Motor performance was also assessed with the Purdue Pegboard test (PPG) comprising sub scores for the *Individual* hands and *Both* hands tasks, total (sum of each *Individual* hand and *Both* hands), and *Assemblies* score (Tiffin and Asher 1948; Buddenberg and Davis 2000).

5.1.6.2.3 Pain related disability of the hand

Subjects answered the AUSCAN™ questionnaire (Bellamy, Campbell, Haraoui, Buchbinder, et al. 2002; Bellamy, Campbell, Haraoui, Gerecz-Simon, et al. 2002; Moe et al. 2010) that is comprised of three sub-segments for pain, stiffness, and disability. Higher scores indicate more severe impairment.

5.1.6.3 Measures of cortical excitability and Fwaves

5.1.6.3.1 Subject preparation

Skin preparation was performed following standard procedures. Ag/Ag Cl Electrodes (Ambu® Blue Sensor M-00-S) were applied in a belly tendon montage of the Abductor Pollicis Brevis (APB) muscle. Subjects were seated with their forearms and hands uncrossed for measures at rest.

5.1.6.3.2 Data acquisition

Electromyography (EMG) signals were amplified (x1000), band pass filtered (1Hz-1KHz) using a second order Butterworth filter, sampled (10 KHz) with a laboratory A/D conversion system (PCI-MIO-16E-4, National Instruments, Texas, USA), displayed, and recorded. Electrophysiological analysis of EMG responses was performed off-line.

5.1.6.3.3 Transcranial magnetic stimulation

Single pulse monophasic magnetic stimulations (Magstim®200, UK) were delivered by an angled TMS figure of eight focal coil to the contralateral hemisphere to elicit MEP responses in the APB. The coil orientation was tangential to the scalp resulting in a posterior to anterior direction of current flow (Brasil-Neto et al. 1992; Werhahn et al. 1994).

5.1.6.3.4 Hotspot and Resting Motor Threshold (rMT) of the Abductor Pollicis Brevis (APB)

The location of the hotspot was recorded utilizing neuronavigation equipment (Brainsite™, Rogue Research, Montreal Canada). The site producing 5/10 visibly discernable MEPs of at least 50uV with the lowest stimulator intensity was determined as the "hotspot" and the percentage of maximum stimulator output was recorded as the rMT (Rossini et al. 1994; Groppa et al. 2012). Trials with excessive EMG background activity in the 50ms prior to TMS were discarded (Rossini et al. 1994; Groppa et al. 2012).

5.1.6.3.5 Input-output (I-O) curves and motor evoked potential amplitudes during active contractions

The I-O curves were constructed with blocks of ten stimuli at seven randomized stimulation intensities (95, 100, 110, 120, 130, 140, and 150% of rMT) (Boroojerdi et al. 2001). The median peak to peak amplitude values of the 10 MEP responses at each of the stimulus intensities in each subject were utilized for further analysis (Awiszus 2005). Ten TMS stimuli were also applied in both groups at 1.2 rMT while the subjects performed an isometric contraction of the APB at 50% (±3%) of the maximum voluntary contraction force guided with a visible display of force direction and output.

5.1.6.3.6 Maximum Compound Muscle Action Potential (Mmax) and Fwave evaluation

Mmax and Fwaves were recorded in 11 pain-free and 12 subjects with wrist/hand pain (the intensity of stimulation was too painful for some subjects) from 32 supra-maximal consecutive stimuli to the median nerve, approximately 3 cm proximal to the distal wrist crease with a square wave pulse of 0.2ms (Digitimer DS7A, UK) at a frequency of 0.5Hz and a stimulation intensity of 1.3xMmax (Fischer 1992; Panayiotopoulos and Chroni 1996). Fwave parameters collected included latency, number of detectable Fwave responses (persistence), mean amplitude of Fwaves, and Fwave mean amplitude normalized to Mmax (Peioglou-Harmoussi et al. 1985; Fischer 1992; Fujisawa et al. 2011).

5.1.6.4 Analyses

5.1.6.4.1 Data analysis

The analysis of MEP, Mmax and Fwave was performed off line utilizing custom-built software by the same evaluator (RP). For the MEP, the onset of the stimulus artefact in the EMG of the ABP was detected (Solnik et al. 2010) and the EMG signal following the stimulus artefact was filtered using a 50 Hz low-pass filter. The low pass signal and the stimulus artefact were

subtracted from the original EMG signal to remove low frequency effects of the artefact. In a second pass, the EMG response was filtered using a fourth order high pass Butterworth filter at 20Hz. The Mmax was also processed with a 20 Hz whereas the Fwave signals with a 100 Hz fourth order Butterworth high pass filter (Eisen and Fisher 1999; Espiritu et al. 2003).

Peak-to-peak amplitudes of MEP (Awiszus 2005), Mmax and Fwaves were utilized for statistical analysis. To compare results between groups, the choice of hand (left or right) of the participant in the pain-free group was chosen according to the side of the affected hand of the participant closest in age in the pain group.

5.1.6.4.2 Statistical analyses

Statistical analysis was performed with SPSS version 22 and GraphPad Prism6 software. Unpaired t-tests (with Welch corrections for unequal variances when present) were utilized to determine if differences in demographics, Fwave measures, pain, hand motor performance, disability, and rMT were present between groups. PPG individual hand measures were analysed utilizing a Mixed model ANOVA with a between factor Group (pain-free, pain) and a within repeated measure factor Side (Affected Hand /Non-Affected Hand) and dominance entered as a covariant.

I-O curves were analysed by first determining best fit curve estimations with non-linear models (Ray et al. 2002). The data for each of the data sets were fitted to exponential functions ($Y=Y_0*\exp^{K*X}$), which was a priori determined to best fit the data. The exponential curves were analysed to determine if the rate of rise values (K) differed between pain-free and pain groups for the APB (see figure 1).

Rate of rise (k) values were also determined for the exponential growth functions for each subject in the pain and pain-free groups and were utilized for calculation of Pearson correlation coefficients to investigate relationships between electrophysiological measures, motor performance, disability and pain. Values in the text are expressed as means ± standard deviations.

5.1.7 Results

5.1.7.1 Differences between groups in demographic, hand motor performance and disability

Subject demographics, diagnosis, pain intensity and scores on measures of hand motor performance for subjects with pain are presented in Table 5.1.1. There were no significant differences between pain-free ($\bar{x}$= 49.1±13.8 years) and pain groups ($\bar{x}$=55.6±15.7 years) for age (p=0.24, t=1.21 df=28). Table 5.1.2 presents differences on measures of hand motor performance and disability. There were no significant differences between key pinch grip and isometric force values between groups.

There was no group*side interaction for PPG values for the *Hands* task ($F_{1, 54.42}$=3.04, p=0.09). However, there were main effect differences between groups for the Hand task where subjects with pain performed more poorly ($F_{1, 54.42}$=6.29, p=0.02) and no main effect difference for side ($F_{1, 54.42}$=0.96, p=0.33). Subjects with pain tended to perform more poorly on all measures of the PPG (Table 5).

5.1.7.2 Differences between groups in corticospinal and Fwave measurements

5.1.7.2.1 Resting motor threshold of the APB

RMT values (% of maximum stimulator output) were similar between pain-free ($\bar{x}$=30.3±9.4) and pain ($\bar{x}$=33.1±8.3) groups (p=0.41, t=1.52, df=28).

5.1.7.2.2 Input-Output curves and motor evoked potential amplitudes during active contraction

Input-Output curves were different between the pain-free and pain groups for the APB ($F_{2,206}$=8.89, p<0.01) (see Figure 5.1.1).

The APB MEP amplitude during active contraction between the pain-free ($\bar{x}$=3.38±1.60 mV) and pain ($\bar{x}$=4.21±2.25 mV) groups was not statistically significant (p=0.26, t=-1.16, df=25.56).

5.1.7.3 Mmax and Fwaves

Mmax values were similar between pain-free subjects ($\bar{x}$=11.61±2.03 mV) and subjects with pain ($\bar{x}$=12.63±3.74 mV) (p=0.40, t=0.86, df=18.8). All Fwave parameters assessed with the exception of Fwave persistence, were not significantly different between groups. Fwave persistence was decreased in subjects with pain ($\bar{x}$=20.9±6.7) compared to the pain-free subjects ($\bar{x}$=28.7±4.9) (p<0.01, t=3.17, df=21).

Table 5.1.1: Subject demographics and measures of pain and disability

	Diagnosis	Symptom Location	Age	Handed Ness/ Affected	Pain Duration (months)	VAS Pain	AUSCAN™			
							1	2	3	Total
1	Trapeziometacarpal osteoarthritis	Base of 1st MCP	60	R/L	60	1.0	291	26	385	702
2	Trapeziometacarpal osteoarthritis	Base of 1st MCP	62	R/R	6	2.5	263	25	350	638
3	Trapeziometacarpal osteoarthritis	Base of 1st MCP	60	L/R	120	2.0	221	58	454	733
4	Trapeziometacarpal osteoarthritis	Base of 1st MCP	70	R/R	120	2.1	244	42	501	787
5	Trapeziometacarpal osteoarthritis	Base of 1st MCP	57	R/L	96	3.5	310	74	669	1053
6	Trigger finger 3rd digit	Palm and 3rd digit	47	R/R	48	4.0	266	74	364	704
7	Osteoarthritis	MCP, PIP, DIP digits 1-5	71	R/R	120	7.0	363	47	644	1054
8	DeQuervain's tenosynovitis	Radial border thumb and wrist	22	R/L	24	0.8	67	24	159	25
9	Chronic wrist pain	Dorsal hand 2-4th digits	70	R/R	6	3.6	263	33	289	585
10	Displaced fracture of ulna	Distal ulna, wrist and 4-5th metacarpal	44	R/L	6	1.0	119	7	198	324
11	Chronic wrist and hand pain	Medial carpal and 2-4th digits	31	R/L	22	0.8	139	40	309	488
12	Chronic wrist and hand pain	1st carpometacarpal and medial wrist	46	R/R	84	0.2	145	3	273	421
13	Dupuytren's contracture 3rd digit (2 surgeries)	Palmar surface of hand	81	R/R	288	0.0	193	28	308	529
14	Post-surgical colles fracture	Distal radius and medial carpal bones	51	R/L	5	0.8	161	67	411	639
15	Post-surgical proximal row carpectomy	Wrist and dorsal and palmer surfaces metacarpals	62	R/R	54	2.5	203	17	487	707
$\bar{x}$			55.6		67.7	2.21	218	38	387	641
SD			15.7		72.9	1.85	80	23	146	227

$\bar{x}$: mean; SD: standard deviation; VAS: Visual Analog Scale; AUSCAN: Australian Canadian Osteoarthritis Hand Index.

Table 5.1.2: Strength and Purdue pegboard results

Measures of hand motor performance and hand function	Pain-free	Pain	p-value
Strength	**$\bar{x}$ ± SD**	**$\bar{x}$ ± SD**	
Isometric Strength APB Affected Hand (kg)	10.5±4.3	8.4±3.1	p=0.14 (t=1.52, df=28)
Key Grip Strength Affected Hand (kg)	7.8±2.0	7.4±2.5	p=0.65 (t=0.46, df=28)
Purdue pegboard			
Group	14.5±1.9	13.0±2.8	p=0.02 ($F_{1, 54.42}$=6.29)
Affected Hand	14.9±1.8	12.8±2.3	
Non-Affected Hand	14.1±1.9	13.1±3.2	
Both	12.3±1.6	10.5±2.3	p=0.02 (t=2.48 df=28)
Total	40.7±4.8	36.3±7.1	p=0.06 (t=1.94 df=28)
Assemblies	32.3±8.1	26.6±8.9	p=0.11 (t=1.66 df=28)

APB: Abductor Pollicis Brevis

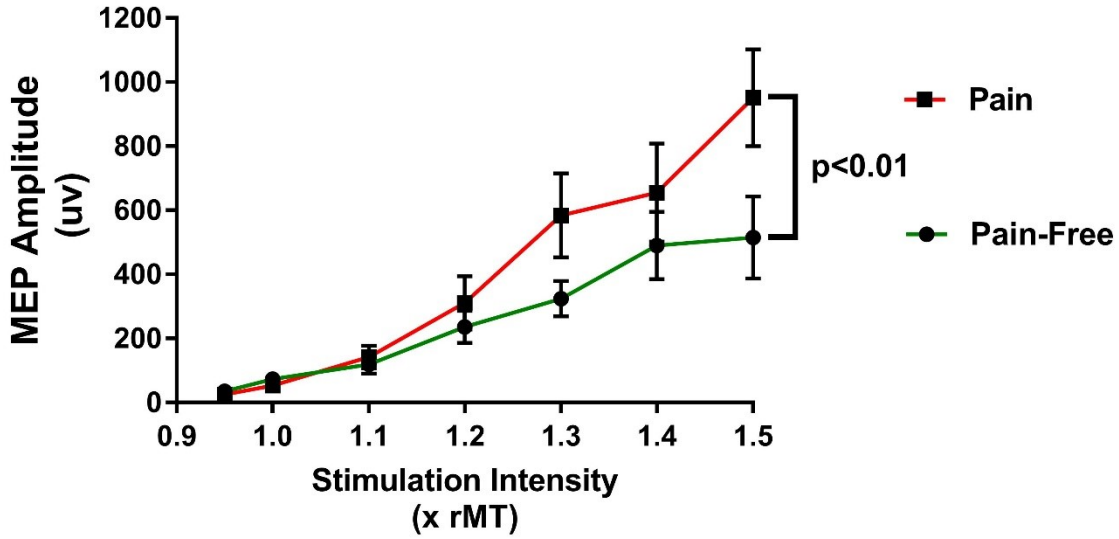


Figure 5.1.1: Input-Output Curves for the abductor pollicis brevis

Motor Evoked Potentials (MEP) at increasing stimulus intensity strengths as a function of resting motor thresholds (rMT). The curves were found to be significantly different between the PAIN and PAIN-FREE groups ($p<0.01$). Columns indicate mean±SEM

5.1.7.4 Association between measures of corticospinal excitability and measures of spinal motoneuronal excitability, pain intensity, hand motor performance and hand disability

Correlations are presented in Table 5.1.3 and Figure 5.1.2. In subjects with pain, corticospinal excitability as measured by the rate of rise values (k) was strongly positively associated with pain related hand disability (AUSCAN™ pain, disability and total scores) as well as with pain intensity (VAS, AUSCAN™ Part 1) in the affected hand. Corticospinal excitability was strongly negatively correlated with Fwave persistence in the affected hand only.

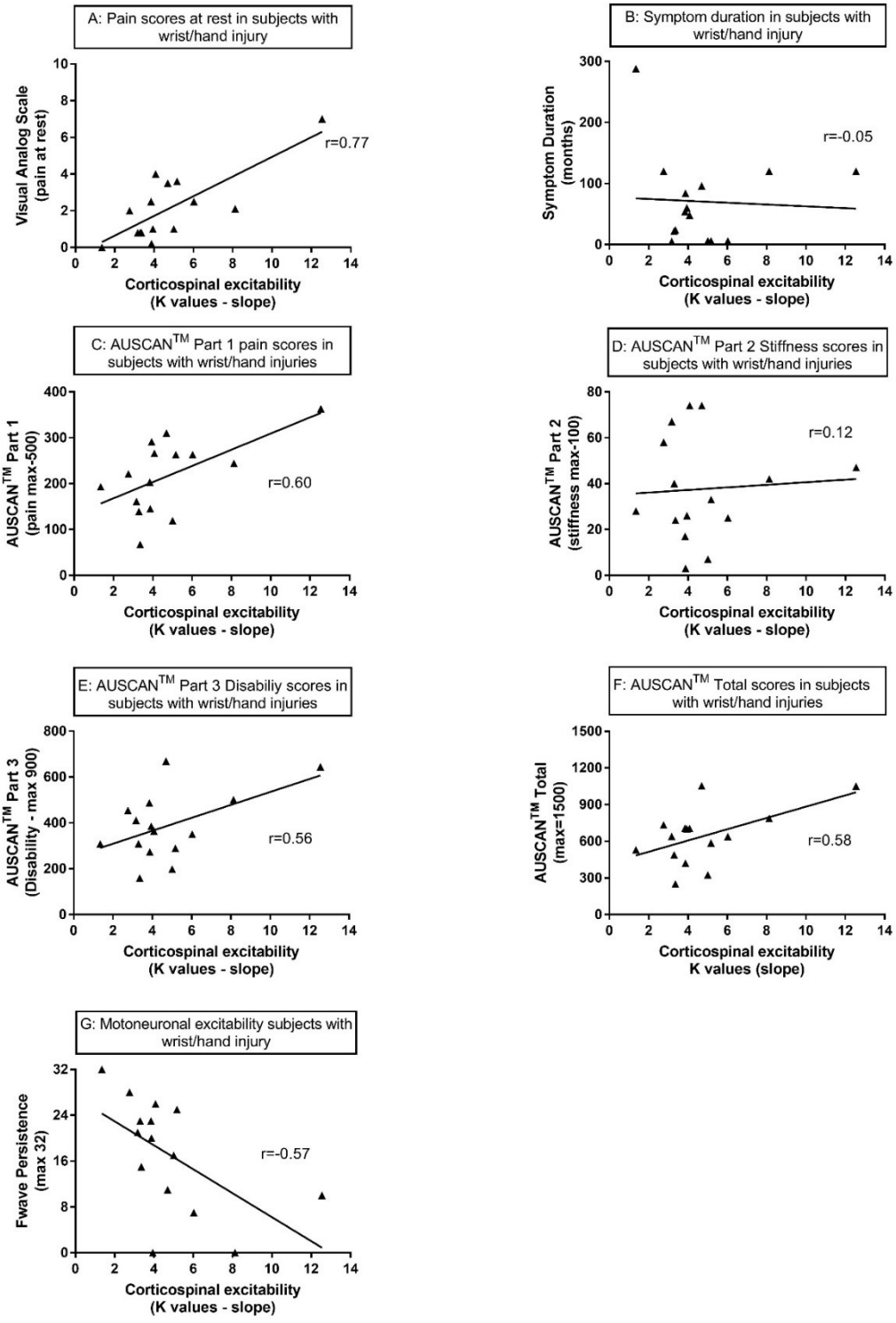
For the pain free group, k values were negatively correlated with PPG results for the Assemblies tasks but with no other measures. This correlation was not significant in pain-free subjects.

Table 5.1.3: Pearson correlation coefficients between measures of corticospinal excitability and electrophysiological and functional measures.

	Measures		
Corticospinal excitability	**Pain intensity, disability, motoneuronal excitability and motor performance**	**Group**	**Pearson's correlation coefficient (r) (bold indicates p values <0.05)**
Rate of rise (k)	Pain Intensity (VAS)	PAIN	**0.77**
exponential growth curve	AUSCAN™ « Pain »	PAIN	**0.56**
	Symptom Duration	PAIN	- 0.05
	AUSCAN™ « Disability »	PAIN	**0.60**
	AUSCAN™ « Total »	PAIN	**0.58**
	Fwave persistence	PAIN	**- 0.56**
	Purdue pegboard « Assemblies »	PAIN	-0.41
		PAIN FREE	**-0.53**

APB: Abductor Pollicis Brevis; MEP: Motor Evoked Potential; VAS: Visual Analog Scale

Figure 5.1.2: Correlation Plots between corticospinal excitability (rate of rise functions of exponential curves) and measures of pain, motor performance, disability, and Fwave persistence.



5.1.8 Discussion

Novel findings of this study include increased corticospinal excitability in subjects with heterogeneous injuries to the wrist and hand that displayed moderate to strong associations with pain intensity and hand disability. Opposing changes of increased corticospinal excitability and Fwave persistence (suggestive of decreased spinal motoneuronal excitability) which were strongly negatively correlated in subjects with pain were also found.

5.1.8.1 Corticospinal excitability and the association with measures of pain, hand motor performance and disability

The I-O curve provides an indication of area and volume of representation of the corticospinal projections to a muscle in M1 (Ridding and Rothwell 1997; Devanne et al. 1997). Augmented I-O curves have been found to be consistent with increased map volume/area (Zanette et al. 2004). Results of increased I-O curves in the present study are therefore likely to be consistent with other studies that found increased map volume/area (Zanette et al. 2004; Elgueta-Cancino et al. 2015) suggestive of increased excitability across subjects with MSD affecting different joints.

Increased corticospinal excitability in a heterogeneous sample of subjects with wrist and hand pain observed in the present study suggests that pain (or the subjects' response to pain), rather than pathology per se, is the likely instigator of changes in corticospinal excitability. Direct thalamic excitatory projections to M1 arising from nociceptive afferents have been demonstrated and may account for the increase in excitability (Frot et al. 2013). Alternatively pain and its effect on behavior (i.e. fear-avoidance) may change motor control strategies in an effort to minimize pain but maintain function (Hodges and Tucker 2011). As neuroplastic changes in M1 are use dependent (Nudo et al. 1996; Ziemann et al. 2001), altered motor behavioral strategies may result in changes in corticospinal properties within M1 and explain changes in corticospinal excitability observed in different MSD affecting different joints. Further studies are required to determine if increased corticospinal excitability compensates for impairments such as strength but is detrimental to other aspects of more complex motor function as seen with the results for the PPG and AUSCAN^{TM} scores.

5.1.8.2 Corticospinal and spinal motoneuronal excitability

Fwaves have been proposed as a measure of spinal motoneuronal excitability (Fischer 1992) however recent evidence suggests that it is imperfect in this regard as only a small number of the largest diameter spinal motoneurons participate in the Fwave response (McNeil et al. 2013; Burke 2014). Fwaves are also less responsive to transient changes in motoneuron excitability than H-reflexes, (Espiritu et al. 2003; Lin and Floeter 2004; Burke 2014) although they are easier to elicit in intrinsic hand muscles. Among Fwave measures, persistence is believed to be the most conservative measure and reflects spinal motoneuronal excitability in "a general way" (Lin and Floeter 2004; Rivner 2008). The present findings of decreased Fwave persistence would suggest decreased spinal motoneuronal excitability in subjects with pain. The mechanisms involved in decreasing spinal motoneuronal excitability may be the result of iontropic or neuromodulatory influences such as serotonin (5-HT) and norepinephrine (see (Heckman et al. 2009)). These neuromodulatory influences originate in the brainstem, are implicated in descending pain modulatory pathways and influence interneurons and motoneurons in the spinal cord (see (Suzuki et al. 2004; Heinricher et al. 2009).

The opposing results of decreased spinal motoneuronal and increased corticospinal excitability found in persons with pain is not a novel finding (On et al. 2004; Zanette et al. 2004; Martin et al. 2008; Hodges et al. 2009). However, to our knowledge, the present study is the first to demonstrate a strong, statistically significant negative correlation between cortical and spinal measures of excitability, suggesting a dynamic interaction of cortical and spinal processes involved in motor control in subjects with chronic pain.

5.1.9 Study Limitations

Although an attempt was made to have healthy, pain-free and pain groups with similar demographics, they were not gender-matched. The same evaluator (RP) who performed offline analysis of electrophysiological measures was not blinded to the grouping of the subjects. Subjects with pain had relatively low pain scores at rest that may not be considered clinically meaningful. However, their AUSCAN^{TM} scores during functional activities were higher than normative values (Bellamy et al. 2010). Finally, motor threshold and I-O curves were determined in inactive muscles. It is possible that different results may be found under active conditions as reflected by studies that have found differences in active motor threshold values

in subjects with chronic MSD (Tsao et al. 2008; Tsao, Danneels, et al. 2011; Ngomo et al. 2015).

5.1.10 Conclusion

The findings from this study suggest that changes in excitability are part of differing cortical and spinal changes driven by peripheral injury. Although it is not possible at this time to delineate the exact mechanisms involved in corticospinal changes, these findings suggest that nociceptive pain rather than a specific pathology per se is implicated, that there is a complex interplay between spinal and cortical mechanisms, and that these changes are associated with disability and decreased motor performance. These findings contribute to the emerging picture of CNS changes associated with chronic MSD and highlight the importance of taking into consideration neurophysiological changes occurring in the CNS as well as peripheral structural injury when devising rehabilitation treatments.

