The Effect of Experimental Knee Pain on Contralateral Quadriceps Strength and Thigh Muscle Activity.

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A research thesis submitted in partial fulfillment of the requirements for the degree of Master of Osteopathy

Unitec Institute of Technology
Declaration

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This thesis entitled “The effect of experimental knee pain on contralateral quadriceps strength and thigh muscle activity” is submitted in partial fulfillment of the requirements for the Unitec degree of Master of Osteopathy.

Candidate’s declaration:

I confirm that:

• This thesis project represents my own work
• The contribution of supervisors and others to this work was consistent with the Unitec Regulations and Policies
• Research for this work has been conducted in accordance with the Unitec Research Ethics Committee Policy and Procedures, and has fulfilled any requirements set for this project by the Unitec Research Ethics Committee

Research Ethics Committee Approval Number: 2014-1064

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And to Ilia Saraev, although you test my patience you were always there to keep me focused on the task at hand. Thank you.
This research study explored the effects of experimentally induced knee pain on the muscle activity of the unstimulated contralateral homologous limb in order to determine whether pain may contribute to muscle inhibition via central mechanisms.

This thesis is presented in two main sections. Section one is a literature review to provide the reader with a background of the effects of pain on muscle activity and to show the link between muscular adaptations during pain to the clinical phenomenon of arthrogenic muscle inhibition.

Section two is a manuscript and is followed by appendices containing documents of ethics approval, participant information, and the Pain Catastrophizing Scale questionnaire.
Abstract

**Objective:** To determine the effects of experimentally induced pain on the strength of the contralateral quadriceps.

**Methods:** Fourteen healthy participants were recruited to attend two separate data collection sessions so that participants could be used as their own controls. The experimental condition consisted of hypertonic saline injection into the infrapatellar fat pad of the resting leg; isotonic saline was used in the control condition. Surface electromyography (EMG) from vastus medialis (VM), vastus lateralis (VL), biceps femoris (BF) and medial hamstrings (MH), and quadriceps torque measurements of the active leg were recorded during maximum effort isometric knee extension, which was performed before and immediately following injection. Quadriceps peak torque, maximum rate of torque development (MRTD), and the root mean square (RMS) of EMG signals from VM, VL, BF and MH were analyzed.

**Results:** Peak torque, MRTD and quadriceps RMS were significantly reduced following hypertonic saline injection into the contralateral infrapatellar fat pad. No significant changes in hamstrings RMS amplitude were seen following hypertonic saline injection. Isotonic saline produced no significant changes in peak torque, MRTD, or RMS of quadriceps or hamstrings.

**Conclusion:** The findings of the present study suggest that increased nociceptive output from the knee joint contributes to contralateral quadriceps muscle inhibition.
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Introduction to Thesis

The preface to this thesis orientates the reader to the structure of the thesis. The following introduction familiarizes the reader to the author’s background and the purpose of this research.

As a student of osteopathy I have a strong interest in the neurophysiology of pain and the mechanisms behind dysfunctional movement patterns. Existing research has provided evidence linking various dysfunctional motor adaptations to the presence of pain, but the mechanisms behind many of these observations have yet to be explained. This 90-credit thesis has been completed in accordance with the requirements to fulfill the Master of Osteopathy qualification, alongside 1000 hours of clinical practicum, and has been taken as an opportunity to further explore the effects of pain on muscle activity. My motivation behind this research study extends from a desire to better understand the role of pain in provoking mechanisms of human physiology that result in altered movement patterns. I hope that the results of this research may help to inform future rehabilitation strategies.

Musculoskeletal injury often results in disturbed range of motion and altered muscle activation patterns. Osteopaths and other manual therapists frequently see this in patients and direct treatment to the restoration of function in the symptomatic area, often using the contralateral homologous body structure to guide what is normal function for each individual. However, clinical case studies of knee joint pathology have provided evidence to suggest that dysfunctional motor adaptations occur bilaterally. Bilateral motor adaptations would imply that the functional normal for each individual would not be equal to that of the contralateral homologous structure, but likely even greater than this. If this is true, then rehabilitation strategies employed by osteopaths and other clinicians should incorporate both sides of the body, aiming for greater functional ability than is observed in the asymptomatic homologous structure.
A commonly observed motor adaptation present in both clinical case studies and experimental pain studies is reduced strength of painful muscles or those which move painful joints. In clinical studies of knee joint pathology this strength deficit is frequently observed in not only the ipsilateral quadriceps muscle, but also its contralateral counterpart. While it has not been determined what exact mechanisms are responsible for these strength deficits, findings of reduced muscle activity suggest a neural mechanism of muscle inhibition is responsible. Bilateral muscle inhibition, occurring after a unilateral stimulus, such as soft tissue damage, inflammation or pain, suggests the involvement of centrally mediated processes.