5.1.11 Acknowledgements

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5.1.13 Supplemental Results

5.1.13.1 Methodology and analysis

The same measurements (rMT, I-O curve, M and Fwave) that were performed for the APB were also performed for the FDI. The methodology was identical to that outlined in section 5.5.3. Electrodes were positioned in a tendon-belly montage. Hotspot and rMT were performed in a similar manner as described in section 5.5.3.4.

Furthermore, the CSP was also measured in both the APB and the FDI in both groups of subjects. The CSP were investigated by applying TMS stimulation at an intensity of stimulation of 120% rMT with an inter-pulse interval of a minimum of 4 seconds (Saisanen et al. 2008). TMS was applied to the hotspot of the contralateral motor cortex for the CSP while the subject performed an isometric contraction at 50% of MVC of the muscle in question (APB vs FDI) (Saisanen et al. 2008). EMG data was recorded for 400ms, 100ms prior to the TMS pulse and 300ms subsequent for analysis of the CSP. Subjects were provided with a visual display of the exerted force with a target location to ensure the generation of the appropriate direction and level of force.

The analysis of CSP was performed offline utilizing custom-built software by the same evaluator (RP). CSP MEP amplitudes and duration were recorded. For the CSP, the latency and the duration of the SP were measured from the cessation of the MEP, the beginning of EMG silence, until the initial deflection (either positive or negative) of the EMG signal associated with the resumption of voluntary EMG activity for a period greater than 50ms (Groppa et al. 2012; Damron et al. 2008). CSP MEP amplitudes for the APB are found in the manuscript. CSP duration was analyzed utilizing a mixed model ANOVA with a between factor (Group-CTRL and PAIN) and a repeated measure factor (Hand: affected hand vs non-affected hand).

5.1.13.2 Resting motor threshold of the First Dorsal Interossei (FDI)

There was no difference in the FDI rMT between the CTRL ($\bar{x}$=28.3±8.2 % of MSO) and PAIN ($\bar{x}$=32.4±7.6 % of MSO) Groups (p=0.15, t=1.49, df=28) (Figure 5.1.3).

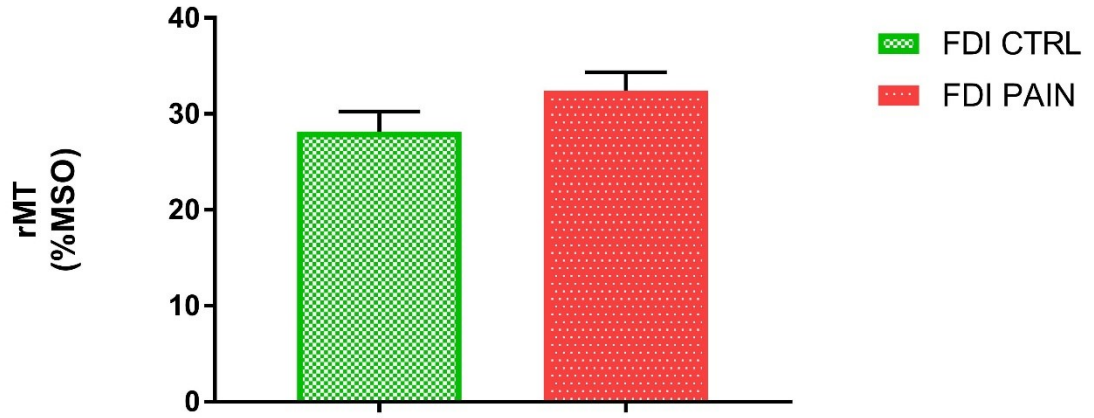

Figure 5.1.3: Resting motor threshold for the first dorsal interossei in the Control and Pain groups.
No significant difference was found between values. Values reflect $\bar{x}$±SEM.

5.1.13.3 Input-Output curves for the FDI

The Input-Output curves for the CTRL and PAIN groups for the FDI were best fitted by a linear curve, although exponential functions produced almost identical results. There was no significant difference between curves ($p=0.88$, $F_{2,206}=0.13$) for the CTRL ($m=1809\pm332$) and the PAIN ($m=1632\pm247$) groups for the FDI and the data was best explained by a single function ($F_{2,206}=0.13$, $p=0.88$) (Figure 5.1.4).

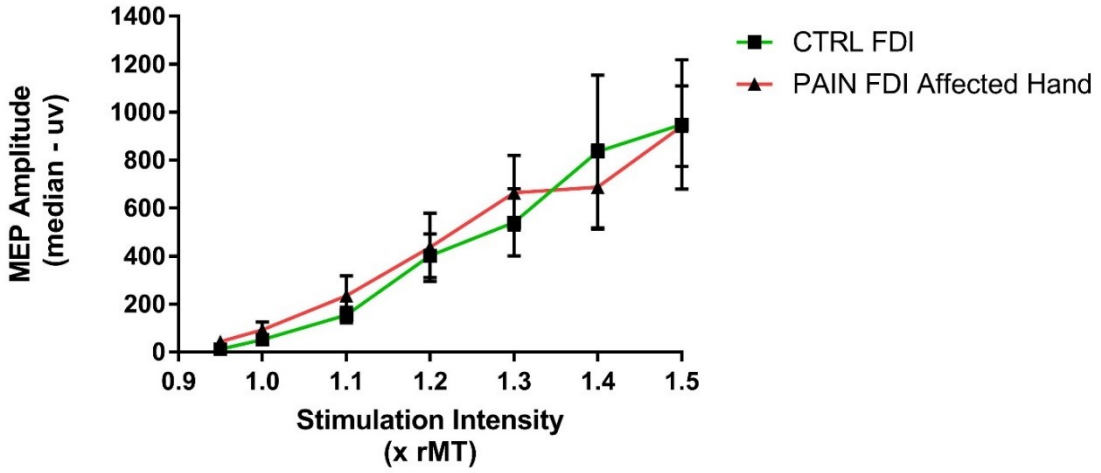

Figure 5.1.4: Input-Output curves for the first dorsal interossei of the affected hand and matched control participants.
No significant difference was found between the curves.

5.1.13.4 Spinal motoneuronal excitability and the FDI

There was no difference in Mmax values between the CTRL ($\bar{x}$=11.97±2.53 mV) and PAIN ($\bar{x}$=13.82±6.47 mV) groups for the FDI (p=0.34; t=0.99, df=17.12). There was no difference in Fmax values between the CTRL ($\bar{x}$=272.5± 128.9 uV) and PAIN ($\bar{x}$=431.8± 457.8uV) groups (p=0.25; t=1.21, df=13.89). Fwave persistence was also similar in the CTRL ($\bar{x}$=24.8±5.3) and PAIN ($\bar{x}$=24.6±7.7) groups (p=0.95; t=0.06, df=21.43). Finally, Fmax/Mmax ratios were the same for the CTRL ($\bar{x}$=0.029±0.015) and PAIN ($\bar{x}$=0.026±0.015) groups (p=0.54; t=0.62, df=24.95). There was therefore no difference in Fwave and Mmax values between groups suggesting that spinal motoneuronal excitability was the same for the FDI in both groups.

5.1.13.5 Cortical silent period for the APB and FDI

There was no interaction of group*muscle for the CSP average duration ($F_{1,55.82}$=0.021, p=0.89). There was also no main effects difference for group ($F_{1,55.82}$=1.03, p=0.32) or muscle ($F_{1,55.82}$=0.09, p=0.77). There were therefore no differences in CSP duration between muscles and groups suggestive of no change in this measure of inhibition for the APB or the FDI (Figure 5.1.5).

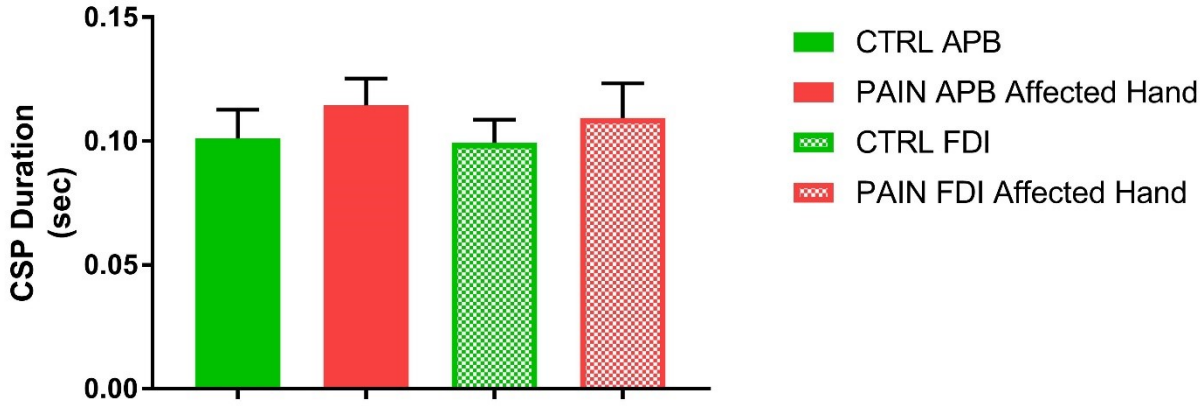

Figure 5.1.4: Cortical silent period duration (seconds) for the abductor pollicis brevis and the first dorsal interossei muscles in matched Control group and in subjects with Pain in their Affected Hand. There were no significant differences between groups. Values indicate $\bar{x}$±SEM.

5.1.13.6 Motor evoked potential amplitude at 1.2xrMT and APB strength

A significant correlation was also found between MEP amplitudes in response to stimulation at 1.2xrMT and strength values in the APB in participants with chronic wrist/hand pain in the affected (see Table 5.1.4). These correlations were not found in the healthy control participants.

Table 5.1.4: Correlations between motor evoked amplitudes and isometric strength

	PAIN	**CTRL**
	Affected Hand r, p value	Matched Affected Hand r, p value
Strength APB	0.55, 0.03	-0.07, 0.79
Strength FDI	-0.17, 0.55	0.17, 0.55

Pearson Product Correlations between Motor Evoked Potential Peak to Peak Amplitudes evoked at 1.2xrMT and isometric strength values when the subjects performed an isometric contraction of the APB and FDI at 50% of maximum force output and Isometric strength measures**.** R=Pearson Product Correlation

5.2 Laterality recognition of images, motor performance, and aspects related to pain in participants with and without wrist/hand disorders: an observational cross-sectional study.

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As the principal author of this manuscript, I confirm that I was responsible for subject recruitment, participated in all the experimentation, data processing, statistical analysis and writing of the manuscript. Dr Higgins participated in the experimentation. Dr Higgins and Dr Bourbonnais provided supervision and revision of the manuscript.

5.2.1 Preface

LRJT performance, a proposed measure of the body schema, has been found to be affected in some persons with MSD. As the body schema is tightly coupled with motor processes and involves motor imagery that is related to actual motor performance, LRJT performance should in theory be related to measures of motor function. As was presented in the literature review, motor function/performance is usually affected in subjects with MSD.

The general objective of the thesis is to determine if participants with MSD demonstrate changes in altered cortical sensorimotor processes and the relationship of any changes with measures of motor function/performance, pain and disability. The present article is utilizing an indirect measure of cortical sensorimotor processes. The article addresses the third specific objective of the thesis, to determine if LRJT performance would be different between participants with and without MSD of the wrist/hand and the fourth specific objective to determine the relationship between LRJT performance with measures of motor function and performance. We hypothesized that LRJT performance would be negatively affected in the participants with MSD of the wrist/hand compared to healthy control participants. We also hypothesized that the relationship between LRJT motor performance would be altered in the participants with MSD of the wrist/hand.

5.2.2 Abbreviations

AUSCAN^{TM}: Australian Canadian Osteoarthritis Hand Index

LRJT: Left/Right Judgement Task

MSD: Musculoskeletal Disorders

RT: Reaction Time

WHYMPI: West Haven Yale Multidimensional Pain Inventory

5.2.3 Abstract

Objective: Musculoskeletal disorders are associated with altered sensory, proprioceptive and cognitive processes. Sensory processes affect the internal cortical representation of the body in space, the body schema, which in turn influences motor control. The purpose of this study was to determine if participants with wrist/hand disorders had impaired performance on a task associated with the body schema, the Left/Right Judgement Task (LRJT) and secondly how LRJT performance, motor performance, disability, pain and related aspects are associated.

Methods: Fifteen healthy control participants and 15 participants with hand/wrist pain were asked to determine the laterality of images of hands. Measures of motor performance (Purdue pegboard test), self-reported disability (Australian Canadian Hand Index), and pain related aspects (pain intensity, symptom duration, pain interference and affective distress) were recorded.

Results: Participants with wrist/hand pain scored lower on all segments of the Purdue pegboard test. There were differences in LRJT performance between groups for both Accuracy ($p=0.03$) and Reaction Time (RT) ($p<0.01$). There was no correlation between RT and Accuracy with pain intensity, pain duration, and disability. Both motor performance ($r=0.58$-0.64) and LRJT performance Accuracy ($r=0.59$) and RT ($r=-0.56$) were correlated with affective distress. A significant correlation was observed between RT and motor performance in healthy control participants ($r=-0.56$, $p=0.03$) but not in participants with wrist/hand pain ($r=-0.26$, $p=0.44$).

Conclusions: LRJT and motor performance was correlated with affective distress in participants with wrist/hand pain suggestive of complex interactions between cognitive-affective processes and sensorimotor integration.

5.2.4 Keywords: Body schema, sensorimotor integration, Left/Right Judgement Task, musculoskeletal disorders, pain, disability, distress

5.2.5 Highlights

- Motor performance on the Purdue pegboard test was decreased in participants with pain
- LRJT performance (reaction time and accuracy) was affected in participants with pain
- LRJT reaction time and motor performance were related in healthy control participants
- LRJT and motor performance were correlated with affective distress

5.2.6 Introduction

Altered sensory and proprioceptive processes are well characterized in participants with musculoskeletal disorders (MSD). These include findings of increased two-point discrimination threshold, changes in perception threshold to noxious and innocuous stimuli, sensory stimuli being processed more slowly, incorrect localization, and decreased accuracy in recognizing tactile stimulation (Sharma and Pai 1997, Tinazzi et al. 2000, Wilder-Smith et al. 2002, Brumagne et al. 2004, Giesecke et al. 2004, Jensen et al. 2008, Fernandez-Carnero et al. 2009, Fernandez-de-las-Penas et al. 2009, Wand et al. 2010, Luomajoki and Moseley 2011, Wilgen et al. 2011, Moseley et al. 2012, Stanton et al. 2013). Sensory changes in participants with MSD have been demonstrated bilaterally and in sites remote to the initial injury (Smeulders et al. 2002, Jensen et al. 2008, Fernandez-Carnero et al. 2009) including increased pain thresholds in participants with osteoarthritis of the thumb (Chiarotto et al. 2013, Chiarotto et al. 2013). Participants with MSD may also experience proprioceptive deficits (Garn and Newton 1988, Warner et al. 1996, Sharma and Pai 1997, Newcomer et al. 2000, Treleaven et al. 2006, Coombes et al. 2009, Huysmans et al. 2010, Hodges 2011) including decreased joint position sense (Brumagne et al. 1999, O'Sullivan et al. 2003, Huysmans et al. 2010), decreased ability to detect joint motion (Gill and Callaghan 1998, Field 2009), and difficulty to adopt postures seen on a photograph (Luomajoki and Moseley 2011, Moseley et al. 2012).

Sensory and proprioceptive information is utilized to create an internal representation of the body in peri-personal space, the body schema, that is accessed for effective engagement with the environment. The Left/Right Judgement Task (LRJT) requires participants to determine if images of body parts are of the left or right side (Parsons 2001, Moseley 2004). The LRJT is believed to involve the body schema as performance on this task is affected by the complexity of transformations to be performed to adopt the position of the participant's anatomical part congruent to the image presented (Schwoebel et al. 2001, Ionta et al. 2007, Coslett et al. 2010, Reinersmann et al. 2012). Studies in participants with MSD have found variable changes in LRJT performance including Reaction Time (RT), the time taken to identify the laterality of the image of a body part, and Accuracy, the correctness of the given response (Schwoebel et al. 2001, Coslett et al. 2010, Coslett et al. 2010, Schmid and Coppieters 2012, Stanton et al. 2012,

Pedler et al. 2013, Stanton et al. 2013, Elsig et al. 2014) suggesting that the body schema is affected in at least some persons with MSD.

Altered motor processes such as bilateral changes in strength and motor control are also characteristic of participants with upper limb MSD (Bisset et al. 2006), including hand injuries (Forget et al. 2008) suggesting that participants with upper limb MSD may experience bilateral changes in motor processes. In addition, participants with MSD also experience changes in cognitive-affective-motivational areas of the brain (see (Apkarian et al. 2009, Apkarian et al. 2011, Wiech and Tracey 2013)). These cognitive-affective-motivational areas are associated with psychological and behavioral changes (see (Campbell and Edwards 2009)). Psychological factors would appear to impact sensorimotor processes. For example, fear of movement measured with the Tampa Scale of Kinesiophobia is associated with an increase of electromyographic activity during performance of tasks in participants with MSD (Masse-Alarie et al. 2016). Changes in corticospinal excitability including decreased modulation of intracortical motor cortex inhibitory processes has been associated with acute mental stress associated with a complex mental task (Marker et al. 2014). Psychological factors associated with positive Waddell signs have also been found to impact changes in somatotopic organisation in the primary somatosensory cortex (Lloyd et al. 2008). Depression and stress has also been shown to mediate the relationship between pain and disability in participants after wrist/hand fractures (Ross et al. 2015). Study results therefore suggest that MSD are associated with cognitive-affective changes that interact with sensorimotor processes.

As sensorimotor processes as well as cognitive affective processes appear to be affected in participants with MSD, it is conceivable that the relationship between LRJT, motor performance and cognitive affective aspects related to MSD of the hand would be different between participants with and without wrist/hand pain. We therefore hypothesised that motor performance of the hand would be affected in participants with heterogeneous MSD of the hand and wrist. Additionally, we hypothesized that motor performance and aspects related to pain such as pain intensity, pain interference and affective distress would be associated with poorer LRJT performance. This information is important for deciphering the relationship between neurophysiological changes in sensorimotor processes and MSD as these changes are

considered as a potential avenue of treatment in this population (Snodgrass et al. 2014, Pelletier et al. 2015).

5.2.7 Methods

5.2.7.1 Participants

Participants experiencing unilateral wrist/hand pain (PAIN) for greater than three months and reported that their injury interfered with the performance of daily activities were recruited in the greater Montreal area, Canada from private rehabilitation clinics, social media and web-based advertising between September 2013 and January 2015. Healthy Control (CONTROL) participants were a sample of convenience and were free of previous injury to the upper extremity. Participants were excluded if they were diagnosed with dyslexia or experienced neurological or visual impairment. Participants were assessed for handedness with the Edinburgh Handedness Inventory (Oldfield 1971). Fifteen participants with wrist/hand pain (7 female, 14 right hand dominant) and 15 CONTROL (10 female, 14 right hand dominant) participants participated in this observational cross-sectional study. Sample size was based upon experiments with significant findings utilising LRJT performance as their outcome measure (Schwoebel et al. 2002, Nico et al. 2004, Moseley et al. 2005, Hudson et al. 2006, Ionta et al. 2007, Reinersmann et al. 2010). Experiments were performed at the Centre intégré universitaire de santé et de services sociaux du centre-sud-de-l'île-de-Montréal, Montreal Gingras-Lindsay Rehabilitation Institute. The study received ethical approval from the institutional review board (CRIR-793-1113), participants provided written informed consent, and the study was performed in accordance with the Declaration of Helsinki.

5.2.7.2 Measures

5.2.7.2.1 Left right judgment task

Accuracy and RT for the recognition of images of hands were assessed using the Recognise™ (Neuro-orthopaedic Institute, Adelaide, Australia) application installed on an 8-inch computer tablet (Linder et al. 2016, Breckenridge et al. 2017). Participants were presented with 50 images of hands in different conformations on a plain background (vanilla images) with a maximum duration time per image of 5 seconds. Participants were instructed to provide a verbal response "as accurately and quickly as possible" as LRJT performance in both Accuracy and RT is better when participants provide verbal rather than manual responses, accuracy for the laterality of

images is negatively affected on the side of the hand utilized to manually indicate laterality (Cocksworth and Punt 2013), and it is also possible that changes in motor hand function to manually indicate laterality due to MSD of the hand would impact results (Fiorio et al. 2005). Participants were instructed not to move their hands during the task. The same examiner depressed the left and right keys on the tablet in both groups of participants. Participants practiced on 10 images prior to data collection. Total Accuracy was expressed as a percentage of correct responses while RT was the average of the trials for each hand expressed in seconds.

5.2.7.2.2 Pain

Pain severity and pain-related aspects such as pain interference and affective distress were assessed utilizing the West Haven Yale Multidimensional Pain Inventory (WHYMPI), with maximum values per subscale of 6 (Kerns et al. 1985), and part 1 of the Australian Canadian Osteoarthritis Hand Index (AUSCAN™, www.womac.com) (Bellamy et al. 2002, Bellamy et al. 2002). Pain interference in the WHYMPI consists of nine items that pertain to how pain interferes (ability and satisfaction) in the patient's life including activities of daily living, work, social and familial activities. Affective distress involves three items pertaining to mood, irritability and anxiety.

5.2.7.2.3 Hand motor performance

Hand motor performance was assessed with the Purdue pegboard test (Tiffin and Asher 1948). The Purdue pegboard test (Lafayette Instrument, model #32020, Lafayette, IN) is a time constrained motor task assessing gross and fine motor function of the arms, wrist, and fingers (Raad 2016). The Purdue pegboard test has four segments and five scores: (1,2) inserting pins with each hand individually (score for each hand), (3) Both hands inserting the pins simultaneously, within 30 second time epochs, a (4) Total score comprised of the scores of each individual Hand and Both hands tasks, and (5) the building of small Assemblies involving pins collars and washers utilizing both hands in a 1-minute epoch. The Purdue pegboard test has documented validity in participants with wrist and hand disorders (Shahar et al. 1998, Amirjani et al. 2011) and distinguishing between participants with and without hand injury (Shahar et al. 1998). Higher scores in the Purdue pegboard test reflect better performance.

The visual analog scale version of the AUSCAN™ was utilized and consists of three parts with a total of 15 items each scored on a 100mm scale. Part 1 assesses five items specifically related

to pain at rest and during gripping, lifting, turning, and squeezing objects in the previous 48 hours. Part 2 consists of 1 item related to stiffness. Part 3 consists of nine items related to hand disability assessing the difficulty with turning, fastening, opening, carrying, grabbing, and squeezing. The maximum scores per section are 500, 100, and 900 respectively for a total score of 1500 where higher scores indicate greater pain and disability. The construct and factorial validity are documented, as is the internal consistency in participants with and without hand pathology (Allen et al. 2006).

5.2.8 Statistical Analysis

Statistical analysis was performed using SPSS version 23 (IBM Corporation, Armonk, New York) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA) software. Participants with wrist/hand pain were matched for side to the closest aged participant in the CONTROL group. Demographic information between groups was compared utilizing unpaired T-tests.

To determine if there were differences within and between groups ANCOVA with a between factor (Group – PAIN vs CONTROL) and a repeated measure factor (side) with Gender entered as a covariate was utilized to compare for differences between groups in LRJT performance. To investigate differences between groups in motor performance of Purdue pegboard test values a Multivariate Analysis of Variance was performed with group entered as the between subject factor and the Purdue pegboard Scores entered as the dependent variables. Multivariate Analysis of Variance also produces univariate test results to determine differences in scores between each of the Purdue pegboard sub-scores between groups.

To investigate if changes in LRJT performance Accuracy can be associated with slower RT in participants in the PAIN group (accuracy-speed trade-off), Spearman rho correlations were performed between LRJT Accuracy and RT in both groups.

Pearson correlation coefficients were performed between LRJT performance and measures of pain intensity, pain interference, affective distress, motor performance and disability to determine the association between these measures. Assumptions for normality were assessed by visual examination of the residual plots and the D'Agostino-Pearson omnibus test. Grubb's test was utilized to determine the presence of outliers in the LRJT at an alpha =0.05. In the presence of a significant outlier the value would be removed for both hands. Corrections were made for

unequal variance when reporting p-values. Unless otherwise stated, values are presented as $\bar{x}$ ± standard deviations.

5.2.9 Results

5.2.9.1 Demographics, baseline characteristics and motor performance

The PAIN group consisted of five participants with first carpometacarpal osteoarthritis, three participants with postsurgical stabilization of fractures of the wrist and hand, three participants with chronic wrist pain, and one participant with each of the following conditions: hand osteoarthritis, DeQuervain's tenosynovitis, Dupuytren's contracture, and Trigger finger. Participants in the PAIN group had WHYMPI measures of pain severity of 2.2±1.1, pain interference 2.3±0.5 and Affective distress of 2.2± 1.5. Participants in the PAIN group had AUSCAN^{TM} values for pain ($\bar{x}$=218±80), stiffness ($\bar{x}$=38±23), disability ($\bar{x}$=387±146) and total scores ($\bar{x}$=641±227). Symptom duration was 67.7±72.9 months. There were no significant differences between CONTROL ($\bar{x}$= 49.1±13.8 years) and PAIN groups ($\bar{x}$=55.6±15.7 years) for age (p=0.24, t=1.21 df=28).

Hand motor performance was measured with the Purdue pegboard Test which fell within normative values for CONTROL participants (Agnew et al. 1988). Using Phllai's trace, there was no significant effect of group on Purdue pegboard Results (V=0.27, F5,24=1.75, p=0.16). However, separate univariate ANOVAs on the outcome variables revealed significant differences between groups for the Affected Hands and Both hands subscale, the Total (sum of RH+LH+both hands) subscale demonstrated a strong trend, and the Assemblies and Non-Affected Hand where not statistically different (Table 5.21).

Table 5.2.1: Difference in motor performance measures between participants in the CONTROL and PAIN groups

	Measures of hand performance	GROUP		Difference between groups		
	Purdue pegboard test	CONTROL (mean±SD)	PAIN (mean±SD)	Mean difference	95% CI Lower, Upper	P-value
1	Affected Hand	14.93±1.79	12.73±2.37	2.20	0.64, 3.77	0.01
2	Non-Affected Hand	14.07±1.91	13.20±3.32	0.87	-1.16, 2.89	0.38
3	Both hands	12.33±1.63	10.47±2.42	1.87	0.32, 3.41	0.02
4	Total Score	40.67±4.78	36.27±7.36	4.40	0.24, 9.04	0.06
5	Assemblies Score	32.33±8.09	27.20±8.87	5.13	-1.21, 11.48	0.11

SD: Standard deviation; CI: confidence interval; P-value: probability value

5.2.9.2 Left right judgement task - accuracy

Laterality Accuracy is illustrated in Figure 5.2.1 for both groups. One CONTROL participant was found to have a statistically significant outlier value ($p<0.05$) in both the affected and non-affected hands. These values were removed from the analysis of accuracy. There was no group*side interaction for Accuracy ($F_{1,49.90}=0.17$, $p=0.69$). There was a main effect difference of LRJT Accuracy between groups ($F_{1,51.99}=4.57$, $p=0.04$) but not for side ($F_{1,49.90}=0.23$, $p=0.64$). Accuracy in the CONTROL group ($\bar{x}=82.89\pm8.32$) was greater than the PAIN group ($\bar{x}=75.5\pm14.92$) (Figure 5.2.1). There was no group*gender interaction suggesting that the homogeneity of regression slopes where the same for the covariate Gender ($F_{1,49.57}=0.436$, $p=0.512$).

5.2.9.3 Left right judgement task - reaction time

There was no group*side interaction for RT ($F_{1,52.00}=0.09$, $p=0.77$). There was a main effect difference of LRJT RT between groups ($F_{1,51.99}=7.43$, $p<0.01$) but not for side ($F_{1,51.99}=0.03$, $p=0.86$). RT was increased for participants in the PAIN group ($\bar{x}=3.08\pm0.58$) compared to CONTROL ($\bar{x}=2.41\pm0.74$) participants ($F_{1,56.0}=15.0$, $p<0.01$) (Figure 5.2.1). There was no group*gender interaction suggesting that the homogeneity of regression slopes where the same for the covariate Gender ($F_{1,51.99}=0.21$, $p=0.89$). Therefore, participants with PAIN were slower in recognizing the laterality of both hands compared to participants in the CONTROL group (Figure 5.2.1).

5.2.9.4 Accuracy and reaction time trade-off

The correlation between Accuracy and RT was $r_s= -.42$ ($p<0.00$). As the correlation is negative, increased Accuracy was associated with decreased RT, indicating that there was no Accuracy-RT trade-off.

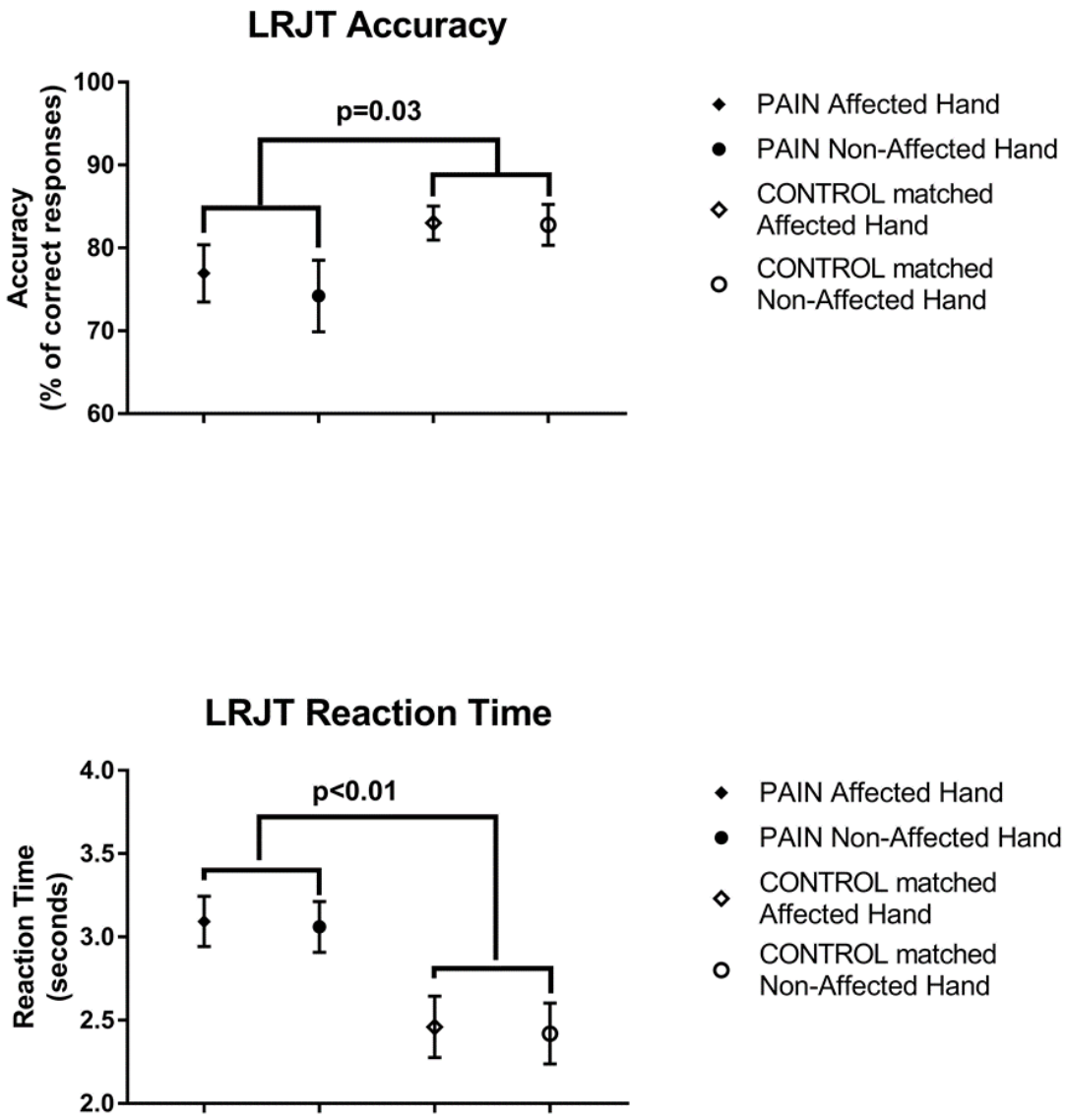

Figure 5.2.1: Performance on the Left/Right Judgement Task (LRJT)

Results are mean values ± SEM.

Table 5.2.2: Pearson product correlations between Left Right Judgement Task performance and age

LRJT Performance	Hand	CONTROL (matched) r , p	PAIN r , p
Reaction Time	Affected Hand	0.29 (0.30)	0.07 (0.82)
	Non-affected Hand	0.28 (0.31)	-0.05 (0.87)
Accuracy	Affected Hand	0.11 (0.72)	-0.08 (0.78)
	Non-affected Hand	-0.27 (0.35)	-0.34 (0.22)

r: Pearson product correlation coefficient; p: probability value

5.2.9.5 Relationship between left right judgement task and measures of motor performance, disability and pain

Age was not significantly correlated with LRJT performance, either RT or Accuracy, in both groups (Table 5.2.2). No statistically significant correlations were present between Accuracy and RT with pain intensity, symptom duration or disability (Table 5.2.3). Both Accuracy and RT were correlated with the WHYMPI subsection Affective Distress (Table 5.2.3). In CONTROL participants there was a statistically significant moderate/strong negative association between the Purdue pegboard test Total and RT for the matched affected hand, non-affected hand, and average of two hands (Table 5.2.4). In participants in the PAIN group the correlation between LRJT RT and motor performance was weak and not statistically significant due to increased variability in Purdue pegboard test scores in this group. The WHYMPI Affective distress

Table 5.2.3: Pearson product correlations (r) between Left Right Judgement Task reaction time and accuracy and measures of motor performance, disability and pain

Measures		Left/Right Judgement Task Performance					
		Pearson correlation coefficient – r (p value)					
		RT			ACCURACY		
		Affected Hand	Non - Affected Hand	Average	Affected Hand	Non - Affected Hand	Average
AUSCAN™	**Part 1**	-0.24 (0.40)	-0.09 (0.77)	-0.18 (0.55)	0.37 (0.20)	0.15 (0.62)	0.27 (0.35)
	Part 2	-0.34 (0.23)	-0.16 (0.59)	-0.27 (0.36)	0.20 (0.51)	0.14 (0.64)	0.18 (0.54)
	Part 3	-0.15 (0.61)	0.10 (0.72)	-0.03 (0.92)	0.19 (0.52)	-0.03 (0.92)	0.08 (0.78)
	Total	-0.21 (0.46)	0.02 (0.94)	-0.11 (0.72)	0.27 (0.35)	-0.05 (0.89)	0.16 (0.58)
WHYMPI	**Pain Intensity**	-0.24 (0.40)	-0.14 (0.63)	-0.19 (0.50)	0.12 (0.68)	-0.05 (0.87)	0.03 (0.90)
	Pain Interference	-0.40 (0.14)	-0.28 (0.32)	-0.35 (0.21)	0.21 (0.44)	0.16 (0.59)	0.20 (0.48)
	Affective Distress	-0.59 (0.02)	-0.49 (0.06)	-0.56 (0.03)	0.59 (0.02)	0.51 (0.05)	0.59 (0.02)
Symptom Duration		-0.11 (0.70)	-0.23 (0.42)	-0.17 (0.54)	-0.10 (0.51)	-0.27 (0.33)	-0.20 (0.47)

r: Pearson product correlation coefficient; p: probability value; AUSCAN™: Australian Canadian Osteoarthritis Hand Index; WHYMPI: West Haven Yale Multidimensional Pain Inventory

Table 5.2.4: Pearson product correlations (r) between Left Right Judgement Task and motor performance (Purdue pegboard Total scores)

LRJT Performance	Group	Hand	Coefficients of correlation – r (p)
Reaction Time	**CONTROL**	Affected Hand (matched)	-0.56 (0.03)
		Non-affected Hand (matched)	-0.62 (0.01)
		Average	-0.59 (0.02)
	PAIN	Affected Hand	-0.26 (0.34)
		Non-Affected Hand	-0.16 (0.58)
		Average	-0.22 (0.44)
Accuracy	**CONTROL**	Affected Hand (matched)	0.27 (0.35)
		Non-affected Hand (matched)	0.43 (0.13)
		Average	0.40 (0.16)
	PAIN	Affected Hand	0.20 (0.48)
		Non-Affected Hand	0.17 (0.54)
		Average	0.20 (0.48)

Average: (Affected Hand + Non-Affected Hand)/2; r: Pearson product correlation coefficient; p: probability value

Table5.2.5: Pearson correlation coefficients (r) between motor performance and pain related measures in participants with wrist/hand pain

	Motor performance Purdue pegboard test	Correlation coefficients r , (p)
Pain Interference	Affected Hand	0.33 (0.22)
	Non-affected Hand	0.40 (0.13)
	Both	0.41 (0.11)
	Total	0.42 (0.10)
	Assemblies	0.50 (0.05)
Affective distress	Affected Hand	0.64 (0.01)
	Non-affected hand	0.37 (0.17)
	Both	0.41 (0.11)
	Total	0.46 (0.07)
	Assemblies	0.58 (0.02)

r: Pearson product correlation coefficient; p: probability value

subscale was also positively correlated with WHYMPI Pain Intensity ($r=0.60$, $p=0.01$) and Purdue pegboard scores of the affected hand ($r=0.64$, $p<0.01$) and assemblies ($r=0.58$, $p=0.02$) in participants in the PAIN group (Table 5.2.5).

5.2.10 Discussion

The objectives of the study were to investigate if participants with wrist/hand pain had altered ability to recognize the laterality of images of hands as compared to healthy, control participants and secondly how LRJT performance, motor performance, and pain related aspects such as pain intensity, interference and affective distress were associated. Participants with wrist/hand pain demonstrated altered LRJT performance including increased RT and decreased Accuracy in recognizing the laterality for images. These changes in LRJT performance were not related to pain intensity or symptom duration. Affective distress in participants with wrist/hand pain was associated with pain intensity, motor and LRJT performance however the direction of this association was contrary to what was hypothesized.

Previous experiments investigating LRJT performance in participants with MSD demonstrated changes in Accuracy (Bray and Moseley 2011, Schmid and Coppieters 2012, Bowering et al. 2014, Elsig et al. 2014), in RT (Coslett et al. 2010), both in RT and Accuracy (Coslett et al. 2010), or no changes at all (Pedler et al. 2013, Linder et al. 2016). Observed changes have been localised to the area of injury, to the side of injury (Stanton et al. 2012), bilaterally (Schwoebel et al. 2002, Coslett et al. 2010), or variable, affecting the hand and the neck but not the images of feet (Schmid and Coppieters 2012), or in the knee and back but not the hand (Stanton et al. 2013). Even in participants with pain in the same anatomical region, differences in study results have been found in the cervical (Pedler et al. 2013, Elsig et al. 2014) and back pain populations (Bray and Moseley 2011, Stanton et al. 2013, Linder et al. 2016). The literature remains unclear as to why participants with MSD may demonstrate changes in RT, Accuracy, neither or both within and across different populations. The heterogeneity of results across studies have been attributed to differences in anatomical location of the injury, localised changes in body schema, differing pain mechanisms (nociceptive vs neuropathic), and methodological differences between studies (Linder et al. 2016). Absence of correlations between LRJT performance in participants with heterogeneous MSD of the wrist/hand with pain intensity and duration in the

present study suggest pain itself does not necessarily contribute to these changes, a finding that has been found in previous studies (Reinersmann et al. 2010, Bowering et al. 2014).

Different processes may explain changes of LRJT performance observed in the present study. The body schema may be affected bilaterally (Reinersmann et al. 2010). There is evidence of altered sensory processing bilaterally in participants with unilateral musculoskeletal injuries (Fernandez-Carnero et al. 2009) including the hand (Chiarotto et al. 2013, Chiarotto et al. 2013). Decreased accuracy in the LRJT has been attributed to altered sensory and proprioceptive inputs as the result of injury that impacts cortical bodily representations (Breckenridge et al. 2017). However alternative explanations are possible such as cognitive changes resulting in impaired ability to imagine the movement of the body part (Hoyek et al. 2014) or to changes in central processing involved in the LRJT (Stanton et al. 2012). Imaging studies have demonstrated that the LRJT is associated with activation of subcortical and cortical structures, any or all of which may result in altered performance, including frontal, pre-motor areas, basal ganglia, cerebellum and associative areas in the parietal cortex involving neural mechanisms associated with sensorimotor integration, movement planning and execution but also structures involved in high order functions (Kosslyn et al. 1998, Parsons 2001, Ionta et al. 2007). Further studies are required to decipher the mechanisms implicated in changes in LRJT performance in participants with MSD.

Increases in RT on the LRJT in participants with MSD has been attributed to changes related to disrupted processing of sensory/ proprioceptive stimuli resulting in an increased number of errors (Breckenridge et al. 2017). Increased RT has been attributed to the extra time required to correct the wrong initial judgement (Moseley 2004, Bowering et al. 2014). An alternative hypothesis is that changes in LRJT RT reflect the increased time taken to physically perform the movement resulting from decreased movement speed and performance (Descarreaux et al. 2005, Thomas et al. 2008, Roijezon et al. 2010), pain or the expectancy of pain in participants with pain (Hudson et al. 2006). The LRJT is believed to involve implicit motor imagery where the participant imagines moving the body part in the same position as the image (Moseley 2004). Experimental findings have demonstrated that the time to imagine movements is strongly correlated with actual time to physically perform the movement and share the same neural substrates (Decety et al. 1989, Parsons 1994, Decety 1996). Decreased performance on the

Purdue pegboard test in participants in the PAIN group is indicative of reduced execution speed. Altered motor patterns is supported by the decreased performance in the Purdue pegboard test and the weaker correlation between RT and motor performance in participants with wrist/hand pain reflective of more variability in these participants. Changes in LRJT RT performance may therefore be the result of processes involved in movement planning and execution attributed specifically to injured structures, because of pain or behavioral changes related to pain, possibly to minimize pain and maximize function (see (Hodges and Tucker 2011).

Affective distress was associated with LRJT and motor performance. Interestingly, the correlation suggests that the relationship between Affective distress and performance is beneficial rather than detrimental. The negative correlation between LRJT RT and positive correlation with Accuracy with Affective Distress indicates that higher Affective distress measures were associated with better performance. The literature suggests that psychological factors such as depression and stress mediate the relationship between pain and disability (Weiner et al. 2006, Ross et al. 2015) and that greater levels of distress result in greater disability, a finding that contrasts with the results of the present study. Affective distress may positively impact performance by mobilizing attentional resources towards the injured site responsible for sensory changes (Sanger et al. 2014) and previously suggested for differences in LRJT performance in participants with chronic hand pain (Moseley 2004). These findings may suggest a corollary to the Yerkes-Dodson Law, or inverted U hypothesis, that argues that motor performance can be improved as arousal increases due to mobilization of resources (see (Hartzell et al. 2017)). However, this same law states that if arousal bypasses a certain optimal level there will be degradation in performance. Although speculative, given that the pain and disability in the present sample of participants with wrist/hand pain was relatively low, conditions may be optimal to mobilize arousal and attentional resources towards the injury helping to mitigate the differences in LRJT performance between the groups. However, it is possible that participants with greater pain intensity, interacting with cognitive-affective aspects related to their MSD and pain, may result in greater than optimal levels of arousal and result in a more substantial decrease in LRJT performance. In the study by Bowering et al (2014) participants experiencing back pain at the time of experimentation demonstrated a dichotomous response pattern on the LRJT, some performing better and others worse than healthy (pain free)

experimental participants (Bowering et al. 2014). The authors did not associate these changes to pain intensity values or other pain related aspects but speculated that changes may reflect differences in cognitive-affective interaction with sensorimotor processes between participants who performed better and those who performed worse than healthy participants. Variable results amongst studies of LRJT performance may be reflective of the differing relative sensory/proprioceptive processes associated with the MSD, but the results from the present study also suggest that cognitive-affective processes may also be involved. This hypothesis would require further investigation.

5.2.11 Limitations

There are several issues that should be taken into consideration when interpreting the results of the present study. Pain and disability of participants in the PAIN group were relatively low. The non-significant results between groups, for example on the Purdue pegboard tests, may be attributed to the small sample size and Type II statistical error can therefore not be excluded. No assessment of attentional resources and imagery ability was performed. Participants in the PAIN group experienced pain in their dominant and non-dominant hands; although studies are inconclusive if this impacts the performance of the LRJT. The examiner who recorded LRJT responses for the participants in the LRJT was not blind to the participants' groupings which is a potential source of bias. However, the differences in RT between CONTROL and PAIN groups were consistent with values seen in other studies (≈600ms) that found significant differences between groups (Moseley et al. 2005, Hudson et al. 2006, Coslett et al. 2010, Reinersmann et al. 2010) and suggest that conscious or unconscious attempt to bias results for both RT and Accuracy are unlikely.

5.2.12 Conclusion

Differences in LRJT performance between groups suggest that central neurophysiological processes are implicated although further studies are required to elucidate the mechanisms accounting for altered performance. The results of the present study would appear to suggest complex interactions between psychological factors that interact with sensorimotor and integrative areas and these interactions may differ in relation to pain and disability. These results could explain some of the heterogeneity in the results of studies of the LRJT in participants with MSD. The present experiment in a heterogeneous population of participants with wrist/hand

conditions does suggest that cognitive/affective processes and motor impairments are factors that need to be considered when attempting to understand LRJT studies and that results in the performance of this task is not a simple reflection of pain, symptom duration or the specific musculoskeletal skeletal condition or injury. These factors (cognitive/affective processes and motor impairments) have been largely ignored in the literature. A better understanding of the significance and mechanisms associated with changes in LRJT performance in participants with MSD by associating other clinical and experimental measures of sensory, proprioceptive, motor function, cognitive and affective processes would be necessary. As the LRJT has also been utilized as a top-down form of intervention by targeting cortical rather than peripheral changes with some success (Bowering et al. 2013), similar interventions may be of benefit for individuals with MSD of the wrist/hand.

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5.3 Left Right Judgement Task and sensory, motor, cognitive and psychosocial assessment in participants with musculoskeletal disorders of the wrist/hand

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Disclosure

As the principal author of this manuscript, I confirm that I was responsible for subject recruitment, participated in all the experimentation, data processing, statistical analysis and writing of the manuscript. Dr Higgins, Dr Bourbonnais, Dr Danino, Dr Harris and I were involved in the elaboration of the project and scientific and ethical review processes. Maxime Mireault and I were involved in the experimentation. All authors where involved in the revision of the manuscript.

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All authors are listed and have contributed substantially to the manuscript.

5.3.1 Preface

The previous article had demonstrated changes in LRJT performance in the participants with MSD of the wrist/hand. The review of literature highlighted that persons with MSD often demonstrate an array of changes in sensory and motor function. The review of literature also highlighted that the LRJT involves the activation of a number of cortical areas involved in attention, sensory integration, movement planning and execution. Therefore, altered LRJT performance in the participants in the previous study with MSD of the wrist/hand may not be specifically attributed to changes in the body schema only but may also be a reflection of differences in cognition, psychological factors, and motor performance. We therefore elaborated a study that investigated sensory, motor, cognitive, psychological aspects related to pain as well as self-reported disability and LRJT performance to better understand the associations between LRJT performance and these different measures.

The general objective of the thesis was to determine if there were changes in sensorimotor processes in participants with MSD of the wrist/hand. As several different cortical regions appear to be involved in the LRJT task, an understanding of the relationship between these measures will help to determine if the LRJT performance is specifically related to measures of sensory and motor function or is attributed to other mechanisms in part or in whole which is related to specific objective 4 of the thesis. We hypothesized that LRJT performance would be related to measures in all domains measured, including sensory and motor function, but also cognitive factors, and possibly psychological aspects related to pain consistent with multidimensionality of the pain experience and the imaging studies demonstrating distributed cortical activation with the LRJT.