This research study explores contralateral quadriceps strength in the presence of knee pain without existing tissue injury, in order to determine whether pain can provoke contralateral quadriceps muscle inhibition. This research is the first to explore contralateral muscle effects of experimentally induced pain.
Section One: Literature Review
Introduction

Motor adaptations often occur following musculoskeletal injury and frequently impede functional performance. Disadvantageous motor adaptations such as delayed muscle activation (Hodges, Moseley, Gabrielson, & Gandevia, 2003; Wadsworth & Bullock-Saxton, 1997), altered muscle recruitment patterns (Arendt-Nielsen, Graven-Nielsen, Svarrer, & Svensson, 1996; Madeleine, 2010), reduced muscle strength (Hassan, Mockett, & Doherty, 2001; Schomacher, Farina, Lindstrøm, & Falla, 2012) and reduced muscular endurance (Falla & Farina, 2005; Mannion, 1999; Mannion et al., 2000) have all been observed following musculoskeletal injury and are classic areas of focus for rehabilitation. Typically, rehabilitation strategies are targeted to the affected limb while the unaffected limb is used as a clinical baseline/comparator, and may not be actively included in rehabilitation. However, there is increasing evidence that unilateral musculoskeletal injury may affect motor function in distal muscles as far afield as the contralateral limb (Suter, Herzog, & Bray, 1998a; Urbach, Nebelung, Weiler, & Awiszus, 1999), in which case using the “unaffected” limb as a comparator would not provide a true baseline of motor ability.

Bilateral motor adaptations that have been observed after unilateral musculoskeletal injury include altered muscle activation patterns and reduced muscle strength. Wadsworth and Bullock-Saxton (1997), compared muscle activation patterns in healthy competitive swimmers to those who had been diagnosed with unilateral shoulder pathology and found a significant delay in the onset of bilateral serratus anterior muscle activation in the injured group. Furthermore, reduced maximum voluntary contraction (MVC) strength has been repeatedly demonstrated in both the symptomatic and contralateral limbs in cases of knee joint pathology when compared to healthy control subjects (Becker, Berth, Nehrig, & Awiszus, 2004; Suter, Herzog, De Souza, & Bray, 1998b; Urbach & Awiszus, 2002).

The knee joint is one of the most common sites of musculoskeletal injury/pathology (Bossley & Miles, 2009), accounting for over 197,000 ACC claims and over $234
million in ACC costs between 2014-2015 (ACC Injury Statistics Tool, 2016). At the knee joint specifically, contralateral muscle weakness is frequently observed across a range of different knee injuries/pathologies despite unilateral joint injury (Chmielewski, Stackhouse, Axe, & Snyder-Mackler, 2004; Hurley, Jones, & Newham, 1994; Machner, Pap, & Awiszus, 2002; Suter et al., 1998b; Urbach et al., 1999). In various studies following subjects with unilateral rupture of the anterior cruciate ligament, deficits in MVC strength of both the injured and uninjured quadriceps muscles have consistently been observed in affected subjects when compared with age- and weight-matched control subjects (Chmielewski et al., 2004; Urbach & Awiszus, 2002; Urbach, Nebelung, Becker, & Awiszus, 2001; Urbach et al., 1999). Similar observations of quadriceps MVC strength deficits have been observed bilaterally in subjects with osteoarthritis of the knee despite a lack of degenerative changes in the contralateral knee (Becker et al., 2004). Suter and associates (1998b), also found quadriceps MVC strength deficits bilaterally when investigating subjects with long-term unilateral anterior knee pain.