5.3.2 Abstract

Studies suggest that the Left Right Judgment Task (LRJT) implicates cortical regions involved with attention, sensorimotor integration, movement planning and execution. We hypothesized that LRJT performance would be associated with sensory, motor and cognitive functions. Sixty-one participants with MSD of the wrist/hand participated in an exploratory study assessing sensory (two-point discrimination, pressure pain thresholds), motor (grip strength, Purdue pegboard test), cognitive (Stroop tests, motor imagery ability) and pain related (West Haven Yale Multidimensional Pain Inventory) as well as disability (Disability of the Arm, Shoulder and Hand). Multiple linear regression found measures of cognitive and motor function, participation in general activities, and the taking of pain medications as independent variables of LRJT hand accuracy performance. A subset of the sample who took pain medications performed more poorly in both LRJT accuracy ($p=0.001$) and reaction time of the right hand ($p=0.009$). These participants had higher pain severity scores ($p=0.010$), were more likely to describe their pain as constant ($p=0.024$) and had poorer cognitive ($p=0.014$) and motor function ($p=0.005$). The results suggest the need to consider sensory, motor and cognitive factors when attempting to understand differences in study findings and identifying persons who may benefit from cognitive based interventions in addition to conventional treatments.

5.3.3 Perspective

This study suggests that the recognition of laterality of images is related to sensory, cognitive, and motor processes. These factors help to understand discrepancies in study results involving the mental rotation task and may help to identify those persons who would benefit from cognitively driven rehabilitation in addition to peripheral treatment.

5.3.4 Keywords

Pain, implicit motor imagery, sensorimotor integration, disability, motor function, motor imagery ability, attention

5.3.5 Abbreviations

DASH:	Disability of the Arm, Shoulder and Hand
JPS:	Joint Position Sense
LRJT:	Left Right Judgment Task
MIQ-VMI:	Motor Imagery Questionnaire – Visual Motor Imagery
MLR:	Multiple Linear Regression
MPI:	West Haven Yale Multidimensional Pain Inventory
MSD:	Musculoskeletal Disorders
PPG:	Purdue Pegboard Test
PPT:	Pressure Pain Threshold
TPD:	Two Point Discrimination

5.3.6 Introduction

Studies with persons experiencing Musculoskeletal Disorders (MSD) demonstrate peripheral (Hurley et al. 1997; Lysholm et al. 1998; Brumagne et al. 1999; Fischer-Rasmussen and Jensen 2000; O'Sullivan et al. 2003) and cortical sensory (Flor et al. 1997; Giesecke et al. 2004; Lloyd et al. 2008) and motor changes (Ochi et al. 1999; Ochi et al. 2002; Strutton et al. 2003; On et al. 2004; Strutton et al. 2005; Héroux and Tremblay 2006; Tsao et al. 2008; Kapreli et al. 2009; Berth et al. 2009; Berth et al. 2010; Schwenkreis et al. 2010; Tsao, Druitt, et al. 2010; Tsao, Galea, et al. 2010; Schabrun, Hodges, et al. 2014; Elgueta-Cancino et al. 2015; Bradnam et al. 2015; Ngomo et al. 2015; Shanahan et al. 2015). Peripheral sensory and cortical sensorimotor changes appear to be related to the concept of body schema, a representation of the body position in relation to the environment (Lotze and Moseley 2007). The body schema in turn is implicated in sensorimotor integration, the ability of the central nervous system to integrate different sensory stimuli and to transform this input into motor actions to effectively engage with the environment (Machado et al. 2010). An altered body schema is believed to account for some of the experimental and clinical findings including the ability to recognise the laterality of presented images (Lewis et al. 2007; Reinersmann et al. 2010; Bray and Moseley 2011; Reinersmann et al. 2012; Schmid and Coppieters 2012).

The Left Right Judgement Task (LRJT) involves determining, as accurately and as quickly as possible, if an image of a body part is of the left or right side. LRJT performance is assessed with Reaction Time (RT), the time taken to identify the laterality of the image of a body part, and Accuracy, the correctness of the given response. The LRJT appears to involve the body schema as accuracy and RT are affected by both the position of the participant's anatomical part in space and the number of conformations that would be required to perform the movement from

the participant's starting position to that seen on the image (Schwoebel et al. 2001; Schwoebel et al. 2002; Shenton et al. 2004; Ionta et al. 2007). Imaging studies demonstrate that the LRJT is associated with activation of subcortical and cortical structures including frontal, pre-motor areas, basal ganglia, cerebellum and associative areas in the parietal cortex (Kosslyn et al. 1998; Parsons 2001; Ionta et al. 2007). The LRJT therefore appears to be related to processes involved with attention, sensorimotor integration, movement planning and execution (Parsons 2001; Moseley et al. 2005).

Studies involving the LRJT have been performed with persons experiencing MSD with variable findings. Participants with arm/shoulder pain have demonstrated increased RT bilaterally compared to controls with (not in the hand and shoulder) and without pain (Coslett et al. 2010b). Participants with chronic back pain have demonstrated decreased LRJT accuracy that was most affected in subjects with bilateral back pain (Bray and Moseley 2011) while another study found no difference in accuracy and RT between participants with low back pain and healthy controls (Linder et al. 2016). Participants with knee osteoarthritis had decreased accuracy for images of the feet on both sides and hands on the left side (Stanton et al. 2012). Participants with carpal tunnel syndrome have decreased accuracy compared to healthy control subjects when viewing an image on the same side as their affected hand and of neck images, but no change with images of feet (Schmid and Coppieters 2012). Participants with chronic cervical pain demonstrated no differences in LRJT performance of neck and feet images compared to healthy controls (Pedler et al. 2013) and decreased accuracy in another study (Elsig et al. 2014). We have recently found impaired performance in this LRJT in subjects with chronic wrist/hand pain (Pelletier et al. 2018). There is presently limited understanding of why some participants with MSD demonstrate changes in accuracy, others RT, and some demonstrate no changes at all. Studies

involving the LRJT often have neglected to control for the factors of attention and motor imagery ability and may help to explain some of the variability across studies.

As imagery studies suggest that LRJT requires activation of cortical regions involved with attention, sensorimotor integration, movement planning and execution and these processes are affected in persons with MSD we therefore hypothesized that the LRJT performance in persons with MSD would be related to clinical measures of sensory, motor and cognitive function. Elucidating the different functional processes associated with LRJT performance in persons with MSD will help to determine those individuals that may benefit from cognitively driven treatments in addition to peripheral conventional rehabilitation and may also provide some clarity for the diversity of findings in the literature.

5.3.7 Methods

This was an exploratory observational cross-sectional study. The protocol and procedures conformed to the Declaration of Helsinki. The study was conducted at the hand clinic at the Centre hospitalier de l'Université de Montréal, Notre Dame hospital between June and December 2017. Ethical approval was granted from the institutional review board (CÉR-CHUM 16.372). Participants for the study were recruited when attending the hand clinic for consultation with plastic surgeons specialising in wrist and hand disorders. Participants were screened in the waiting area to explain the nature of the study, the requirements for their participation, and eligibility. Participants were required to be 18 years and older, experiencing a MSD of the wrist/hand in their right dominant side that impacted their activities of daily living, were able to follow instructions and answer questionnaires in English or French, suffer from no known neurological condition that impacted cognitive function, and no MSD of the lower extremities. Verbal and written informed consent were obtained prior to the commencement of the study.

Demographic and descriptive information including gender, age, education, diagnosis, symptom duration, education, areas of pain, and taking of pain medications were documented. Handedness was verified utilizing the Edinburgh Handedness Inventory (Oldfield 1971).

5.3.7.1 Dependent variable

The LRJT involved determining if an image of hands and feet were of the left or right side utilizing the Recognise™ (Neuro-orthopedic Institute, Adelaide, South Australia) software (Wallwork et al. 2013; Linder et al. 2016; Breckenridge et al. 2017). The LRJT involved a block of 40 images of hands and of 40 images of feet presented on a plain (vanilla) background, with a maximum duration per image of 5 seconds, on an 8-inch computer tablet. Images for feet were included given the variability in the literature of altered LRJT performance in non-injured/painful areas (Schmid and Coppieters 2012; Stanton et al. 2012) and as a control. Participants were instructed not to move their hands or feet to assist in determining laterality and to answer, "as quickly and accurately as possible" by depressing the Left or Right button on the tablet screen that matches the laterality of the image presented. Participants were given the chance to practice on 10 images before proceeding with the actual tasks. The order of the block of images of hands and feet was randomized across participants. Results were displayed for accuracy (percentage of correct responses) and reaction times (seconds).

5.3.7.2 Independent variables

5.3.7.2.1 Sensory measures

The West Haven-Yale Multidimensional Pain Inventory (MPI) (Kerns et al. 1985; Riley III et al. 1999) was utilized to assess subjective pain and measure the impact on patients' activities of daily living of their condition. The MPI consists of fifty-one questions answered on a 7-point Likert scale. Subscales involve grouping of questions scored between 0 and 6 on a 7-point Likert scale. In addition to pain severity, the measure assesses pain interference, life control, affective

distress as well as participation in leisure, social, household and work activities that are scored between 0 and 6. It is a well-researched and utilized instrument in research. Participants were also asked if their pain was constant or intermittent. Constant has been described by patients with osteoarthritis as distressing and may have behavioral implications (Hawker et al. 2008). It has also been proposed that constant pain may be more important in for inducing neuroplastic changes in the CNS (Moseley and Flor 2012).

Pressure Pain Threshold (PPT) was determined by using a digital pressure algometry (Wagner Instruments, Greenwich, CT, USA, model# Wagner FPX25). PPT was measured bilaterally on the palmer aspect of the first carpometacarpal joint and the hook of the hamate. The average of three trials was recorded (Nussbaum and Downes 1998; Chiarotto et al. 2013). The order of assessment for the site of the hand was randomized across subjects.

Tactile acuity was assessed with the Two-Point orientation Discrimination tasks (TPD) utilizing a hand-held caliper (Fowler, Model # 54-101-150-2, Newton, MA, USA) (Dellon et al. 1987; Catley et al. 2013). The participants were blindfolded and asked to indicate if they felt one or two points of contact. When two points were indicated, they were required to state if the points of contact were oriented vertically of horizontally (Tong et al. 2013). The test was performed in both hands over the hypothenar and thenar eminences. To attempt to control for pressure of application the caliper was held at the end and only the weight of the caliper head was utilized to apply pressure. Assessment was performed in ascending and descending order with separations between 4 and 14 mm. Two vertical and horizontal trials were performed at each site for each distance of separation. The distance at which the participant consistently had 75% correct responses for the thenar and hypothenar eminences were recorded.

Proprioception was measured by evaluating Joint Position Sense (JPS). JPS was performed in the same manner as described by Kalisch et al (2012) where subjects were blindfolded and instructed to compare sizes of two polystyrene balls of different diameters placed in their hands. Three different diameter polystyrene reference balls (7.0, 8.0, 9.6 cm diameter) were placed in the participant's left hand by the examiner. A second polystyrene ball, of seven possible different diameters (6.6, 7.0, 7.3, 8.0, 9.0, 9.6, 10 cm diameter), were placed in the right (affected) hand. Participants were instructed to squeeze the polystyrene balls and then relax the tension to control for thixotrophy effects influencing JPS (Tsay et al. 2015). They were not permitted to manipulate or turn the balls. The participants were required to verbalize if the polystyrene ball in the right hand was smaller, larger or the same size as the reference ball placed in the left hand within 5 seconds. Therefore, 3 reference balls were compared to 7 different polystyrene balls of different diameters for a total of 21 comparisons (Kalisch et al. 2012). The number and direction of errors were recorded.

5.3.7.2.2 Motor performance measures

Motor performance was assessed by dynamometric evaluation of strength performed utilizing a hand-held Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL, USA) following recommended protocols (Mathiowetz et al. 1984). Participants were asked to squeeze the handle as hard as possible and were provided with verbal encouragement. Three trials were performed on each side, alternating from side to side. The maximum value was recorded. The reliability and validity of the this task has previously been documented (Mathiowetz et al. 1984).

Fine and gross motor function was assessed with the Purdue Pegboard test (PPG) (Lafayette Instruments, Lafayette IN, USA, Model #32020A) a standard manual dexterity test commonly utilized in research and in a clinical setting that involves placing pins in slots with their right

hand, left hand and both hands in 30 second time epochs. A total score consists of these three measures. Finally, participants perform the building of small assemblies involving pins, washers and collars in a one-minute epoch. The PPG has been assessed for reliability and validity (Tiffin and Asher 1948; Buddenberg and Davis 2000).

5.3.7.2.3 Disability measure

Disability of shoulder, arm and hand questionnaire (DASH) was utilized to assess both symptoms and functional status in patients with upper extremity MSDs. It is a self-rated assessment with documented construct validity and reliability (Hudak et al. 1996; Gummesson et al. 2003)

5.3.7.2.4 Cognitive measures

Studies of the LRJT allude to attention and motor imagery ability as possible confounding factors explaining experimental results in LRJT studies (Roelofs et al. 2002; Dick and Rashiq 2007; Stanton et al. 2012). Therefore, selective attention was evaluated utilizing a modified Stroop test (Stroop 1935) with the Encephalapp application installed on an 8 inch computer tablet (Bajaj et al. 2015). The task involved the words red, green, blue or a neutral stimulus (number signs - ###) randomly presented and written in red, green or blue colours. Participants indicated as quickly and as accurately as possible the colour in which the word or neutral stimulus was presented by depressing the keys at the bottom of the screen (Red, Green, Blue). The keys indicating the colours were also randomized and not fixed in a specific order. The participants were given practice runs until they successfully preformed the task with 10 images without making an error. The time taken to perform 2 successful trials of 10 images without making an error was recorded. Motor Imagery Ability was assessed by the Movement Imagery Questionnaire – Revised Second version (MIQ-RS) (Gregg et al. 2010).

5.3.8 Sample size and statistical analysis

Sample size was predetermined based upon an $\alpha = 0,05$, power $(1-\beta) = 0,8$, 6 independent variables, and a moderate effect size of 0.25 (corresponding to coefficient of determination values of roughly 0.3-0.4). The minimal sample size required is 61 (http://www.statstodo.com/SSizMReg_Pgm.php).

Statistical analysis was performed utilizing GraphPad Prism 7 (GraphPad Software Inc, La Jolla, CA, USA) & and SPSS 24 (IBM Corporation, Armonk, New York, USA) statistical software. Normality of data was assessed by visual inspection of the data and D'Agostino Pearson Normality Test.

Differences between LRJT performance measures between hands and between feet were performed utilizing paired T-tests. Pearson correlation coefficients were performed between LRJT performance (Accuracy and RT) with the independent variables. Adjustments for multiple comparisons were made when necessary using the False Discovery Rate Benjamini-Hochberg procedure with an $\alpha<0.05$ (Benjamini et al. 1995; Verhoeven et al. 2005).

Multiple Linear Regression (MLR) models were performed for each of the dependent variables (LRJT Accuracy and LRJT RT for the hands and feet) with the sensory, motor and cognitive measures. Models were checked for multicollinearity and homoscedasticity. The best Multiple Linear Regression Model was performed by first inserting confounding variables, measures of cognitive function (Stroop Test) and Motor Imagery Ability, and subsequently inserting different permutations of the independent variables, the choice influenced by correlation coefficients values and relevance. Choice of best model was based upon minimizing of the Mean

Squared Error (MSE), including independent variables were the coefficients had p values below p=0.10, and had the highest R and R^2 adjusted values.

As Pain Medication was a strong and significant predictor in the multiple linear regression model for LRJT performance Accuracy, a post hoc analysis was performed to compare differences between participants who did (PainMeds) and did not take pain medication (NoPainMeds). Paired T-tests were performed on demographic, pain and disability measures between groups with Welch corrections as not to assume equality of variances. Paired comparisons where performed for LRJT Accuracy and Reaction Time between these groups. As LRJT performance data violated the assumptions of homogeneity and equality of variance, Mann Whitney U nonparametric tests were performed.

5.3.9 Results

Sixty-one subjects participated in the experiment (31♂, 29♀). Participants experienced heterogeneous MSD of the wrist and hand including post-operative fractures/amputation, tendinitis, first carpometacarpal osteoarthritis, Dupruytren's, Trigger finger, and wrist sprains. Descriptive information is found in table 5.3.1. Thirteen subjects took pain medication on the day of the evaluation. Twenty-nine participants described their pain as constant.

5.3.9.1 Left right judgment task - hand accuracy and reaction time

No difference was found in LRJT accuracy or reaction time between hands and between feet (see Figure 5.3.1).

Table 5.3.1: Descriptive and demographic information

	Mean	Standard Deviation
Age (years)	55.82	13.57
Symptom Duration (months)	43.68	45.79
West Haven Yale Multidimensional Pain Inventory (max scores – 6)		
Pain Severity	3.09	1.17
Pain Interference	3.11	1.38
Life Control	3.88	1.24
Affective Distress	2.79	1.27
General Activities	2.69	0.95
Disability of Arm, Shoulder and Hand (DASH)	42.98	17.62
Pressure Pain Thresholds (kg)		
Right Hand	6.93	3.83
Left Hand	8.42	4.89
Two Point Discrimination (mm)		
Right Hand	10.92	2.89
Left Hand	10.16	2.72
Joint Position Sense (errors)	3.82	1.51
Purdue pegboard scores		
Right Hand	12.44	3.48
Left Hand	13.20	2.29
Both Hands	10.43	3.30
Total	35.31	9.50
Assemblies	21.89	7.86
Grip Strength (kg)		
Right Hand	23.60	13.35
Left Hand	30.65	14.20
Stroop Time (seconds)	37.25	7.99
Motor Imagery Questionnaire (maximum score - 98)	67.34	23.94

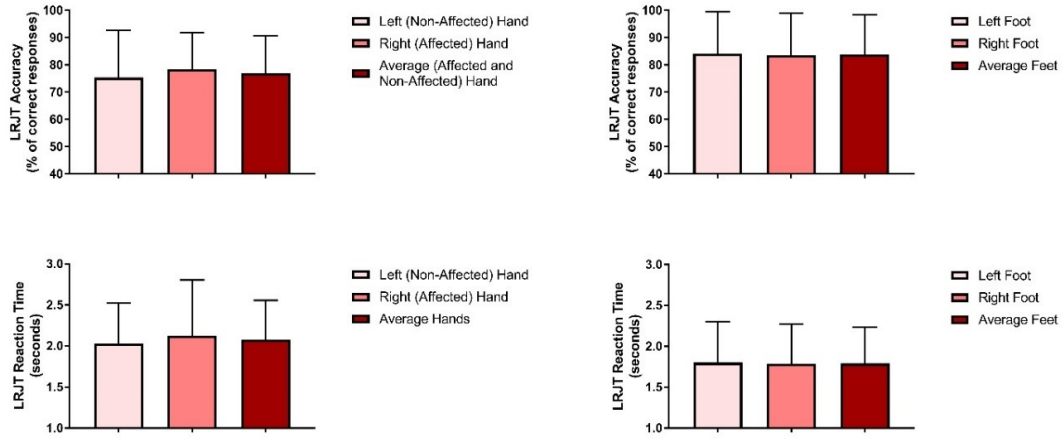

Figure 5.3.1: Left Right Judgment Task (LRJT) performance in participants with musculoskeletal disorders of the wrist/hand Mean±Standard Deviation.

5.3.9.2 Multiple Linear Regression (MLR) models

5.3.9.2.1 Left right judgment task right (affected) hand accuracy

The best fitting MLR model ($F_{2,56}$=4.11, p=0.002) included pain medication, MPI General Activities, Two Point Discrimination of the Right Hypothenar, and Purdue pegboard values of the left hand, and after entering Stroop Test and motor imagery ability scores, accounted for an additional 20% of explained variance (R^2 adjusted) (see Tables 5.3.2 and 5.3.3).

Table 5.3.2: Linear regression model for Left Right Judgment Task accuracy for the hands

LRJT Accuracy						**Change Statistics**				
		R	**R^2**	**Adjusted R^2**	**Std. Error of the Estimate**	**R^2 Change**	**F Change**	**df1**	**df2**	**Significant F Change**
Right Hand										
	1	.26	0.07	0.04	13.09	0.07	2.105	2	56	0.131
	2	.57	0.32	0.24	11.61	0.25	4.819	4	52	0.002
Left Hand										
	3	.46	0.21	0.18	15.67	0.21	7.353	2	56	0.001
	4	.55	0.30	0.25	15.03	0.09	3.430	2	54	0.040

1. Predictors: (Constant), Motor Imagery Questionnaire Visual Motor Imagery, Stroop Time
2. Predictors: (Constant), Motor Imagery Questionnaire Visual Motor Imagery, Stroop Time, Purdue pegboard test Left Hand, MPI General Activities
3. Predictors: (Constant), Motor Imager Questionnaire Visual Motor Imagery, Stroop Time
4. Predictors: (Constant), Motor Imager Questionnaire Visual Motor Imagery, Stroop Time, Purdue pegboard test Left Hand, MPI General Activities

5.3.9.2.2 Left right judgment task left hand accuracy

The best fitting MLR model ($F_{4,54}$=5.71, p=0.001) included pain medication, MPI General Activities and Purdue pegboard values of the left hand, and after entering Stroop Test and motor imagery ability scores, accounted for only an additional 4% of explained variance (R^2 adjusted) (see Tables 5.3.2 and 5.3.3).

Table 5.3.3: Coefficients of best fitting linear regression model for Left Right Judgement Task hand accuracy

LRJT Accuracy							Confidence Intervals (95%)	
		Unstandardized Coefficients B	Standard Deviation	Standardized Coefficients Beta	t	p	Lower Bound	Upper Bound
Right Hand								
1	**(Constant)**	69.75	13.49		5.169	0.000	42.71	96.78
	Stroop Time	-0.06	0.24	-0.037	-0.252	0.802	-0.55	0.43
	MIQ VMI	0.29	0.17	0.245	1.686	0.097	-0.05	0.63
2	**(Constant)**	53.61	18.70		2.867	0.006	16.09	91.13
	Stroop Time	0.24	0.23	0.15	1.039	0.304	-0.27	0.71
	MIQ VMI	0.07	0.17	0.06	0.381	0.705	-0.28	0.40
	Pain Medications	-8.34	4.14	-0.26	-2.017	0.049	-16.64	-0.04
	MPI General Activities	3.36	1.85	0.24	1.818	0.075	-0.35	7.07
	TPD Hypothenar right hand	-1.12	0.57	-0.24	-1.965	0.055	-2.26	0.02
	Purdue pegboard left hand	1.39	0.73	0.24	1.815	0.075	-0.15	2.92
Left Hand								
3	**(Constant)**	74.70	16.15		4.625	0.000	42.35	107.06
	Stroop Time	-0.470	0.29	-0.22	-1.613	0.112	-1.05	0.11
	MIQ VMI	0.48	0.20	0.31	2.331	0.023	0.07	0.88
4	**(Constant)**	43.43	21.19		2.050	0.045	0.96	85.91
	Stroop Time	-0.34	0.29	-0.16	-1.183	0.242	-0.92	0.24
	MIQ VMI	0.24	0.22	0.15	1.084	0.283	-0.20	0.67
	MPI General Activities	4.73	2.33	0.26	2.030	0.047	0.06	9.40
	Purdue pegboard left hand	1.74	0.94	0.23	1.844	0.071	-0.15	3.62

MIQ VMI: Motor Imagery Questionnaire – Visual Motor Imagery; MPI: West Haven Yale Multidimensional Pain Inventory; TPD: Two Point Discrimination

5.3.9.2.3 Left right judgment task right hand reaction time

The best fitting MLR model for LRJT right hand reaction time ($F_{2,56}$=4.42, p=0.017) included only the variables Stroop time and motor imagery ability (see Tables 5.3.4 and 5.3.5).

Table 5.3.4: Linear regression model for the Left Right Judgement Task right hand reaction time

					Change Statistics				
	R	R^2	Adjusted R^2	Std. Error of the Estimate	R^2 Change	F Change	df1	df2	Significant F Change
1	.37	0.14	0.11	0.64	0.14	4.418	2	56	0.017

1. Predictors: (Constant), Motor Imager Questionnaire Visual Motor Imagery, Stroop Time

Table 5.3.5: Coefficients of best fitting linear regression models for Left Right Judgement Task right hand reaction time

						Confidence Intervals (95%)	
	Unstandardized Coefficients B	**Standard Deviation**	**Standardized Coefficients Beta**	**t**	**p**	**Lower Bound**	**Upper Bound**
(Constant)	1.71	0.61		2.583	0.012	0.38	3.03
Stroop Time	0.02	0.1	0.26	1.828	0.073	-0.00	0.05
MIQ VMI	-0.01	0.008	-0.17	-1.226	0.225	-0.03	0.01

MIQ VMI: Motor Imagery Questionnaire – Visual Motor Imagery

5.3.9.2.4 Left right judgment task left hand reaction time

No statistically significant model could be produced with LRJT left hand reaction time entered as the dependent variable.

5.3.9.2.5 Left right judgment task feet accuracy and reaction time

Multiple linear regression models using LRJT feet accuracy and reaction time as the dependent variables explained (R^2 adjusted) 27-35% of the variance and the Stroop time and MIQ-VMI scores accounted for 78% and 86% of the explained variance of the models.

5.3.9.3 PainMed vs NoPainMed

LRJT performance was compared for the data of two groups, those who took Pain Medication (PainMeds) (n=13) (10 participants - acetaminophen, 2 participants – Lyrica, and 1 participant Tramadol) on the day of the evaluation and those who did not (NoPainMeds) (n=48). A difference in LRJT accuracy between the two groups was found for both the left and right hands (see Figure 5.3.2). LRJT performance values were lower in the participants who had taken pain medication on the day of the evaluation.

There was no difference in age, gender or symptom duration between these two groups. After controlling for multiple comparisons, pain severity, motor function, Stroop test times, and DASH scores were significantly different between groups. Participants in the PainMeds group ($\bar{x}$=3.82±0.32) had higher Pain severity scores (p=0.01, t=2.67, df 58; mean difference: -0.93±0.35; CI: -1.63 - -0.23) than the NoPainMeds ($\bar{x}$=2.89±0.16). Self-reported disability of the DASH scores were higher in the PainMeds group ($\bar{x}$=54.25±6.40) than the NoPainMeds group ($\bar{x}$=40.10±2.22) (p=0.01, t=2.60, df=57; mean difference: -14.14±5.44; CI95%=-25.03 to -3.26). Purdue pegboard Both hands score was lower in the PainMed group ($\bar{x}$=7.62±1.01) compared to the NoPainMed ($\bar{x}$=11.09±0.40) group (p=0.005, t= t=3.29 df=16.01, mean

difference = 3.57 ± 1.09, $CI_{95\%}$= 1.27 to 5.88). Stroop times were greater in the PainMeds group ($\bar{x}$=42.9±2.33) than the NoPainMeds group ($\bar{x}$=35.8±1.08) and was statistically significant (p=0.01, t=2.77, df=16.04, mean difference: -7.09 ± 2.56, $CI_{95\%}$= -12.53 to -1.66). Participants in the PainMed group ($\bar{x}$=0.77±0.12) were more likely than the NoPainMed group ($\bar{x}$=0.42±0.07) to indicate that they had constant pain (p=0.02, t=2.32, df=59; mean difference=-0.35±0.15, $CI_{95\%}$= -0.66 to -0.05) however this was not statistically significant after controlling for multiple comparisons (Benjamini-Hochberg P-value=0.058). MPI Affective Distress values were greater in the PainMeds group ($\bar{x}$=3.31±0.33) than the NoPainMeds group ($\bar{x}$=2.64±0.19) but was not statistically significant (p=0.09, t=1.77, df=20.5, mean difference: -0.66 ± 0.37, $CI_{95\%}$= -1.44 to 0.12). There were no differences in Motor Imagery Ability between groups (p=0.60, t=0.53, df=18.72, mean difference: 4.03 ± 7.56, $CI_{95\%}$= -11.81 to 19.87).

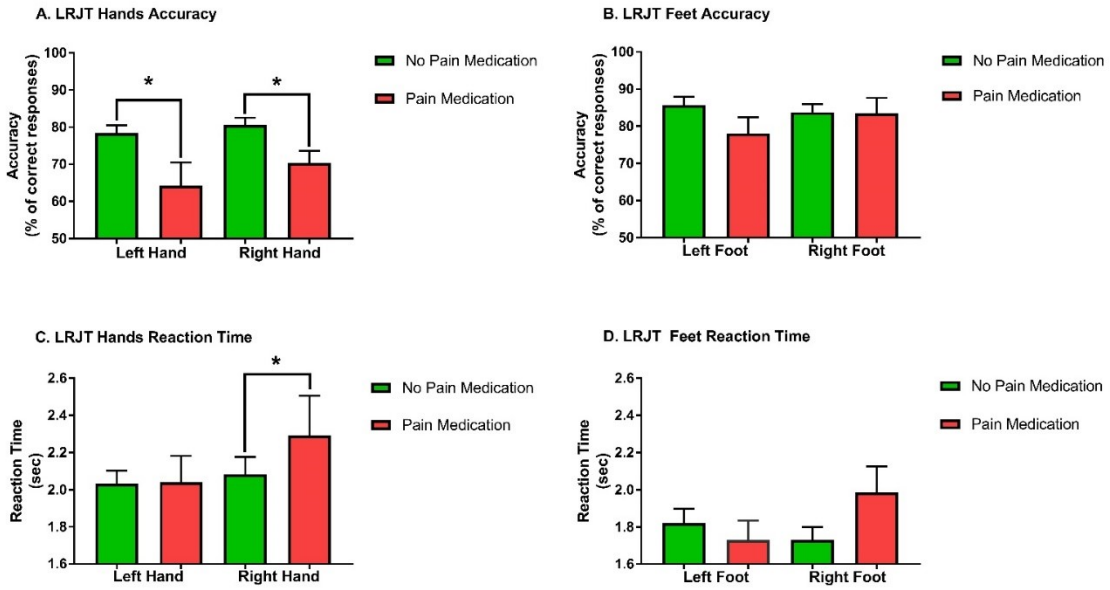

Figure 5.3.2: Left right judgment task accuracy and reaction time in participants who did and did not take pain medications on the day of the evaluation

LRJT performance accuracy and reaction time in participants who were taking pain medication (Pain Medication) and not taking pain medication (No Pain Medication) on the day of the evaluation. $\bar{x}$±SEM. * False Discovery Rate Statistical significance below α=0.05

5.3.10 Discussion

We hypothesized that LRJT performance of the hand would be related to measures of cognitive, sensory and motor function. We found that measures of cognitive function, Stroop test scores and motor imagery ability significantly explained the variance of LRJT in all linear regression models with the exception of LRJT left hand reaction time. Sensory and motor processes explained most (86%) of the variance in the linear regression model for LRJT accuracy in the right, affected hand only. Novel findings include the presence of variables related to motor function, a measure of participation in social and leisure activities (MPI General Activities) and the taking of pain medication in the multiple linear regression model with LRJT accuracy of the right (affected) hand entered as the dependent variable. In contrast, the models for LRJT RT of the hands and LRJT accuracy and RT for the feet were largely determined by the confounding variables of attention and imagery ability that accounted for 72-100% of the explained variance in the linear regression models.

5.3.10.1 Left right judgment task, motor imagery ability and the Stroop test

The LRJT is believed to involve implicit motor imagery where the participant makes an initial impression of laterality, and then mentally imagines moving their hand in the same position as the image, and then either confirming or rejecting their initial impression of laterality (Moseley 2004c). The belief that the LRJT involves implicit motor imagery is based upon at least two experimental findings. Imaging studies involved in the LRJT demonstrate a similar pattern of activation as motor imagery (Kosslyn et al. 1998; Ganis et al. 2000). Secondly, the time to imagine the task is similar to the time to execute the task (Parsons 1994). However, there appears to be some variability in the ability of persons to perform motor imagery. When evaluating the use of motor imagery as a tool to enhance motor performance, motor imagery ability is associated with improved performance (Gregg et al. 2010). Therefore, it is unsurprising that

motor imagery ability was correlated with LRJT performance and explained a significant portion of the variance in all the models except LRJT accuracy in the right hand. Differences in LRJT performance may be, at least in part, attributed to differences in motor imagery ability and not simply changes in the body schema.

The ability to perform the LRJT also requires selective attention. This is supported by imaging studies that demonstrate the activation of the cortical structures involved in working memory including the dorsolateral prefrontal cortex (Kosslyn et al. 1998; Ganis et al. 2000). It is therefore important, when attempting to understand the different processes involved in LRJT performance to control for attention and motor imagery ability (Reinersmann et al. 2010). The findings that the multiple linear regression models of LRJT accuracy and RT of the feet and LRJT RT of the hands are consistent with imaging findings of activation of frontal areas, support the importance of including these variables in the linear regression models, and when utilizing the LRJT to assess the body schema as factors that must be investigated and controlled.

5.3.10.2 Left right judgment task, sensory and motor function

A measure of sensory function, TPD, was also was included in the linear regression model of LRJT performance accuracy in the right, affected, hand only. Stanton et al (2013) previously found a correlation between TPD thresholds and LRJT Accuracy in participants with back pain, but not in subjects with knee osteoarthritis (Stanton et al. 2013). In healthy subjects Botnmark and al (2016) found no correlation between TPD of the shoulder and LRJT performance (Botnmark et al. 2016). TPD is believed to be correlated with organisation in S1 (Pleger et al. 2006) and therefore may be associated with processes involved in sensorimotor integration. In light of the present results in symptomatic patients TPD appears to be one of several variables that are correlated with LRJT performance in the affected area.

In a previous study we found a stronger relationship between LRJT performance and Purdue pegboard test scores in the healthy control group (Pelletier et al. 2018). The present findings, in a much larger sample, found linear regression models of both hands with LRJT accuracy entered as the dependent variable in both hands had stronger correlations with motor performance of the left, unaffected, hand of the Purdue pegboard test. Purdue pegboard scores were higher for the left ($\bar{X}$=13.2±3.48) than the right side ($\bar{X}$=12.44±2.49) contrary to normative values that tend to be higher on the dominant side (Agnew et al. 1988). Botnmark et al (2016) found a significant correlation between LRJT RT and motor performance in healthy subjects. It is possible that the influence of motor function on LRJT performance is stronger on the uninjured side and healthy subjects, indicative that altered motor function is involved in changes in sensorimotor integration impacting LRJT performance.

5.3.10.3 Left right judgment task, pain medication and general activities

Two interesting findings were the inclusion of pain medications and MPI General Activities sub-scale in the linear regression models for LRJT right (affected) hand accuracy. The regression model and subsequent non-parametric tests found that participants who reported taking pain medications on the day of assessment performed more poorly on the LRJT Hand Accuracy. It is possible that taking the pain medication was simply a function of increased pain scores, and that pain severity is associated with the poorer LRJT performance. However, the link between pain severity and LRJT performance is unclear with several studies finding no association (Coslett et al. 2010b; Bray and Moseley 2011; Schmid and Coppieters 2012; Stanton et al. 2013). Furthermore, the weak/moderate correlation between pain severity and LRJT performance (R=-0.21 to 0.01) and pain medication and pain severity scores (R=0.38) makes this unlikely. Alternatively, it can be argued that pain medication may influence cognitive

function and is responsible for their inclusion in the regression model for the hands. We would have hypothesized that if the taking of pain medication would influence LRJT performance negatively by their influence on cognitive processes alone, it would decrease LRJT performance for both hands and feet and for reaction time more than accuracy. However, LRJT performance differences between those who took and did not take pain medications were largely specific to the right hand strongly suggestive that the impact of taking of pain medication was not attributed to a generalized effect of pain medication on cognitive function.

The participants who took pain medications demonstrated several differences with the participants who had not taken medication. They had higher pain severity scores, had high self-reported disability scores, poorer motor function and selective attention, and describing their pain as constant was close to statistical significance. Differences between nociceptive and neuropathic pain on central nervous system changes has previously been attributed to the differences between these two types of pain and the belief that neuropathic pain is more constant and unrelenting (Schwenkreis et al. 2010; Moseley and Flor 2012). Due to the multidimensionality of the pain experience associated with MSD there may be a cumulative effect of sensory (including pain), motor and cognitive factors that cause changes in LRJT performance. Further identification of these factors may help to determine those persons who would benefit from the inclusion of cognitively driven rehabilitation strategies in addition to conservative rehabilitative treatments (Dilek et al. 2018).

LRJT Hand Accuracy performance was also positively correlated with the MPI subset of General Activities. This subset is comprised of 18 questions related to the participation in household, work, leisure and outdoor activities. There was no correlation between MPI General

Activities with pain measures. There was however a statistically significant yet moderately strong negative correlation between MPI General Activities with the DASH regular and work modules scores (R=-0.33 and R=-0.52). This suggests that higher general activities scores are related to less self-reported disability. Although speculative, increased activities and participation may help to maintain the integrity of the body schema of the injured area through use. However, the participation in General Activities was specifically related to LRJT performance in the hands and not the feet. We would expect that increased participation in activities would equally affect the body schema and sensorimotor integration of the feet. A more plausible explanation is that participants involved in greater activities and participation have higher self-efficacy. Self-efficacy is defined as the confidence in performing/managing a particular behavior and in overcoming barriers (Denison et al. 2004). Greater self-efficacy has consistently been associated with better outcomes in persons with pain (Jackson et al. 2014). In participants with fibromyalgia, greater self-efficacy for pain and function significantly predicted physical activity measured with the Arthritis Impact Measurement Scale, Physical Function (includes mobility, physical and household activities as well as activities of daily living) explaining greater variance than demographics, disease severity, and psychological distress (Buckelew et al. 1995). In women with hand osteoarthritis, multiple linear regression found self-efficacy as the most significant predictor of performance measured with the Canadian Occupational Performance Measure comprising subsections related to self-care, productivity and leisure (Kjeken et al. 2005). Further research is required to understand these relationships.

Limitations

All experiments were performed in a single setting. The study included participants who were right handed and had a MSD of the right hand and may not be generalizable for the left hand. The participants who take pain medication was a small sample and a larger study would help to confirm results. Although the sample size was calculated a priori it possible that the MLR models may have been underpowered for the analysis of LRJT hand accuracy given the number of variables. The adjusted R^2 values for the multiple regression models did not explain the majority of the variance and therefore other variables are also implicated in the LRJT performance not included in the models.

5.3.12 Conclusion

The LRJT appears to be a multidimensional task that is related to sensorimotor but also cognitive processes. LRJT Accuracy in the right affected hand of participants with MSD was related to measures of cognitive, sensory and motor function. These differences in sensory, motor and cognitive function need to be addressed when attempting to understand differences in LRJT performance between groups. Differences in LRJT performance and conversely improvement in this task and clinical improvement associated with the performance of he LRJT may be associated with changes in any of these processes.

5.3.13 References

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Chapter 6 General Discussion

The objective of this thesis was to investigate for the presence of altered sensorimotor processes (corticospinal excitability and the body schema measured with the LRJT) in participants with chronic MSD of the wrist and hand. The second objective was to determine how these sensorimotor processes (corticospinal properties, LRJT performance) were related to pain, pain related factors, motor performance and disability. We hypothesized that there would be changes in sensorimotor processes (corticospinal properties and the body schema represented by changes in LRJT performance) in participants with MSD of the wrist/hand compared to healthy control participants. We also hypothesized that sensorimotor processes would be related differently with pain-related factors and motor performance between participants with and without MSD of the wrist/hand suggestive of altered sensorimotor integration.

Consistent with our first hypothesis changes in cortical sensorimotor processes (corticospinal excitability and LRJT performance) were found in participants with MSD of the wrist/hand compared to healthy control participants. Participants with MSD of the wrist/hand demonstrated increased corticospinal excitability of the APB in their affected hand that was related to pain severity and disability. Importantly, the relationship between measures of corticospinal excitability with measures related to pain, motor performance, and disability are novel findings that have not been consistently investigated and reported in the literature.

Also consistent with our hypothesis, participants with MSD of the wrist/hand demonstrated changes in LRJT performance. However, unlike corticospinal changes, the changes in LRJT performance were not associated with pain intensity, pain duration, or disability. LRJT performance was related to affective distress in participants with wrist/hand pain suggestive that cognitive-affective processes may influence LRJT performance. Consistent with our second hypothesis, there was a different relationship between LRJT performance and Purdue pegboard scores between participants with and without MSD suggestive of altered sensorimotor integration in the participants with MSD of the wrist/hand.

Finally, in a larger sample of participants with MSD of the wrist/hand we found that cognitive factors (Stroop test scores and Motor Imagery Ability) were related to LRJT performance for both feet and hands. These confounding factors for LRJT performance are at times mentioned

in the literature but have not been controlled for in the majority of studies involving the LRJT. LRJT performance accuracy was explained by cognitive factors (motor imagery ability, Stroop test). The addition of sensory (TPD), motor (Purdue pegboard scores), the taking of pain medications, and participation in general activities into the linear regression model explained a significant portion of the variance in the model for the affected hand. The findings from the multiple linear regression model suggest that LRJT performance in the right (affected) hand reflects changes in sensorimotor processes. Interestingly, a segment of this larger sample that took pain medication on the day of the treatment had decreased LRJT performance accuracy and RT of the affected hand compared to those persons who did not. The participants who had taken pain medication on the day of the evaluation had higher pain severity, more likely to describe their pain as constant, decreased Stroop test scores and had greater disability scores. The findings of a segment of the participants that had decreased LRJT performance may provide valuable insight into discrepancies of results in studies utilising the LRJT in participants with MSD. Collectively, these findings suggest that LRJT performance in general is associated with cognitive processes. LRJT accuracy of the affected hand specifically is related to measures of cognition, sensory function and motor performance that suggests altered body schema and sensorimotor integration. However, the inclusion of participation in varied work, social and leisure activities in the linear regression model for LRJT performance accuracy is a new finding. Altered LRJT accuracy is, in general, reflective of the multidimensionality of factors associated with chronic MSD and pain. Cognitive factors need to be accounted for when assessing differences in LRJT performance. Furthermore, the findings allude to the interrelationship between cognitive-affective, behavioural and sensorimotor processes in the sample population studied.

6.1 Changes in Corticospinal Excitability

Electrophysiological changes found in participants with MSD of the wrist/hand include a steeper slope of the I-O curves of the APB, but not of the FDI. The I-O curves are believed to reflect membrane excitability, the depolarization of an increasing number of corticospinal neurons influencing spinal motoneuronal projections to the targeted muscle, and possibly spinal motoneuronal excitability (van Kuijk et al. 2009; Smith et al. 2011). As the TMS intensity increases corticospinal neurons around the periphery of the core of excitable projections are

depolarized. These “new” previously subliminal corticospinal neurons have divergent and differing projections in the spinal cord, impinging onto possibly the same as well as different spinal motoneurons of the homonymous and synergistic muscles (Devanne et al. 2006; Lemon 2008).

An increase in the slope of the I-O curve may reflect a decrease in inhibition of corticospinal neurons, processes similar to long-term potentiation of existing synapses resulting in increased synaptic strength, reorganization including the growth of new synaptic connections, and/or changes in spinal motoneuronal excitability (Ridding and Rothwell 1997). The slope of the I-O curve provides an indication of general cortical excitability (Devanne et al. 1997) and changes in the area and volume (i.e density and strength) of corticospinal projections (Ridding and Rothwell 1997). However, I-O curves do not provide information as to the mechanisms responsible for the increase in MEP amplitudes at higher TMS intensities, and therefore does not indicate if the increased slope results from increased strength of the corticospinal projections and/or number of corticospinal neurons projecting onto the APB. It is however unlikely that the increase in the slope of the I-O curve for the APB in participants with MSD of the wrist/hand was the result of spinal motoneuronal changes. The decrease in Fwave persistence suggests that spinal motoneuronal excitability of the APB was decreased in the participants with MSD of the wrist/hand. The mechanisms underlying these changes in spinal motoneuronal excitability are unknown. Changes in spinal motoneuronal excitability may be the result of synaptic influence that act directly on the voltage gated ion channels of the spinal motoneurons. Neuromodulators may have a profound effect on spinal motoneuronal excitability as they affect the properties of the voltage gated ion channels and therefore affect the stimulus-response characteristics of the spinal motoneurons to synaptic input (Heckman et al. 2009). These neuromodulators include brain stem mediated mechanisms such as the locus coeruleus (norepinephrine) and the caudal raphe nucleus (serotonergic) that project to both the dorsal and ventral horn of the spinal cord (Hornung 2003; Samuels et al. 2008). However, the findings of the present study imply that the site of increased excitability of the APB is found within M1. The findings also suggest interaction between spinal and cortical processes to regulate motor activity.

There was no change in the measures of corticospinal excitability of the FDI. No change in excitability measures of the FDI and increased excitability in the I-O curve of the APB may

appear to be contradictory. However, these muscles have different innervations and are largely antagonist muscles during most functional tasks. Within M1 corticospinal neurons appear to be organized with a mixture of discrete and overlapping representations (Dechent et al. 2003; Devanne et al. 2006). Discrete representations allow for more refined motor control of individual motor units and muscles (Dechent and Frahm 2003; Devanne et al. 2006). Overlapping representations allow for the coordination of synergistic muscle recruitment (Dechent and Frahm 2003; Devanne et al. 2006). Enhanced somatotopic organization compared to other anatomical regions is reflective of the dexterity and intricate nature of the hand's movements and functions. There are strong horizontal connections between neurons in the motor cortex that function to coordinate different muscle synergies (Sanes and Donoghue 2000). However, these connections involve both excitatory and inhibitory connections. For example, muscle activation of the FDI results in a decrease in intracortical inhibition of the homonymous muscle, but is associated with an increase in intracortical inhibition in muscles not involved in the task (Stinear et al. 2003). The increase in corticospinal excitability in the APB, with no corresponding changes in corticospinal excitability in the FDI may be indicative of intracortical mechanisms to suppress involuntary muscle activity and reflect the prominent role of the thumb in hand movements. It is believed that the thumb is responsible for 60% of hand function (Kjeken et al. 2005). It is important to note that corticospinal excitability was assessed with these muscles at rest. Differences in corticospinal excitability may be found between resting and active muscles (Zoghi et al. 2003; Ortu et al. 2008; Jono et al. 2015).

The increased slope of the I-O curve for the APB in the affected hand of participants with MSD of the wrist/hand may be indicative of altered representation of the muscles in M1 (Ridding and Rothwell 1997). Experiments performed with participants utilizing experimentally induced pain consistently find decreased corticospinal excitability (Bank et al. 2013). Decreased corticospinal excitability is believed to be related to protection of the area of pain by impeding movement (Bank et al. 2013; Hodges and Tucker 2011). However, experiments performed in persons with chronic MSD demonstrate variable findings in regard to corticospinal and spinal motoneuronal properties.