In several studies, the potential mechanisms explaining contralateral MVC quadriceps weakness have been explored further using twitch-interpolation or burst superimposition techniques (Becker et al., 2004; Chmielewski et al., 2004; Suter et al., 1998a; Urbach & Awiszus, 2002). These techniques involve superimposing an electrical stimulation upon a muscle during a voluntary contraction in order to stimulate inactive muscle fibres (Gandevia, McNeil, Carroll, & Taylor, 2013), and have been shown to be reliable methods of demonstrating deficits in voluntary activation of the muscle (Behm, St Pierre, & Perez, 1996; Dousset & Jammes, 2003). The use of these techniques has provided evidence of quadriceps voluntary activation deficits despite conscious effort to produce a maximal muscle contraction. The fact that not all muscle fibres are being activated during quadriceps MVC suggests that neural inhibitory mechanisms may at least partly explain the contralateral quadriceps weakness observed after unilateral joint damage.

Muscle inhibition following injury is a commonly observed phenomenon and is hypothesised to occur as a protective mechanism controlled by the central nervous
system (CNS) to prevent further injury (Ervilha, Farina, Arendt-Nielsen, & Graven-Nielsen, 2005; Hodges, 2011; Van Wilgen, Akkerman, Wieringa, & Dijkstra, 2003). However the resulting muscle weakness may have detrimental clinical implications. Quadriceps weakness is a known risk factor for incident knee pain, patellofemoral cartilage loss and joint space narrowing (Amin et al., 2009; Segal et al., 2010), and is associated with increased load upon the knee joint (Mikesky, Meyer, & Thompson, 2000). Quadriceps inhibition may persist bilaterally for as long as 4 years following original joint damage (Becker et al., 2004). Long-term quadriceps weakness has been associated with compromised dynamic knee joint stability (Felson et al., 2007) and physical function (Hurley, Scott, Rees, & Newham, 1997; Liikavainio, Lyytinen, Tyrväinen, Sipilä, & Arokoski, 2008), and may prevent effective quadriceps strengthening and rehabilitation, leading to further muscle atrophy and weakness. Consequently, the presence of bilateral quadriceps weakness is likely to have more important clinical implications.

Presently, the mechanisms underlying deficits in contralateral quadriceps muscle activation remain poorly understood. However it is postulated that quadriceps muscle inhibition involves changes in sensory output from the damaged knee joint. These changes in sensory output may alter the excitability of spinal reflex pathways, reducing the excitability of the quadriceps α-motoneuron pool and thus preventing full activation of the muscle (Ferrell, Wood, & Baxendale, 1988; Hurley, 1997; Iles, Stokes, & Young, 1990; Young, 1993). The knee joint is innervated by three main groups of sensory fibres. Group II afferents have low-thresholds and detect mechanical stimuli such as stretch and pressure. Group III and IV afferents have high-thresholds and act mainly as nociceptors responding to strong mechanical, thermal and chemical stimuli (Grigg, 2001; Heppelmann, 1997). Based on the understanding of these joint afferents and their response to local environmental changes in the injury knee joint, several factors that may alter sensory output have been identified.

**Loss of sensory output:**
When structural damage to the knee joint occurs, articular receptors within these tissues may also be damaged and can result in reduced afferent output (Ochi, Iwasa, Uchio, Adachi, & Sumen, 1999). Such a reduction in normal sensory output from the knee has been implicated in quadriceps inhibition of the ipsilateral limb. In this regard, local injection of anaesthetic into the uninjured knee reduces quadriceps force output and electromyograph (EMG) activity during subsequent maximal voluntary contractions, yet when anaesthetic is injected into the injured knee no changes in quadriceps force output or EMG activity are observed (Konishi, Fukubayashi, & Takeshita, 2002; Konishi, Suzuki, Hirose, & Fukubayashi, 2003). It has been argued that the ineffectiveness of anaesthetic on the injured knee joint indicates the presence of joint receptor damage and a subsequent dysfunction in afferent output that prevents full activation of the quadriceps muscle (Konishi et al., 2002). While this may help to explain ipsilateral quadriceps muscle weakness, it is unknown whether a loss of sensory output from the injured knee also contributes to contralateral quadriceps muscle weakness.