Of the different corticospinal measures performed within experiments in subjects with MSD, TMS mapping has yielded the most consistent results. Several recent studies in participants with

chronic MSD have found changes in organization within M1 assessed with TMS mapping (Tsao et al. 2008; Tsao, Danneels, et al. 2011; Schabrun, Hodges, et al. 2014; Elgueta-Cancino et al. 2015; Massé-Alarie et al. 2017; Te et al. 2017). TMS mapping involves stimulation of grid points around the hotspot and allows for the determination of map volume and area (measure of the strength of the MEP elicited across the number of grid points in M1 that innervates a muscle), changes in representation, and changes of the central loci of activation (shifting of the central core of representation referred to as the centre of gravity) (Groppa et al. 2012). TMS mapping studies in participants with MSD have found decreases in the number of grid points that demonstrate activation peaks of corticospinal excitability of the muscles investigated, an overlapping and shifting of muscle representations, and changes in the central loci of activation of the representation of muscles investigated within the motor cortex in participants with MSD (Tsao et al. 2008; Tsao, Danneels, et al. 2011; Schabrun, Hodges, et al. 2014; Elgueta-Cancino et al. 2015). As previously stated, M1 is organised with a balance between discrete (individual) and distributed (overlapping) representations of muscles. This organisation is called functional somatotopy and is necessary for the selective activation of individual muscles (discrete) and for multi-joint synergistic coordinated movements (overlapping) (Sanes and Donoghue 2000; Schabrun, Hodges, et al. 2014). The overlapping of representation and the decrease in number of peaks found in participants with MSD compared to healthy controls are probably associated with altered motor control of the muscles apparent in persons with MSD (Falla and Farina 2008; Tsao, Danneels, et al. 2011; Hodges and Tucker 2011; Elgueta-Cancino et al. 2015). These neurophysiological changes associated with MSD are consistent with increased co-contraction often found in subjects with MSD (Tsao et al. 2008; Hodges and Tucker 2011; Schabrun, Hodges, et al. 2014; Te et al. 2017). For example, in the study by Tsao et al (2011), the corticospinal representation of the long/superficial fascicles of longissimus erector spinae was shifted posteriorly overlapping the representation of the short/deep fascicles of deep multifidus in participants with LBP (Tsao, Danneels, et al. 2011).

The I-O curves do not provide information on shifts in representation within the motor cortex. However, the differences between corticospinal measures of the APB and FDI may be associated with representational differences and a shifting of the representation of the muscles. The results of the first study presented in chapter 5 of the thesis may be indicative of changes in

representation within M1 that are not reflected by the corticospinal measures of excitability performed in the present experiment, notably rMT and I-O curves. Mapping experiments with TMS are more amenable to determine these representational changes.

Although speculative, as we did not specifically measure motor control changes between muscles performing complex motor tasks, the findings in the present study would be consistent with the model proposed by Hodges and Tucker (2011) to attempt to explain the variability of neurophysiological and clinical findings associated with chronic MSD. The changes in corticospinal properties and organization and altered spinal motoneuronal recruitment both within and between synergistic muscles is believed to be an attempt of the CNS to protect the area of injury, maximize function, and minimize functional loss (Hodges and Tucker 2011).

6.1.1 Factors that may account for the increase in corticospinal excitability of the APB

The increase in corticospinal excitability in the APB may be the result of the direct influence of nociceptive afferents on the motor cortex. Direct nociceptive influences on the motor cortex appear to be excitatory (Chen et al. 2013; Frot et al. 2013). Increased corticospinal excitability of the APB in participants with MSD of the wrist/hand and strong correlation between pain scores and the slope of the I-O curves would support this argument. The participants in the experimental group were, however, comprised of a heterogeneous sample. Only a third of the participants experienced pain specifically in the thumb (i.e. first carpometacarpal osteoarthritis), that would induce local nociceptor transduction and transmission that directly influence motor cortical excitability of the APB. This argues against a direct effect of nociceptive afferents on the motor cortex. The increased corticospinal excitability in the APB in a heterogeneous sample would suggest that direct nociceptive transmission to M1 is not the likely candidate to explain these findings.

Alternatively, changes in corticospinal excitability may be caused by altered peripheral sensory output associated with the MSD (Cohen et al. 1993) which in turn influences corticospinal properties in M1. Several studies have demonstrated changes in quantitative sensory testing not only in pain thresholds, but also changes in tactile acuity (Catley et al. 2014) and joint position sense (Hurley et al. 1997; Sharma and Pai 1997; Felson et al. 2009) suggestive of altered sensory and proprioceptive processes in persons with MSD. Literature indicates that changes in afferent

output from the periphery can alter properties and organization within both S1 (Jenkins et al. 1990) and M1 (Cohen et al. 1993; Plautz et al. 2000; Karl et al. 2001). For example, non-painful peripheral electrical stimulation results in changes in properties of corticospinal neurons in M1 (Chipchase et al. 2011a; Schabrun, Ridding, et al. 2012). There is evidence for long-term potentiation like changes in M1 associated with peripheral afferent stimulation of the median nerve involving the thumb and resulting in increased MEP amplitudes (Ziemann et al. 2004). Therefore, the literature supports the presence of altered sensory and proprioceptive processes in persons with MSD and that sensory peripheral output can result in changes in neuronal properties in both S1 and M1.

Finding altered corticospinal properties in M1 in participants with heterogeneous MSD of the wrist/hand may be indicative that the changes in corticospinal properties are the result of altered movement strategies. Altered movement strategies may result in changes within both S1 and M1 by two processes. First, altered movement patterns change sensory input to S1. S1 and M1 are tightly interconnected and altered movement may impact M1 via changes in S1 inducing changes in corticospinal properties and organization as discussed above. For example, focal hand dystonia is associated with repetitive movement of the digits and is common in musicians. Focal hand dystonia is clinically manifested by a loss of muscular coordination or voluntary control of repetitively trained movements (Altenmuller et al. 2009). Persons with focal hand dystonia demonstrate a blurring of the representations and loss of segregated neuronal activity of neurons both within S1 and M1 (Ikoma et al. 1996; Byl et al. 2000a; McKenzie et al. 2003; Schabrun et al. 2009).

Secondly, the cause of corticospinal changes in M1 may also be related to altered movement strategies that involve mechanisms associated with motor learning. Studies demonstrate that the impetus driving neuroplastic changes in corticospinal properties and organization in M1 are associated with motor learning (Plautz et al. 2000; Kleim and Jones 2008). Evidence also suggests that motor learning is mediated by factors such as attention, repetition, and behavioural salience (Rosenkranz et al. 2004; Stefan et al. 2004; Kleim and Jones 2008). Pain is behaviourally salient and is a powerful motivator for behavioural changes (Navratilova and Porreca 2014). Pain may positively impact motor learning by orienting attentional resources to the area of pain, narrowing of attention, and gating of task-irrelevant stimuli (Dancey et al.

2016b). Motor control changes are well documented in association with MSD and have been attributed to movement related pain (Lamothe et al. 2014) but may also be influenced by psychological factors (Kusters et al. 2011; Mannion et al. 2011).

Changes in motor control in subjects with MSD have been associated with changes in representation in M1, with motor performance changes, and measures of disability in persons with LBP (Tsao et al. 2008; Masse-Alarie et al. 2012; Massé-Alarie et al. 2016), elbow pain (Schabrun, Hodges, et al. 2014), and knee pain (Te et al. 2017). It is therefore possible that the conscious or unconscious desire to minimize pain but preserve function in the presence of pain associated with MSD results in behavioural changes manifested by altered motor control (Hodges and Tucker 2011). These changes in motor control may involve the learning of new motor strategies by altering cortical (and possibly spinal) excitatory and inhibitory activity, resulting in the strengthening (i.e. long-term potentiation like) and weakening in synaptic strength and efficiency of muscle synergies within M1. Although speculative, these changes in corticospinal properties and organization found in some studies in persons with MSD may be reflective of these behavioural responses to pain, psychological factors, and compromise to musculoskeletal structures that, individually or collectively, result in the learning of new motor strategies. Motor learning associated with altered movement patterns in the participants with MSD of the wrist/hand may be relevant to the increase in corticospinal excitability of the APB. As previously stated, the thumb is believed to be involved in more than 60% of hand function (Kjeken et al. 2005).

Cross-sectional studies investigating changes in corticospinal properties and organization and correlation with measures of pain, motor performance, and disability cannot provide answers as to causality. Animal models allow for longitudinal studies that could better decipher questions related to the directionality of these changes found in persons with MSD. Animal models of work-related musculoskeletal disorders involving repetitive altered motor strategies for food retrieval in rodents result in the development of overuse injuries of the upper extremity including tendinitis and carpal tunnel syndrome (Barr et al. 2004; Barr 2006). Histochemical analysis of the injured structures, monitoring of behavioural changes (i.e. reversals or food retrieval failure), assays of inflammatory markers, and intracortical recordings of the sensorimotor areas in rodents has been performed in an animal model of movement related overuse injuries (Coq et

al. 2009). Changes in behaviours, cortical sensorimotor properties and organization, the presence of inflammatory mediators were all found to occur progressively and simultaneously (Coq et al. 2009). However, these models also induce the movement-related MSD by altering food retrieval strategies and are most probably associated with the learning of new movement strategies. Therefore, it is unclear if the changes in the sensorimotor cortical areas are related to the changes in sensory afference and the presence of inflammatory mediators, the acquisition of new motor control strategies, or both.

The learning of new motor strategies in persons with MSD may persist in time and may result in long-term potentiation like changes in M1 similar to changes associated with user dependent plasticity demonstrated in animal models (Nudo et al. 1996; Kleim et al. 1998; Sanes and Donoghue 2000). Experimentally induced tonic pain in human subjects by the application of capsaicin cream applied to the forearm did not result in changes in motor learning, but did result in altered movement strategies that were carried forward even when the subjects did not have the cream re-applied when performance was re-evaluated during the retention phase (Lamothe et al. 2014). Altered motor control associated with changes in properties and organization in M1 may be present in the absence of pain. Participants with recurrent LBP, but who were asymptomatic at the time of experimentation, demonstrated altered motor cortical representation of the transverse abdominus muscle (Tsao et al. 2008). Altered motor control may persist in the absence of pain after low back injury (Hides et al. 1996). Changes in M1 properties and organization have been associated with altered neuromuscular recruitment patterns of muscles in LBP and lateral epicondylitis (Tsao et al. 2008; Schabrun, Hodges, et al. 2014). Corticospinal changes in M1 in persons with MSD may therefore be reflective of altered sensory input to cortical structures and/or altered motor control strategies which have been hypothesized to be associated with altered muscular representations in M1 associated with MSD such as lateral epicondylitis (Schabrun, Hodges, et al. 2014).

Several investigators have asked if pain can interfere with motor learning. This is a clinically critical issue for rehabilitation professionals working with persons suffering with MSD. If the cortical changes in sensorimotor areas are involved in the pathophysiology of MSD and not simply a cause or consequence of peripheral structural damage, can these persons unlearn and reverse these cortical changes? Although some studies have found acute pain to interfere with

motor learning (Boudreau et al. 2007; Boudreau, Hennings, et al. 2010), other studies have found that acute pain has no effect (Ingham et al. 2011) or may actually enhance motor learning (Dancey et al. 2014; Dancey et al. 2016a; Dancey et al. 2016b). Acute pain, induced by the application of capsaicin cream on the elbow while performing a thumb tracing task resulted in altered somatosensory evoked potentials and improved motor learning (Dancey et al. 2016b). The frontal N30 response was increased and is believed to be reflective of sensorimotor integration involving the thalamus, basal ganglia, premotor areas and M1 (Dancey et al. 2016b). Behavioural interventions in subjects with MSD have demonstrated changes in properties and organization in M1, improved motor performance and decreased disability (Flor 2002; Candia et al. 2003; Napadow et al. 2007; Schabrun et al. 2009; Tsao, Galea, et al. 2010; Boudreau, Farina, et al. 2010). Therefore, evidence exists that supports the belief that pain may be associated with changes in M1 as the result of motor learning.

6.1.2 Summary

In summary, increased corticospinal excitability was found in the median nerve innervated APB, but not the ulnar nerve innervated FDI. The increase in corticospinal excitability may reflect an attempt to maintain the same force output and function to compensate for the MSD by increasing corticospinal influences recruiting more/different motor units of the same and possibly synergistic muscles. Variable results between measures of corticospinal excitability between the APB and FDI are consistent with the body of evidence of variable changes in corticospinal properties and organization across studies with chronic MSD. Although the mechanisms remain to be elucidated, the overall results of corticospinal changes in a heterogeneous sample of persons with MSD of the wrist/hand are consistent with the interpretation that the motor cortical changes may reflect unmasking of latent synaptic connections and possibly long-term potentiation like changes in the motor cortex in cortico-cortical connections and dendritic sprouting similar to the mechanisms involved in motor skill learning (Boudreau, Farina, et al. 2010; Dayan et al. 2011).

These findings contribute to the emerging picture of CNS changes associated with MSD. The present findings add to the existing literature that the changes in corticospinal excitability are not only related to pain severity, but also measures of disability and motor performance and therefore appear to have clinical significance. Their role in the pathophysiology of these chronic

MSD needs further elaboration as the causal relationship between structural injury, nociceptive stimulation and CNS changes is still unclear and need to be answered with longitudinal studies and animal models. Current conventional rehabilitative strategies may not specifically address neuroplastic changes in the sensorimotor cortical areas in persons with chronic MSD. Failure to find effective treatment strategies for many chronic MSD may stem from the fact that rehabilitation efforts have been oriented towards peripheral sources with little regard to central neurophysiological changes (Wand and O'Connell 2008).

6.2 Body Schema and Left Right Judgment Task Performance

There is increased interest regarding motor imagery within rehabilitation science as a tool to help improve motor function in both neurological (de Vries et al. 2007; Mulder 2007) and more recently orthopaedic rehabilitation (Moseley and Flor 2012; Snodgrass et al. 2014). Motor Imagery refers to "*the act of imagining a specific action without actually executing it."* (Hetu et al. 2013).

6.2.1 Left right judgment task performance and sensory, motor and cognitive factors

The LRJT involves determining if the image of a body part is of the left or right side. Studies have consistently found that reaction time to perform this task is proportional to the disparity between the actual hand position of the participant and the position of the hand on the image when attempting to determine the laterality of the hand in the image (Parsons 1994; Parsons et al. 1995; Ionta et al. 2007; Coslett et al. 2010b). The LRJT results in similar patterns of activation as motor imagery (Parsons et al. 1995; Kosslyn et al. 1998) and actual physical performance of the task (Decety 1996b). In large part derived from these experimental findings the LRJT is believed to involve implicit motor imagery where the subject unconsciously imagines positioning the hand in the same position as the image (Parsons 2001; Ionta et al. 2007; Moseley 2012).

The LRJT has been proposed as a proxy measure of the body schema. The body schema is an internal representation of the body in peri-personal space. As discussed above, the LRJT appears to involve motor imagery and has similar cortical neuronal activation as the actual performance of the movement. Theoretically the initial position of the body segment is necessary to imagine the movement and hence the necessity of the body schema to perform the LRJT. The body

schema is believed to be affected by changes in sensory output from the area of pain, and alterations in S1 properties and organization (Bray and Moseley 2011). However, mental rotation of the body part is a complex cognitive task that requires attentional and working memory resources, motor imagery, spatial transformations, decision-making, and motor selection and preparation that is reflected by the complex activation of central neural structures activated when performing the LRJT (Parsons et al. 1995; Kosslyn et al. 1998; Osuagwu et al. 2014; Tomasino and Gremese 2015). These imaging findings are consistent with the results presented in the thesis.

LRJT accuracy of the affected hand in a larger sample of subjects with MSD of the wrist/hand was correlated with sensory (TPD), motor (Purdue pegboard scores) and cognitive (Stroop Test, Motor Imagery ability) factors. Participants who had taken pain medications on the day of the assessment performed more poorly on the LRJT. The group of participants who took pain medication on the day of the evaluation had greater pain severity and disability scores, more likely to describe their pain as constant and performed more poorly on the Stroop test. There was a trend for a difference of WHYMPI affective distress values between the participants who did and did not take pain medication on the day of the assessment. These findings suggest that, in a group of participants with MSD of the wrist/hand, factors associated with cognitive function, pain, and sensorimotor processes collectively were associated with poorer LRJT performance in the affected hand. The finding of differences in LRJT performance between healthy controls and participants with wrist/hand pain are suggestive of altered sensorimotor processes that are influenced, not only by measures of sensation that impact the body schema and motor processes, but cognitive and affective factors that are mediated by forebrain mechanisms. Cognitive factors (i.e. attention/concentration and motor imagery ability) have been suggested as confounding factors in studies involving the LRJT, but the results of the study presented is the first to our knowledge to attempt to decipher changes related to cognitive factors, and those attributed to sensorimotor cortical processes.

6.2.2 Left right judgment task and cortical processes

Several neuroimaging studies have been performed in participants performing mental imagery. Decety (1996) found that similar brain regions are activated when performing motor imagery as when performing the actual movements (Decety 1996a). Activation likelihood estimation meta-

analysis of fMRI and positron emission tomography scan studies have found, irrespective of the type of stimuli or strategy utilized in the study of motor imagery, neural activation in the parietal (inferior and superior parietal lobules bilaterally and the supramarginal gyrus), frontal (precentral gyrus, inferior and middle frontal gyrus bilaterally, supplementary motor area), insula, occipital (bilateral inferior and middle occipital gyrus bilaterally) and subcortical structures (putamen, thalamus and posterior cerebellum) (Hetu et al. 2013; Tomasino and Gremese 2015). Studies involving motor imagery of the hand (Hetu et al. 2013) and studies specifically involved in the mental rotation of body parts (Tomasino and Gremese 2015) result in the activation of the same neural areas as those found by Decety et al (1996). Neuroimaging studies specifically involving the LRJT include a positron emission tomography study performed by Parsons et al (1995) of mental rotation of hands in healthy participants resulting in bilateral activation of the premotor areas (superior and inferior premotor areas), basal ganglia and cerebellum (Parsons et al. 1995). Kosslyn et al (1998) performed an fMRI study of mental rotation of the hands and found areas of increased blood flow in the superior and inferior parietal lobes, primary visual cortex, insula, cerebellum, and frontal areas 6 (premotor and supplementary motor) and 9 (dorsolateral and medial prefrontal cortex) (Kosslyn et al. 1998). Therefore, motor imagery involves neural activation in the posterior parietal areas involved in perception and sensory integration, and with the premotor areas involved in sensory motor transformations, and cortical areas involved in short term working memory and attention.

The implication of M1 in mental rotation tasks is debated as activation is not consistently found across neuroimaging studies. Parsons et al (1995) found no evidence of M1 activation in an positron emission tomography study of mental rotation of hands (Parsons et al. 1995). Kosslyn et al. (1998) measuring regional cerebral blood flow utilizing functional magnetic resonance imaging found activation of both S1 and M1 (Kosslyn et al. 1998). Of the 122 neuroimaging experiments examined in the meta-analysis by Hétu and al. (2013) only 21 found activation within M1 (Hetu et al. 2013). The lack of M1 activation in neuroimaging studies may however be a function of the low temporal resolution of this technology (Hetu et al. 2013). Techniques used to increase sensitivity by focusing on regions of interest with fMRI have found M1 activation with motor imagery (Sharma et al. 2012). Even when neuroimaging studies find M1 activation, these findings may be confounded by experimental procedures of the LRJT where

participants are asked to perform motor actions to indicate laterality and may therefore reflect neural activity associated with the motor task and not because of mental rotation of the hand (Cohen et al. 1996; Richter et al. 2000). Furthermore, involvement of different brain areas including M1 may be a function not only of the imagery task, but instructions and stimuli given to the participants, and the strategy utilized by the participants (Hetu et al. 2013; Tomasino and Gremese 2015). For example, imagery can be performed from a visual imagery based strategy, for example when three dimensional images need to mentally rotated to determine symmetry or if the participants are instructed to utilize an external force to rotate the image of the hand (Berneiser et al. 2016), versus a motor imagery based strategy when an image of a body part is involved and motor imagery is performed from the first person, or egocentric perspective (Osuagwu and Vuckovic 2014; Tomasino and Gremese 2015). M1 activation during motor imagery may also be a function of individual differences, an argument that is supported by neuroimaging studies of motor imagery with sub-clusters of participants demonstrating M1 activation (see (Hetu et al. 2013)). These include interindividual differences in relation to motor expertise, gender, and experience (Hetu et al. 2013).

Whereas neuroimaging studies often do not report M1 activation, several TMS studies strongly suggest M1 involvement in motor imagery (see (Loporto et al. 2011)). TMS applied over the hand area in M1 affects LRJT RT suggesting that activation of the motor cortex is not simply a by-product of neuronal activity in other areas but is implicated in the task (Ganis et al. 2000). Single-pulse TMS applied 50, 400 and 650 ms after presentation of the hand image resulted in increased corticospinal excitability of the FDI in relation to baseline measurements in healthy participants performing the LRJT (Hyde et al. 2017). Increased corticospinal excitability of the FDI was greatest the more complex the hand positions requiring more extensive mental transformations to adopt the position of the image (Hyde et al. 2017). There is some evidence that motor imagery practice can modulate corticospinal properties and organisation (Pascual-Leone et al. 1995; Jackson et al. 2003). In an EEG study of the mental rotation of hands, EEG recordings found similar activation to the neuroimaging results in parietal and premotor areas but also found contralateral activation within the pre and post central gyri (M1 and S1) (Osuagwu and Vuckovic 2014).

The posterior parietal areas would appear to be responsible for the representation of the body in peri-personal space utilized in the establishment of the motor plan (Kashuk et al. 2017). Disruption of the superior parietal lobe during motor imagery via TMS also results in reduced motor imagery performance (Kashuk et al. 2017). The posterior parietal areas are strongly interconnected with the frontal premotor areas involved in motor selection, preparation and execution including the supplementary motor and the ventral and dorsal premotor areas (Iacoboni et al. 2004). The ventral premotor cortex, which is predominantly involved in the control of mouth and hand movements, also appears to be involved in higher levels of motor transformations (Kandel et al. 2013). Most neurons in the ventral premotor cortex are bilaterally tuned and only show lateral specification once the action begins (Rizzolatti et al. 2002; Davare et al. 2006; Kandel et al. 2013). The ventral premotor cortex has both motor and cognitive functions (Rizzolatti et al. 2002). The motor functions of the ventral premotor cortex include the transformation of internal representations of objects into hand configurations and spatial locations into hand and arm information (extrinsic frame of reference). The ventral premotor cortex therefore appears to be involved in transformations that match visual space to motor space and transformations from extrinsic to intrinsic coordinates (Kalaska et al. 1997; Hoshi et al. 2007). The cognitive functions of the premotor cortex include imitation, action understanding and selection. Neuronal activity in ventral premotor cortex reflect activity to signal the correct response and appropriate motor action, therefore linking sensory, cognitive, and memory aspects with motor actions. Collectively the findings suggest that the premotor neurons are involved in the perception, cognition and execution of movement, participating in sensory transformation and integration (extrinsic kinematics), action selection, and formulation of appropriate actions fitting the context (Cisek et al. 2005; Hoshi and Tanji 2007). Although speculative, the bilateral changes found in participants with wrist/hand pain may therefore reflect alterations in these bilateral tuned neurons within the prefrontal hand motor areas that are involved in sensorimotor integration and which imaging studies suggest are activated during the LRJT.

According to Hétu et al. (2013), motor imagery likely induces a similar planning and preparation phase prior to the movement simulation, in line with that required of overt movements to take place (Kashuk et al. 2017). Frontal areas involved in motor imagery include the dorsolateral and

medial prefrontal cortex involved in salience, attention, and spatial imagery. The findings of the importance of concentration/attention and motor imagery ability are consistent with these imaging results. The findings in the present thesis of sensory and motor aspects related to LRJT performance accuracy are also consistent with the imaging findings of activity in the cortical areas involved in sensorimotor functions.

6.2.3 Left right judgment task, cognitive and sensorimotor changes

The multiple linear regression model with the accuracy score on the LRJT of the right (affected) hand as the dependent variable found the Stroop Test, TPD of the right hand, WHYMPI General Activities subscale, motor performance, and taking of Pain Medication as the best model. The Stroop test, a test to measure selective attention, involves activation of the medial and anterior frontal structures including the anterior cingulate cortex, dorsolateral prefrontal cortex, insula and the posterior parietal cortices (Bench et al. 1993; Leung et al. 2000). The parietal areas are involved in sensory perception and integration. Altered TPD thresholds have been associated with S1 reorganization in subjects with complex regional pain syndrome (Pleger et al. 2006), an area involved in the body schema and sensorimotor integration. Changes in cognitive function are well documented in subjects with pain (Moriarty et al. 2011). Imaging studies involving the LRJT and motor imagery of sensory motor processes involving posterior parietal and the premotor areas, and areas involved in cognitive function in association with the results from the study presented suggest altered sensorimotor integration in the sample population studied.