**Increased sensory output:**

Increases in sensory output have been associated with a number of factors that are commonly observed to occur with knee joint injury and/or pathology. Joint laxity, commonly occurring as a result of damage to ligaments, causes increased translation of the knee joint. This increases the activation of mechanoreceptors and nociceptors of the knee joint, as it is their role to indicate the limits in joint range of motion. Significantly increased joint afferent activity during knee motion has been demonstrated in animal studies following transection of the anterior cruciate ligament (Gómez-Barrena, Nuñez, Ballesteros, Martinez-Moreno, & Munuera, 1999; Gómez-Barrena, Nuñez, Martinez-Moreno, Valls, & Munuera, 1997). This observation implicates increased joint afferent activity due to increased translation of the joint, further supported by the observation that the joint afferent changes could be partially reversed by reconstruction of the anterior cruciate ligament (Gómez-Barrena et al., 1999). It is currently unknown whether joint laxity
contributes to quadriceps muscle inhibition in either the ipsilateral or contralateral limb.

Swelling is another factor present in knee joint injuries that may lead to aberrant afferent discharge and can be simulated by infusing the knee joint with saline. Using this method, swelling has been shown to enhance inhibition of the ipsilateral quadriceps H-reflex at rest and during voluntary contractions (Iles et al., 1990), reduce quadriceps EMG activity (deAndrade, Grant, & Dixon, 1965; Palmieri-Smith, Kreinbrink, Ashton-Miller, & Wojtys, 2007; Rice, McNair, & Dalbeth, 2009), and inhibit quadriceps force output (Hopkins, Ingersoll, Edwards, & Klootwyk, 2001; Jensen & Graf, 1993; McNair, Marshall, & Maguire, 1996; Rice et al., 2009; Wood, Ferrell, & Baxendale, 1988). These effects may occur with swelling due to increased intra-articular pressure, and thus increased discharge of group II joint afferents (Grigg, Schaible, & Schmidt, 1986; Schaible & Schmidt, 1983). The inhibitory patterns observed in the presence of joint swelling have also been shown to reverse with aspiration, local anaesthetic injection (Spencer, Hayes, & Alexander, 1984; Wood et al., 1988), and cryotherapy (Hopkins et al., 2001; Rice et al., 2009), supporting the link between increased swelling and increased joint afferent activity. In contrast to its effects on the ipsilateral limb, experimentally induced knee joint effusion does not lead to quadriceps H-reflex inhibition in the contralateral limb (Palmieri et al., 2003), suggesting that swelling alone is unlikely to be involved in mediating contralateral quadriceps inhibition.

Inflammation occurs in response to tissue damage so is present with acute musculoskeletal injury and may occur chronically in rheumatologic diseases. Inflammatory chemicals interact with articular free nerve endings, decreasing the thresholds of group III and IV (nociceptive) joint afferents and enabling them to respond to a larger range of mechanical stimuli including normal joint movement (Schaible & Richter, 2004). This phenomenon, known as peripheral sensitisation, has been demonstrated by inducing inflammation in animal studies (Grigg et al., 1986; Schaible & Schmidt, 1988) and is known to greatly increase nociceptive afferent discharge from the knee. Moreover, reduced inflammation following corticosteroid
injection in subjects with arthritis led to corresponding increases in muscle strength and activation (Geborek, Månsson, Wollheim, & Moritz, 1990; McNair, Rice, Lewis, & Dalbeth, 2014), suggesting there may be a direct relationship between the inflammation induced increase in nociceptive output and quadriceps muscle inhibition. Further evidence for this assertion is that knee pain intensity has been shown to correlate with deficits in quadriceps activation while experimentally induced knee pain leads to instant deficits in quadriceps peak torque (Henriksen, Rosager, Aaboe, Graven-Nielsen, & Bliddal, 2011; Park & Hopkins, 2013). Finally, reductions in knee pain intensity in clinical populations have been shown to increase quadriceps muscle strength (Arvidsson, Eriksson, Knutsson, & Arnér, 1986; Hassan, Doherty, Mockett, & Doherty, 2002).

Whether increased nociceptive output from the knee contributes to contralateral quadriceps inhibition is currently unknown. However, nociceptive afferents have been shown to have complex effects on motor function. The following section provides an overview of some of these changes, exploration of which may provide some insight to the potential mechanisms underlying contralateral quadriceps muscle weakness.