The taking of pain medication on the day of experimentation was strongly associated with poorer LRJT accuracy of the right hand. It may be argued that the decrease in LRJT performance accuracy may be a function of the pain medication affecting cognitive function and attentional resources. This latter argument is, however, unlikely as the taking of pain medication was associated with LRJT accuracy for the right (affected) hand only and did not affect LRJT performance for reaction time or accuracy of the feet. Participants who took pain medication also had higher pain severity and disability scores, demonstrated decreased motor performance and cognitive function compared to participants who did not take medication. They were also more likely to describe the pain as constant. Decreased LRJT accuracy may be reflective of increased pain and disability levels in this segment of the participants studied and is therefore simply a reflection of decreased attentional resources and motor performance associated with

the higher pain levels. However, it is also possible that a confluence of factors including concentration, pain intensity, sensory and motor disturbances are involved. The confluence of factors is reflective of the multidimensionality of the experience of MSD involving peripheral and central processes and include altered structure and function in areas involved in sensory and motor function, areas involved in cognitive and affective responses to the injury/condition and the associated pain experience (see figure 6.1).

6.2.4 Left right judgment task and motor performance

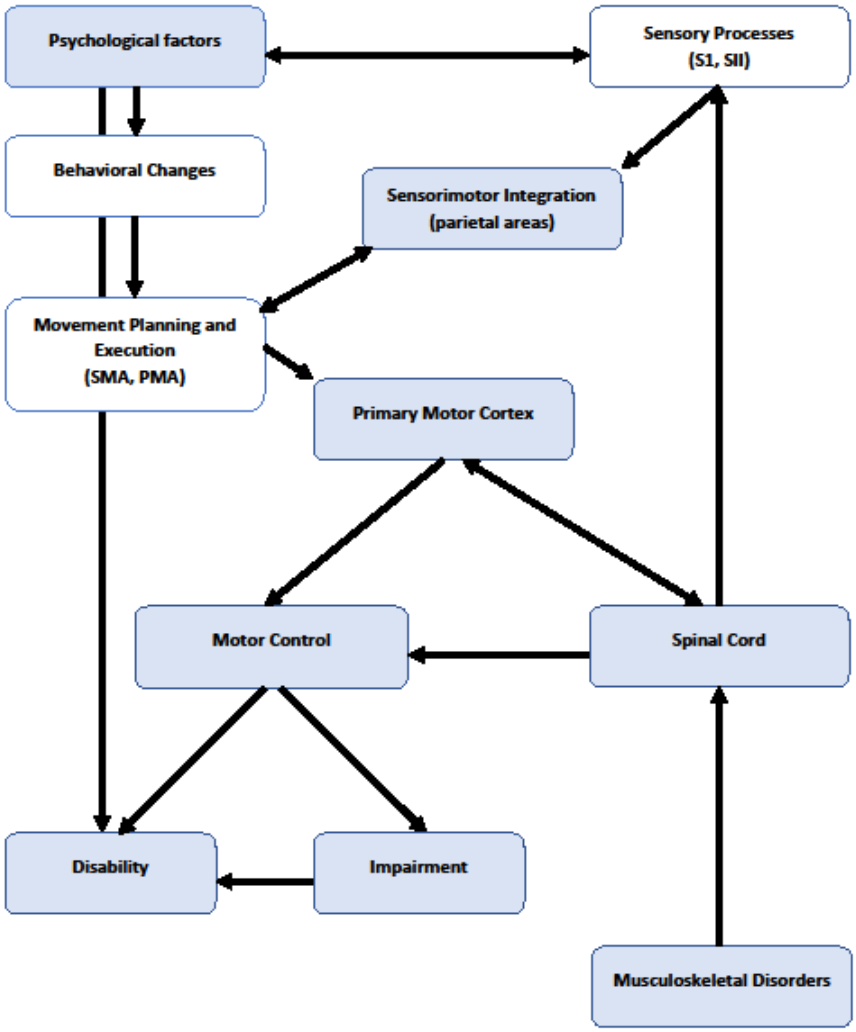
Motor control processes are believed to be tightly coupled with the working body schema and involved in the LRJT performance (Parsons 2001; Moseley 2004c). However, few studies have investigated motor processes and LRJT performance simultaneously (Botnmark et al. 2016). The participants in the present study demonstrated decreased motor performance on the Purdue pegboard test compared to healthy control participants. In the only other study that we are aware of investigating motor performance and LRJT performance, Botnmark et al (2016) found that LRJT accuracy was positively correlated with an upper extremity functional stability test (i.e. better functional performance, better LRJT accuracy) for both shoulders in healthy participants (Botnmark et al. 2016). There are important differences between the Botnmark et al (2016) study and the present study in terms of anatomical location, population and functional performance tests. In the study presented in the thesis investigating the relationship between LRJT and motor performance a statistically significant bilateral moderate correlation was found in the healthy control group but not the participants with MSD of the wrist/hand. The present findings and those of the Botnmark el al (2016) study suggest that motor control processes are related to LRJT performance in healthy participants. Although preliminary, these findings suggest that there is a stronger relationship between LRJT and motor performance in healthy subjects and with the non-symptomatic limb in participants with wrist/hand MSD suggesting altered sensorimotor integration in participants with MSD of the wrist/hand.

There is evidence that training of mental rotation results in improved performance in a variety of tasks and mental skills suggesting a benefit in complex cognitive tasks (Uttal et al. 2013). A fMRI study performed in healthy participants found that training of the mental rotation of hands resulted in significant improvements in LRJT performance (Berneiser et al. 2016). Improvement and greater experience in the LRJT also appears to be associated with a shift in strategy of

imagery performance from a visual to motor imagery-based strategy (Berneiser et al. 2016). These improvements in LRJT performance were also associated with increased brain activation changes in the left posterior putamen, right supramarginal gyrus, bilateral ventral premotor cortex, and a trend toward increased activation of the right primary motor cortex. There was therefore a shift in brain activity pre- to post training from the anterior to posterior putamen. These brain activity changes were associated with a change in strategy, shifting from visual spatial processing to motor-based processing. Prior to training, LRJT response times were not associated with the kinematic properties required to mentally move the hand to conform to the displayed image. However, after the training period, response times were modulated to the kinematic properties of the position of the displayed hand. These findings would explain why visual motor imagery ability was more strongly correlated with LRJT performance compared to kinesthetic motor imagery in the results presented. Motor strategies appear to provide an advantage for the LRJT for the mental rotation of hands (Moreau 2012; Berneiser et al. 2016). These findings may be consistent with the findings of an association of LRJT performance with functional tests in the Botnmark et al (2016) and the present study.

The LRJT has been proposed not only as a method of evaluation but also as a method of intervention for persons with chronic pain conditions such as complex regional pain syndrome (Moseley 2004b; Moseley 2012; Bowering et al. 2013) and recently as part of the Graded Motor Imagery program in the rehabilitation for distal radial fractures (Dilek et al. 2018). Presently all neuroimaging studies of persons performing mental rotation tasks have involved healthy participants. It will be interesting to determine if participants experiencing MSD demonstrate altered patterns of neural activity and if treatment utilizing the LRJT can decrease symptoms and improve function, and if so, is the improvement associated with renormalization of neural activity and in which cortical regions.

Figure 6.1: MSD, sensorimotor integration, corticospinal excitability, and the Left Right Judgement Task



MSD result in changes in sensory processes that result from injury/damage to musculoskeletal structures. Characteristic of MSD are changes in sensory and motor processes. Recent studies, including results presented in this thesis, demonstrate changes in corticospinal excitability that was related to sensory (i.e. pain) and motor function. The changes in corticospinal excitability may be the result of direct influences of nociceptive afferents on the primary motor cortex. Changes in corticospinal properties may also result from sensory changes that result from the injury. The findings of corticospinal changes in participants with heterogeneous MSD of the wrist/hand suggest that the changes may be related to behavioural changes. Implicit and/or explicit changes in behaviours may be influenced by psychological factors and by neurophysiological mechanisms that attempt to protect the area and maximize function. Behavioural changes not only affect motor control but will also change sensory and proprioceptive afferents which may further contribute to altered sensory and corticospinal excitability. Corticospinal changes in the APB were also related to spinal motoneuronal excitability, pain intensity and disability. Participants also presented changes in LRJT performance. LRJT performance in the affected hand may be indicative of an altered body schema, reflected by variables included in the multiple linear regression model of sensory and motor processes. However, the evidence presented also suggests that LRJT performance in the affected hand is a function of an accumulation of factors related to cognitive function, pain, sensorimotor function and disability. Collectively the results suggest that sensorimotor integration is affected in persons with MSD, reflective or altered sensory and motor processes, but influenced by cognitive and psychological factors. Boxes in white where not directly assessed in the experiments presented in the thesis. S1: Primary Somatosensory Cortex; SII: Secondary Somatosensory Cortex; SMA: Supplementary Motor Area; PMA: Pre-Motor Areas

6.2.5 Summary

In summary, LRJT performance was affected in participants with MSD of the wrist and hand. The association between motor performance and LRJT was different between participants with MSD of the wrist/hand and healthy controls. Although the LRJT is often presented as a proxy measure for the body schema, available evidence including the results presented in this thesis suggests that several cortical areas are involved in different cognitive, sensory and motor processes implicated in the task. The study of the relationship between motor, cognitive, sensory and psychological variables and LRJT performance is the first performed with participants with MSD. Very few investigators have controlled for cognitive (Stroop and motor imagery ability) and motor processes the LRJT, which, at least in part, could explain the variability of findings of the performance of the LRJT in participants with MSD across studies. In sum, our findings are in line with considerable evidence for the involvement of motor and cognitive processes in addition to parietal areas in the mental rotation of hands (Berneiser et al. 2016), but add to these findings that altered motor, cognitive and affective factors influence LRJT performance possibly affecting sensorimotor integration (see figure 6.1). The link between LRJT performance and motor performance in a symptomatic population is less well defined, but preliminary evidence suggests that changes in corticospinal properties do influence LRJT performance in persons with MSD of the wrist/hand (Ganis et al. 2000; Hyde et al. 2017).

6.3 Relevance in Rehabilitation Medicine

This area of research into changes in sensorimotor cortical processes and the association with pain, function and disability is of interest to rehabilitation professionals working with persons with chronic MSD. Although the biomedical, or structural-pathology, model suggests that these neurophysiological changes are secondary to the peripheral MSD, several studies suggest the possibility of two-way causality, both top-down and bottom-up processes, between altered sensory and motor processes associated with peripheral MSD and altered cortical properties and organization within S1 and M1. For example, persons experiencing phantom limb pain demonstrate cortical reorganization in S1 (Karl et al. 2001). Anesthesia of the brachial plexus will temporarily restore cortical organization in S1 and decrease phantom limb pain (Birbaumer et al. 1997). However, sensory discriminative training, motor imagery and mirror therapy are also associated with reorganization in S1 that results in a representation closer to that found in

healthy control subjects and associated with a decrease in phantom limb pain (Flor et al. 2001; MacIver et al. 2008; Deconinck et al. 2015). The wearing of a myoelectric prosthesis in persons with phantom limb pain also helps to restore normal neuronal organization in S1 and M1 (Lotze et al. 1999). Behavioural treatment involving a motor learning task activating the transverse abdominus muscle, but not a general walking program, in subjects with LBP demonstrate a renormalization of cortical somatotopy in M1 and decreased pain and improved function (Tsao, Galea, et al. 2010). Graded motor imagery involving the LRJT, motor imagery and mirror therapy added as an adjunct to traditional rehabilitative care has improved functional outcomes, self-reported disability and pain levels in post-operative subjects with distal radial fractures (Dilek et al. 2018). The investigation of cortically directed behavioural and environmental (i.e. TMS, transcranial direct current stimulation, neural biofeedback) interventions to improve outcomes in persons with chronic MSD is an exciting area of expanding research in rehabilitation science.

6.3.1 Addressing Neuroplastic Changes in Distributed Areas of the Nervous System Associated with Chronic Musculoskeletal Disorders

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As the principal author of this manuscript, I confirm that I was responsible for performing the literature review in regard to this article and the writing of the manuscript. Dr Higgins and Dr Bourbonnais provided supervision and revision of the manuscript.

6.3.1.1 Abstract

Present interventions utilized in musculoskeletal rehabilitation are in large part guided by a biomedical model where peripheral structural injury is believed to be the sole driver of the disorder. There are however neurophysiological changes across different areas of the peripheral and central nervous system including peripheral receptors, dorsal horn of the spinal cord, brain stem, sensorimotor cortical areas and in the meso-limbic and prefrontal areas associated with chronic musculoskeletal disorders including chronic low back pain, osteoarthritis, and tendon injuries. These neurophysiological changes appear to be not only a consequence of peripheral structural injury but play a part in the pathophysiology of chronic musculoskeletal disorders. Neurophysiological changes are consistent with a bio-psycho-social formulation reflecting the underlying mechanisms associated with sensory and motor findings, psychological traits, and perceptual changes associated with chronic musculoskeletal conditions. These changes therefore have important implications in the clinical manifestation, pathophysiology and for rehabilitative treatment of chronic musculoskeletal disorders.

Musculoskeletal rehabilitation professionals have at their disposal tools to address these neuroplastic changes including top down cognitive based interventions (such as education, cognitive behavioural therapy, mindfulness meditation and motor imagery), and bottom up physical interventions (such as motor learning, peripheral sensory stimulation, and manual therapy) that induce neuroplastic changes across distributed areas of the nervous system and impact outcomes in patients with chronic musculoskeletal disorders. Furthermore, novel approaches such as the use of transcranial direct current stimulation and repetitive transcranial magnetic stimulation may also be utilized to help renormalize neurological function. Comprehensive treatment addressing peripheral structural injury as well as neurophysiological changes occurring across distributed areas of the nervous system may help to improve outcomes in patients with chronic musculoskeletal disorders.

6.3.1.2 Keywords chronic pain, neuroplasticity, chronic musculoskeletal disorders, chronic low back pain, osteoarthritis, physical therapy, neurophysiology pain education, cognitive interventions, prefrontal, meso-limbic

6.3.1.3 Introduction

Traditionally, treatments for chronic musculoskeletal disorders (CMSD) such as chronic low back pain (CLBP) have been anchored in a biomedical model. This model is based upon a structural-pathology paradigm where insult to anatomical structures is believed to be the sole driver of the condition. Over the last two decades evidence has emerged of neurophysiological changes within the peripheral and central nervous systems associated with CMSD. Studies suggest that CMSD do not simply result from ongoing structural pathology to peripheral tissues but involve a complex interplay between peripheral structural injury, altered afferent information conveyed from peripheral receptors towards the spinal cord, brain stem and cortical areas, changes in neuronal processing of noxious stimuli and psychosocial factors (Pelletier et al. 2015). These neurophysiological changes are consistent with experimental and clinical findings of altered sensory transmission including sensory amplification of pain, motor control changes such as altered muscle recruitment patterns, changes in perceptual processes including altered body image, psychological traits such as catastophization and somatization, and behavioral changes such as fear-avoidance that appear to be implicated both in the clinical manifestation and the pathophysiology of CMSD (see Table 6.3.1).

Neurophysiological changes, or neuroplasticity, refers to changes in structure, function and organisation within the nervous system that occurs continuously throughout our lifetimes in response to internal stressors such as cognitive processes, internal changes in sensory afference, and external stressors such as motor learning and peripheral sensory stimulation (Kleim and Jones 2008). Neuroplasticity is the method by which the brain encodes new experiences, learns, and develops new behaviors. Neuroplastic changes associated with CMSD have been demonstrated in the (1) peripheral nervous system and spinal cord, (2) brain stem, (3) sensorimotor areas, and (4) mesolimbic and pre-frontal areas of the cortex (see (Apkarian et al. 2011; Pelletier et al. 2015)).

6.3.1.3.1 Neurophysiological changes occurring within peripheral receptors and the dorsal horn of the spinal cord

Neurophysiological changes occurring within peripheral receptors and the dorsal horn of the spinal cord include increased responsiveness to nociceptive stimuli resulting from anatomical insult to musculoskeletal structures and neuropathic stimuli in sensory amplification, a process

called sensitisation resulting in hyperalgesia, increased pain perception, and in allodynia, innocuous stimuli that are perceived as painful (Woolf 2011). Peripheral sensitization involving increased responsiveness of the peripheral nociceptors, and central sensitization involving changes in the spinal cord amplifying the transmission of pain is a natural process that has a biological advantage in helping to protect the injury from re-injury (Woolf 2011). However, sensitization should be transient and peripheral and dorsal horn plastic changes should return to their pre-injury state with normalized afferent peripheral input associated with tissue repair (Woolf 2011).

6.3.1.3.2 Neuroplastic changes within the brainstem

Neuroplastic changes also occur within the brainstem, specifically in areas involved in the descending modulation of nociceptive and neuropathic stimuli including the Periaqueductal Grey (PAG) (Lee, Nassikas, et al. 2011) and the Rostral Ventral Medulla (RVM) (Heinricher et al. 2009). The PAG & RVM are influenced by meso-limbic and opioid systems which in turn influence the transmission of noxious stimuli in the dorsal horn of the spinal cord (Bushnell et al. 2013). Evidence suggests that these descending modulatory systems are affected in chronic pain states and may perpetuate sensitization within the spinal cord (Heinricher et al. 2009; Wang et al. 2013).

6.3.1.3.3 Neuroplastic changes in the cortical sensory discriminative areas

The sensory discriminative areas involved in the transmission and processing of noxious stimuli includes the primary (S1) and secondary somatosensory cortices (S2) and the insula (Bushnell et al. 2013). The insula appears to be at the crossroads between the sensory discriminative and affective aspects related to pain sensation in the caudal portion and pain affect in the anterior portion (Bushnell et al. 2013).

Changes in structure, function and in the somatotopic organization in S1(Flor et al. 1997) and the primary motor cortex (M1) (Tsao, Danneels, et al. 2011) have been demonstrated in chronic pain conditions including CLBP and Complex Regional Pain Syndrome (CRPS) but have also been found in patella femoral pain syndrome, patellar tendinopathy (Rio et al. 2015), osteoarthritis (OA), and rotator cuff pathology (see (Pelletier et al. 2015)). Changes in pressure pain thresholds (Bisset et al. 2006) and bilateral findings including decreased strength (Fernandez-de-Las-Penas, Perez-de-Heredia-Torres, et al. 2009), range of motion (Forget et al.

2008), and presence of inflammatory mediators in the contralateral homologous structure (Andersson et al. 2011) also allude to the presence of altered neural transmission and processing in a number of CMSD. The neuroplastic changes in the cortical sensorimotor areas are consistent with sensory (i.e changes in tactile acuity), perceptual (i.e. altered body image) and motor disturbances (i.e. motor control) apparent in different CMSD. The neurophysiological changes in the sensorimotor cortical areas often correlate with pain intensity and symptom duration (Flor et al. 1997; Tsao, Danneels, et al. 2011). Evidence suggests a two-way causality between pain/injury and cortical plasticity in S1 and M1, as the elimination of pain may result in cortical reorganization, and interventions that address cortical reorganization may result in decreased pain and improved function (Moseley and Flor 2012).

6.3.1.3.4 Neuroplastic changes in the cognitive-affective-motivational areas

The cognitive-affective-motivational areas involved in pain processing receive input from ascending projections via the brainstem and the thalamus (Bushnell et al. 2013). This includes the structures within the meso-limbic and prefrontal areas such as the insula, Anterior Cingulate Cortex (ACC), amygdala, and Prefrontal Cortex (PFC) (Bushnell et al. 2013). Arguably the most important neuroplastic changes associated with CMSD occur within the meso-limbic and prefrontal areas, regions associated with threat, fear, aversive conditioning, attention, motivation (dis)engagement, and executive control (Kulkarni et al. 2007). The best biomarker identified for the transition from acute to chronic conditions (Baliki et al. 2012), and for the presence of chronicity in subjects with low back pain and OA involves activity within these regions (Apkarian et al. 2011). Altered structure, function and activity within meso-limbic and prefrontal areas correlate with psychological traits that are often implicated in chronic conditions such as fear-avoidance and catastrophization (a tendency to focus and magnify actual or anticipated pain experience and to feel hopeless in the face of such experience (Seminowicz and Davis 2006; Ochsner et al. 2006; Wertli et al. 2014). Meso-limbic structures, specifically the PFC, ACC and amygdala also influence motor areas and functioning of the descending modulatory systems including the PAG-RVM pathway that are affected in chronic pain states (Heinricher et al. 2009; Bushnell et al. 2013). The PFC and meso-limbic activity appear to lay the foundation for increased vigilance, attention and salience attributed to the injury, and may

therefore contribute to central sensitisation resulting in hyperalgesia and allodynia and provide conditions ripe for inducing neuroplastic changes in the sensorimotor and subcortical areas.

Table 6.3.1: Areas of neuroplastic changes associated with CMSD and possible signs and symptoms manifested by the patient.

Neurophysiological changes associated with CMSD	**Possible physiological consequences of neuroplastic changes in these areas**	**Signs and symptoms that may possible indicate neuroplastic changes in these areas**
Meso-limbic and pre-frontal areas. Areas demonstrated to have been affected include: Insula, Cingulate Cortex, Amygdala, Medial and Dorsolateral prefrontal cortex, and Nucleus Accumbens	Altered neuronal responses to pain especially in regards to the "unpleasantness" associated with pain. Implicit and explicit learning associating pain with movement and negative outcomes.	Spontaneous fluctuations in pain. Problems in affective, cognitive and motivational aspects in relation to pain. These changes **may be associated** with psychological aspects related to pain including fear-avoidance, anxiety, depression, catastrophization, somatization, worry, increased vigilance.
Descending pain modulatory systems, PAG-RVM pathway. Descending modulatory systems receive input from pre-frontal and mesolimbic structures including the Cingulate cortex, amygdala, and mPFC.	Decreased descending inhibition of pain (disturbed Conditioned Pain Modulation)	Central Sensitization (hyperalgesia and allodynia). Pain Thresholds may be decreased (pressure and thermal).
Peripheral receptors	Increased transduction of nociceptive stimuli.	Increase pain transmission in the area of injury resulting from changes in input and output characteristics in peripheral nociceptors (Peripheral Sensitization). Contributes to central sensitization (hyperalgesia and allodynia)
Dorsal Horn of the Spinal cord	Increased transmission of nociceptive and neuropathic stimuli. Result from changes in membrane permeability, decreased inhibition, influenced by descending modulation pathways including the PAG-RVM	Central Sensitization (hyperalgesia and allodynia) Pain Thresholds may be decreased (pressure and thermal)
Somatosensory cortex	Altered somatosensory maps including expansion, retraction or shifting of the representation	Increased Two Point Discrimination Impaired performance of laterality recognition Change in perception of body image including size of the limb, altered body midline.
Primary motor cortex	Changes in muscle/movement representations in motor areas of the brain and corticospinal excitability.	Changes in motor control including co-contraction and loss of ability to selectively recruit individual muscles.
Somatosensory associative areas		Perceptual disturbances in Body image including altered size and altered body midline. Impaired performance of laterality recognition

Increasing attention and salience directed to the injury, threat, and perception of pain appears to result in implicit and explicit learning linking movement with pain (Moseley and Flor 2012).

In summary, neurophysiological changes associated with CMSD include alterations in structure (decrease in grey matter in meso-limbic and prefrontal) (Apkarian et al. 2004), function and organisation (i.e. changes in response properties and cortical representation in S1 and M1) (Pelletier et al. 2015) and neurobiology (changes in brain chemistry concentrations have been found in subjects with CLBP in an area of the PFC and in M1) (Grachev et al. 2000).

6.3.1.4 Implications of distributed neuroplastic changes associated with chronic musculoskeletal disorders for rehabilitation

Neuroplasticity associated with CMSD have important implications for the treatment of conditions such as CLBP, OA and possibly other CMSD (Snodgrass et al. 2014). Conventional rehabilitation interventions are in large part directed towards input (i.e. peripheral structural injury addressing inflammation, repair and remodelling) and output (i.e. muscular strength, endurance, motor control and proprioception) mechanisms associated with CMSD (Nijs, Meeus, et al. 2014). Although these interventions may have an impact on peripheral structures they in themselves may not be sufficient to restore cortical properties and function and alleviate pain particularly in chronic injuries (Lundbye Jensen et al. 2005). In musculoskeletal rehabilitation limited resources have been directed to the problems of transmission, processing, and control mediating afferent stimuli and motor output (Nijs, Meeus, et al. 2014). Failure to effectively treat conditions such as CLBP may stem from the fact that these central neuroplastic changes occurring across distributed areas associated with this condition have largely been ignored and may explain why treatment effects are consistently small regardless of the type of intervention (Wand and O'Connell 2008; Pelletier et al. 2015).

Principles of neuroplasticity emerging from animal and human studies can be harnessed to induce positive neuroplastic changes. Studies in subjects with and without neurological injury suggest that the stimuli necessary to promote neuroplastic changes, at least in sensorimotor cortical areas, must be repetitive, of sufficient intensity to stimulate adaptive changes, require attention and behavioral salience, involve learning, and that changes will be specific to the neuronal structures implicated in the task (Kleim and Jones 2008; Boudreau, Farina, et al. 2010). Neuroplasticity is stimulus driven and the stimuli can be mediated by top-down, from higher to

lower hierarchical structures within the nervous system, and bottom-up, peripheral to central structures of the nervous system, processes (Schabrun, Jones, et al. 2014). As CMSD involves neuroplastic changes within distributed areas, it is logical to believe that treatment should be directed across the different affected structures in the nervous system including the sensorimotor areas and the meso-limbic prefrontal areas. Although this area of study is in its infancy it appears that rehabilitation professionals have at their disposal tools and resources to promote adaptive changes in the sensorimotor areas as well as the meso-limbic and pre-frontal areas associated with CMSD.

6.3.1.4.1 Interventions

6.3.1.4.1.1 Top-down

6.3.1.4.1.1.1 Reconceptualising pain

Health care practitioners and persons with CMSD tend to view pain with a bio-medical focus (Shaw et al. 2011) despite of the failings of this model both to explain clinical and experimental findings and to guide effective rehabilitative strategies. Studies indicate that the relationship between threat and tissue damage is altered in chronic pain states, the stimulus response relationship between structural injury and pain perception is nebulous, neuroplastic changes associated with chronic pain is mal-adaptive, and no longer performs the biological function of protection (Apkarian et al. 2011; Woolf 2011; Moseley and Flor 2012; Pelletier et al. 2015). It is imperative that updated and current knowledge regarding pain and a biopsychosocial perspective stemming from the wealth of research findings that has emerged over the last two decades be transferred to health care professionals and in health care curriculum (Nijs, Girbés, et al. 2014; Nijs et al. 2013; Nijs, Meeus, et al. 2014).

Recognition of misguided beliefs, values, and behavioral strategies that persons with CMSD may display regarding pain and their injury that are incongruent with the rehabilitation principles of graded activity to promote mobilization and positive adaptive changes should be addressed early and continuously in the rehabilitative process (Nijs et al. 2013). The conceptualisation that pain and movement are associated with structural damage and the belief that structural insult to anatomical structures is the source of all pain needs to be reformulated (Moseley 2003).

Experimental findings demonstrate that neurophysiology pain education (NPE) which includes information regarding the anatomy, physiology and processing of noxious stimuli, the perceptual nature of pain, and the altered processing with chronic pain is associated with improvement in function and attenuation of pain (Moseley 2004a). The information and concepts presented in the NPE programs are accessible to patients experiencing chronic pain (Moseley 2003) and can have an immediate impact on behavior (Moseley 2004a). Although the scientific literature is limited in regards to these programs they would appear to perform better than educational programs that stem from a biomedical model to explain structural pathology and biomechanics as the driver of the CMSD (Louw et al. 2011; Clarke et al. 2011). A single session of neurophysiology education of pain in subjects with CLBP has proven to result in a transient decrease in pain and improvement in function (Moseley 2004a) and may be associated with changes in brain activation patterns (Moseley 2005). For more permanent changes in belief and behavior the concepts stemming from neurophysiology education will most probably need to be repeated consistently in the rehabilitation program (Nijs, Girbés, et al. 2014). Although education has been demonstrated to be beneficial in outcome for chronic back pain (Engers et al. 2008), recent meta-analysis and systematic reviews of neurophysiological pain education demonstrate that these programs are promising but that results are presently tenuous due to the limited number of studies (Louw et al. 2011; Clarke et al. 2011).

6.3.1.4.1.1.2 Addressing maladaptive thoughts and behaviours

Cognitive Behavioral Interventions (CBI) seeks to identify and address thoughts, ideas and beliefs that are inconsistent, erroneous and unproductive resulting in maladaptive behavior patterns such as worry and avoidance (Ehde et al. 2014). These include traditional Cognitive Behavioral Therapy (CBT) that is a control-oriented treatment attempting to address catastrophic thinking through cognitive re-structuring, promotion of problem solving skills and addressing mal-adaptive behaviors through exposure-oriented interventions to address avoidance behaviors (Jensen et al. 2012; Wetherell et al. 2011). CBT appears to result in improvement in function, decrease in anxiety, and depression which are correlated with increases in activation within the prefrontal cortex (Ehde et al. 2014; Jensen et al. 2012). These findings suggest that CBT results in an increase in executive control that modulates dysfunctional activity in the meso-limbic areas (Jensen et al. 2012; Ehde et al. 2014). A

prospective study of CBT in subjects with chronic back pain demonstrated decreased functional connectivity between the areas in the PFC and ACC with the amygdala/PAG which positively correlated with decreased pain and improved self-efficacy (Shpaner et al. 2014). Systematic reviews of CBT in subjects with chronic pain indicate that CBT has small to moderate effects on mood, catastrophization and pain intensity and to a lesser extent pain related disability and avoidance behaviors for up to 6 months (Ehde et al. 2014; Bernardy et al. 2010).

6.3.1.4.1.1.3 Acceptance based interventions

Other forms of CBI have also been studied in regards to pain including approaches that involve the development of awareness and non-judgemental acceptance of pain in contrast to attempting to control or fight pain. Two such approaches include Acceptance Commitment Therapy (ACT) and Mindfulness Based Stress Reduction (MBSR) (Wetherell et al. 2011; Veehof et al. 2011). ACT involves the acceptance of positive and negative experiences, the elucidation of values, commitment to these values, and appropriate goals and actions that support these values (Veehof et al. 2011). Pain is seen as an interference to goal directed, value driven action (Veehof et al. 2011; Wetherell et al. 2011). MBSR incorporates meditation, yoga, and a body scan/relaxation technique providing instruction on acceptance without cognitive assessment, to minimize anxiety and its detrimental effects on pain processing, encourages movement and relaxation and the transference of these skills and mindset to everyday life (Hofmann et al. 2010). Different variants have been developed including Mindfulness Based Cognitive Therapy that incorporates principles of CBT within MBSR. MBSR decreases stress, anxiety and depression associated with chronic pain states and, similar to CBT, has an impact on prefrontal structures and their control of mesolimbic structures (Hofmann et al. 2010; Santarnecchi et al. 2014). In healthy subjects a six-week program of MBSR resulted in neuroplastic changes in the insula, S1 and changes in functional connectivity between the medial prefrontal cortex and the insula (increased connectivity between these structures is found in OA patients (Apkarian et al. 2011)), changes that also correlated with improvement on psychological indexes including worry, anxiety and depression (Santarnecchi et al. 2014). In healthy subjects exposed to a noxious stimulation, MBSR resulted not only in the activation of areas in the PFC involved in the reformulation of the contextual evaluation of the noxious stimuli, but also influenced activity within S1 and the thalamus, areas involved in the transmission and sensory discriminative

aspects of pain, alluding to possible effect of MBSR on the gating of noxious transmission (Zeidan et al. 2012).

There is positive evidence for the use of CBI in the treatment of chronic pain, however outcomes are variable and the effects are small for pain intensity, anxiety, depression, quality of life and physical well-being (Veehof et al. 2011; Wetherell et al. 2011). The beneficial effects are greatest for mood, catastrophizing thoughts and disability and there is evidence that effects are maintained at six months (Williams et al. 2012; Eccleston et al. 2013).

In summary, reconceptualisation involves education that challenges negative and faulty beliefs regarding pain. Issues regarding stress/anxiety/worry that contribute to a heightened response to pain, guarding and fear-avoidance need to be addressed continuously and patients should be provided with the tools to better understand and manage their pain and disability including information regarding pain neurophysiology and a bio-psycho-social formulation of CMSD (Nijs, Meeus, et al. 2014). Collectively these interventions appear to improve self-efficacy, the ability of the person to self-manage through actions and interventions to cope with their pain and disability and promote active coping styles (Shpaner et al. 2014; Jackson et al. 2014). Greater self-efficacy is associated with better outcomes in patients with chronic pain (Jackson et al. 2014). Cognitive-based interventions also address the mesolimbic and prefrontal changes associated with chronic pain, which in turn may impact descending pain modulatory systems within the brain stem (that perpetuate sensitization) and cortical sensorimotor areas (Bushnell et al. 2013). NEP and CBI should be addressed at the onset of treatment, even in acute and sub-acute phases and should be continuously addressed during the rehabilitation process. Failure of these interventions to demonstrate more positive effects and for longer durations may stem from the fact that substantial changes in neurophysiological correlates of faulty beliefs and values have not been reconceptualised sufficiently.

6.3.1.4.1.1.4 Priming the brain for movement

The creation of adaptive changes in musculoskeletal structures requires graded and progressive interventions, performed repetitively and with sufficient intensity (Mueller et al. 2002). These principles appear to apply equally in addressing neuroplastic changes to promote positive adaptive outcomes (Kleim and Jones 2008).

Graded exposure can begin with interventions that require implicit activation of sensory and associative areas in the parietal cortical areas through interventions such as laterality recognition where the patient is asked to determine the laterality of an anatomical image without moving their body part (Parsons 2001). Studies have shown that subjects with experimental and chronic pain including CLBP, CRPS, OA and Carpal Tunnel Syndrome (CTS) make more errors and the speed in the performance of this task is affected when visualising the injured body part, reflective of altered somatosensory organisation and processes in sensory areas including S1 and the inferior parietal regions (Schmid and Coppieters 2012; Bowering et al. 2014). Interventions incorporating implicit imagery results in changes in S1 properties and organisation as well as decreased pain and improved function (Bowering et al. 2013).

Explicit cognitive exposure involves motor imagery of painful or fearful movements. Motor imagery has a long history of use in kinesiology and has well documented positive benefits for performance. In people experiencing chronic pain, motor imagery may help to improve physical performance (Hoyek et al. 2014) but also may help to address cortical changes in meso-limbic and prefrontal areas associated with the physical performance of active movements and possible learned associations (implicit and explicit) of pain and movement (Nijs, Girbés, et al. 2014). Motor imagery utilized for the learning of a new motor skill results in improvement in performance and changes in the motor areas similar to that from actual physical practice.

Cognitive based interventions such as motor imagery can influence brain function and cortical processes including sensorimotor areas. They may have an advantage in highly anxious and fearful patients as they do not involve physical movement and should not elicit an anxiety response. The progressive nature of these interventions appears to be important at least in certain pain conditions such as CRPS when pain severely limits the capacity for movement, and simply imagining movement can increase pain and swelling (Moseley 2004b; Moseley, Zalucki, Birklein, et al. 2008). To induce changes in properties and organisation in sensorimotor cortical areas tasks involving motor acquisition of new skills involving sustained attention appears to be necessary.

6.3.1.4.1.1.5 Novel approaches for promoting cortical neuroplasticity

Direct non-invasive stimulation of cortical neurons to promote neuroplastic changes both in isolation or in association with other modalities has been investigated in a limited number of research studies (Williams et al. 2009; Schabrun, Ridding, et al. 2012). Non-invasive cortical stimulation includes transcranial Direct Cortical Stimulation (tDCS) and Transcranial Magnetic Stimulation (TMS). TDCS involves the application of a direct electrical current to the surface of the cranium. Combined tDCS and Peripheral Electrical Stimulation (PES) in subjects with CLBP resulted in map reorganisation in M1, improvement in sensory function and decrease in pain that was superior to their individual application (Schabrun, Jones, et al. 2014).

TMS involves an electrical current passing through a coil producing a magnetic field that traverses the skull and results in the depolarization of neurons under the coil. Repetitive TMS (rTMS) applied at low frequencies (below 5 Hz) produces an inhibition of the area of stimulation while rTMS applied at higher frequencies (greater than 5 Hz) results in a facilitation. Studies have been performed in neurologically compromised subjects including stroke patients to help promote positive neuroplastic changes and improve motor function. Repetitive TMS over the somatosensory cortex can also result in improved tactile acuity (Tegenthoff et al. 2005). Repetitive TMS and anodal transcranial Direct Current Stimulation of the motor cortex help to attenuate chronic pain (Lefaucheur et al. 2008). Studies have also been performed that combine peripheral electrical stimulation paired with TMS to promote neuroplastic changes in M1.

6.3.1.4.1.2 Bottom-up

6.3.1.4.1.2.1 Addressing changes in sensorimotor areas of the brain

Bottom up modulation of altered processing and organisation in S1 includes interventions such as sensory discrimination training and PES. Tactile acuity, specifically Two-Point Discrimination (TPD) utilized as a form of treatment has been associated with decreases in pain, improvement in function and with renormalisation of properties and organisation within S1 in subjects with CRPS but only when subjects are attentive to the experimental interventions (Pleger et al. 2005; Moseley, Zalucki, and Wiech 2008). These findings are consistent with studies that renormalized cortical organisation in S1 in subjects with CTS and improve pain and disability in subjects with CLBP that appear to be mediated by the discriminative nature of sensory stimulation associated with acupuncture (Wand et al. 2013). Sensory retuning programs

involving different forms of sensory stimulation have also been performed in patients with CLBP and CTS and, although limited in scope, preliminary evidence is promising (Pleger et al. 2005; Wand, O'Connell, et al. 2011).

PES can be utilised to affect neuronal properties in both S1 and M1 in healthy subjects (Chipchase et al. 2011a). PES can cause alterations in the somatotopic map within S1 and improve sensory function (Veldman et al. 2014). PES can both augment and attenuate neural excitability in both S1 and M1 depending upon the parameters of stimulation (Chipchase et al. 2011a; Chipchase et al. 2011b). PES of a mixed nerve for 120 minutes, at frequencies <10 Hz, at an intensity of stimulation at or close to motor threshold, results in increases in corticospinal excitability and in improvement of motor performance in healthy subjects (Chipchase et al. 2011a). Higher stimulation frequencies appear to result in decreases in excitability of neurons in the motor cortex (Chipchase et al. 2011a). TENS applied daily for three weeks to the hand in healthy subjects' results in an increase in map volume and area of representation of muscles of the hand within M1 (Meesen et al. 2011).

To induce plastic changes in M1, active interventions need to focus on motor learning (Lundbye Jensen et al. 2005; Boudreau, Farina, et al. 2010). The simple repetition of movement will not result in plastic changes in the motor cortex (Lundbye Jensen et al. 2005). Excellent reviews have recently been published on principles of neuroplasticity, motor learning and their utilisation in patients with CMSD (Boudreau, Farina, et al. 2010; Snodgrass et al. 2014; Nijs, Meeus, et al. 2014). Principles including the utilisation of motor learning, functional reacquisition and external focus of attention can be incorporated into rehabilitation programs to address changes in the sensorimotor areas associated with CMSD (Boudreau, Farina, et al. 2010; Snodgrass et al. 2014). Motor learning requires focused attention and salience and involves increased interaction and feedback (Snodgrass et al. 2014). The importance of attention in promoting plastic changes in M1 has been demonstrated in a number of studies. Indeed, it is possible that effects related to motor learning may simply be mediated by the increased attention required to perform new tasks (Stefan et al. 2004). Active movements to promote motor learning and associated cortical changes should involve functional progressions with increasing task complexity (Boudreau, Farina, et al. 2010). Finally, an external focus of attention involved with motor learning may be beneficial to shift attention towards the accomplishment of a task, **as**

distraction helps to modulate pain perception, as opposed to an internal focus, which results in increased vigilance towards pain and can exacerbate pain perception (Boudreau, Farina, et al. 2010; Snodgrass et al. 2014).

6.3.1.4.1.3 Clinical application of treatment addressing distributed neuroplastic changes with chronic MSD

Active interventions addressing motor and mobility disturbances should also be graded and progressive. The use of laterality recognition training, motor imagery, and mirrors in an approach of graded motor imagery may be helpful in addressing neurophysiological changes associated with CMSD (Bowering et al. 2013). The question as whether to begin with painful movements to challenge the mal-adaptive changes in the nervous system or to progressively begin exercise in non-painful ranges and movements or with graded imagery before progressing to movements that are associated with fear and anxiety is a matter of debate (Boudreau, Farina, et al. 2010; Nijs, Meeus, et al. 2014). The choice may be dictated by patient attitudes, beliefs and behaviors, the more fearful and anxious, the more non-threatening should be the progression of exercise as early pain may simply re-inforce their existent values and operant learning linking movement to pain. However, pain should not be utilised as the sole measure of progression because of the nebulous relationship between pain and threat of impending further tissue injury in chronic pain states. Exercise should be guided by form, the ability to perform the movement correctly, and functional progressions in volume and intensity (resistance and difficulty of task) (Boudreau, Farina, et al. 2010; Snodgrass et al. 2014).

The cognitive strategies reviewed earlier need to be addressed continuously as to dampen the effects of anxiety and fear, to limit guarding, and to progressively integrate movements that were previously perceived as threatening. Patient's beliefs, apprehension and behaviors must be challenged repetitively (Nijs, Girbés, et al. 2014). Graded functional progressions should, over time, help extinguish learned associations reflective of neuroplastic changes in the meso-limbic and prefrontal areas, and secondly address the cortical changes in the sensorimotor areas associated with CMSD. Cortical, subcortical and the spinal cord have strong interconnections and interventions targeting one area should impact the others including sensorimotor and meso-limbic areas. Finally, the positive yet limited effects of many of these approaches in isolation

suggest that a multimodal approach that is coherent, consistent, and incorporates interventions specifically targeting neuroplastic changes may yield more positive outcomes.

6.3.1.4.1.4 Reconceptualising treatment provided to patients with chronic MSD

The growing evidence for changes in distributed areas of the nervous system in chronic pain conditions may also provide greater comprehension of methods of action presently utilized by physical rehabilitation professionals and lead to more effective interventions which may involve neurophysiological changes. Treatment goals in patients with CMSD have largely been directed by a biomedical paradigm which has proven to be limited in efficacy (Wand and O'Connell 2008; Darlow et al. 2012). Rehabilitation presently performed with patients with CMSD may result in peripheral and central changes. The reconceptualising of treatment provided to patients with CMSD would therefore involve an approach that targets peripheral structural sources of pain, but also interactions and specific interventions to encourage plastic changes in the nervous system by addressing faulty values and beliefs regarding pain, attempting to minimize fear and anxiety, and perform exercises and interventions that target sensorimotor and perceptual changes. It is imperative that the therapist remains consistent in the messages conveyed both explicitly and implicitly through their actions and behaviors. The message conveyed to the patient should not imply implicitly or explicitly that a structural-pathology model alone of local biomechanical problems is the sole driver of the CMSD. The implicit or explicit perception by the patient would be inconsistent with experimental findings and may perpetuate faulty beliefs, encourage fear-avoidance, anxiety and guarding, resulting in decreased movement and contributing to a biomedical focus of local tissue insult as the driver of the condition and possibly negatively impacting self-efficacy and outcomes (Girbés et al. 2014; Nijs, Meeus, et al. 2014). This is important as therapist-patient interaction and communication is important for treatment success (Ferreira et al. 2013). Our current understanding of principles of neuroplasticity may help to understand the method of action of current interventions and develop interventions that help promote positive long-term adaptive changes within the CNS associated with CMSD.

6.3.1.5 Conclusion

CLBP, OA and probably other CMSD are associated with neuroplastic changes across distributed areas of the nervous system including the peripheral, spinal cord, brain stem,

sensorimotor cortical areas and meso-limbic and prefrontal structures. These changes correlate with the clinical and experimental findings within this population including psychological traits, perceptual and sensorimotor disturbances. Addressing the changes across the distributed network may help to yield greater understanding and outcomes for the treatment of these conditions. This involves cognitive based interventions such as education to reconceptualise beliefs regarding pain, and interventions to modify patients' thoughts and reactions to help control anxiety and improve self-efficacy. Neuroplastic changes in the sensorimotor cortical areas are also affected in CMSD, and interventions that modulate sensory input and involve motor learning need to be incorporated into existent rehabilitation programs. The focus of interventions oriented towards renormalisation of distributed cortical areas is consistent with a bio-psycho-social paradigm and may result in improved outcomes. Imaging studies of these cortical areas associated with CMSD will help to determine how widespread are these cortical changes, provide an additional means to address efficacy of these interventions, and to determine how well interventions correlate with positive outcomes and renormalisation of cortical properties, processes and organization. Musculoskeletal rehabilitation professionals are well positioned and have resources at their disposition to influence positive adaptive neuroplastic changes by addressing psychological and biological factors within the nervous system associated with CMSD.

6.3.1.6 References

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6.4 Limitations

Several important factors should be considered when interpreting the results from the studies presented. A recent systematic review of reliability studies for TMS has highlighted concerns of these studies, including methodological and statistical errors. Importantly, methodical issues in TMS studies may result in significant measurement errors that must be accounted for in order to demonstrate differences over time (Beaulieu et al. 2017). However, the information highlighted by the authors regarding error measurements and methodological concerns appears to be applicable cross-sectional studies utilizing TMS comparing between groups. The studies presented in the thesis have relatively small sample sizes and are best described as exploratory and will require further validation. Data acquisition and analysis were all performed by myself and I was not blinded to group allocation and therefore the risk of bias is present. In the manuscripts found in sections 5.1 and 5.2, no corrections were made for multiple comparisons for the correlations. The studies were all observational cross-sectional studies and therefore provide little information as the direction of changes. Longitudinal studies and animal model studies are required to further clarify the relationship between pain, sensory and motor function, cognitive affective changes with MSD.

Chapter 7 Conclusion

There is a growing interest of the changes in structure and function in the CNS associated with chronic MSD. This growing interest stems, at least in part, from the failure of current interventions to produce positive outcomes for these populations and the inconsistencies found within the present biomedical model that largely influence beliefs of health care providers and patients and guides conventional treatment (Darlow et al. 2012). The findings presented in this thesis contribute to the growing body of evidence of changes in sensorimotor areas of the CNS associated with chronic MSD. The novelty of the present thesis, in addition to information not only demonstrating changes in sensorimotor processes, lies in the findings that there is a relationship of these changes in sensorimotor areas with sensory, motor, and cognitive-affective factors.

Chapter 8 Future Directions

The results of this thesis help to demonstrate that the cortical sensorimotor changes are related to clinical measures of function, pain and disability. We are presently completing the experiment involving the cognitive, psychosocial, sensory and motor assessment as well as the LRJT in healthy control participants. We also have ethical approval to perform a study involving cognitive, psychological, sensory and motor assessment as well as cortical measures of sensorimotor integration utilizing TMS and the LRJT in participants diagnosed with first carpal-metacarpal osteoarthritis. Future research interests involve simultaneous measurement of clinical and electrophysiological measurements of sensory and motor processes and determining how these processes are impacted by cognitive, psychological and social factors. We are also interested in understanding how rehabilitative treatments may influence these processes and impact outcome measures.

From a fundamental science perspective, the further investigation into the relationship between spinal and cortical excitability changes and their modulation in motor control and in persons with MSD is of interest. Longitudinal studies would need to be performed to understand underlying mechanisms and direction of causality between pain, cortical changes, sensorimotor processes and MSD. There have been few studies that have attempted to understand the relationship between cortical changes associated with MSD and pain, altered sensation, motor control and behavioral changes. In rehabilitation sciences this information is critical as they will govern the allocation of resources to help relieve pain and restore function by addressing underlying mechanisms. There is also a need to better understand the functional implications of these cortical changes.

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