The Neuromuscular Response to Nociception

Alterations in Functional Performance

Changes in skeletal muscle behaviour in the presence of nociception are of great interest to clinicians and researchers as these motor adaptations inform rehabilitation strategies. Consistently observed changes include altered muscle recruitment patterns (Arendt-Nielsen et al., 1996), changes in muscle strength (Lindstrøm, Schomacher, Farina, Rechter, & Falla, 2011), delayed responses in postural muscles (Falla, Jull, & Hodges, 2004a; Tsao, Galea, & Hodges, 2008), and increased fatigability (Falla, Rainoldi, Merletti, & Jull, 2003; O’Leary, Jull, Kim, & Vicenzino, 2007).
Alterations in muscle recruitment patterns during nociceptive stimulation are apparent in studies of the flexion relaxation response, the phenomenon observed in pain-free subjects of reduced muscle activity in erector spinae muscles during full flexion of the trunk. An absence of the flexion relaxation response, shown by continued facilitation of erector spinae muscles, has been observed in people with chronic and experimental low back pain (Ahern, Hannon, Gorenczny, Follick, & Parziale, 1990; Shirado, Ito, Kaneda, & Strax, 1995; Watson, Booker, Phil, Main, & Chen, 1997). This phenomenon is thought to have a protective role by reducing load upon ligamentous structures during movements towards the end of joint range, yet facilitation of muscular activity has also been observed during rest, when ligamentous structures are not loaded, in the presence of muscle pain (Bodéré, Téa, Groux-Metgea, & Woda, 2005; Sterling, Jull, Vicenzino, Kenardy, & Darnell, 2003; Zedka, Prochazka, Knight, Gillard, & Gauthier, 1999). This continued muscle facilitation suggests that absence of the flexion relaxation response could be a maladaptive process potentially originating from changes in sensory output from nociceptors.

In contrast to continued facilitation of muscles, delayed muscle responses and increased rates of muscle fatigability have also been observed in the presence of nociceptive activity. Subjects with chronic musculoskeletal pain demonstrate a reduced ability to sustain isometric contractions in painful muscles compared with asymptomatic control subjects (Falla, Jull, Rainoldi, & Merletti, 2004b; Falla, Rainoldi, Jull, Stavrou, & Tsao, 2004c; Falla et al., 2003; O’Leary et al., 2007). Symptomatic subjects also exhibit increased response times of postural muscles compared with asymptomatic controls in studies of chronic neck and low back pain (Falla, Jull, & Hodges, 2004a; Hodges, 2001; Silfies, Mehta, Smith, & Karduna, 2009; Tsao et al., 2008).

It has been suggested that motor adaptations may occur due to changes in loading of muscles over time following musculoskeletal injury. Increasing the load upon the asymptomatic limb in order to reduce load on the symptomatic limb, for example.
However, experimentally induced muscle pain has enabled the investigation into motor adaptations in subjects without existing musculoskeletal injury. Experimentally induced pain is frequently used for research purposes to overcome the difficulty in recruiting subjects with similar clinical conditions, or in order to simulate pain without the presence of tissue damage. This method of mimicking the pain experience is useful as it allows researchers to control the pain duration and location, and enables participants to act as their own controls, removing the need to account for inter-participant physiological variants. Using methods of experimentally inducing pain, excitation patterns during voluntary movements have been further investigated, and studies have show that multiple muscle groups are often affected by nociceptive afferent stimulation. Both synergist and antagonist muscles have shown altered motor unit excitation patterns in the presence of experimentally induced pain without direct stimulation (Ciubotariu, Arendt-Nielsen, & Graven-Nielsen, 2007; Falla, Farina, Kanstrup Dahl, & Graven-Nielsen, 2006; Hodges & Moseley, 2003). Even muscles distal to the site of pain have shown altered excitation patterns. Noxious fingertip stimulation has demonstrated inhibition of ipsilateral thenar eminence motor evoked potentials (MEPs) and simultaneous facilitation of ipsilateral biceps brachii MEPs (Inghilleri, Cruccu, Argenta, & Polidori, 1997; Kofler et al., 1998; Kofler et al., 2008), further inferring that nociceptive input has the ability to alter the output of distant motoneuron pools, beyond the local area of pain.

Despite the variation in pain-induced muscle recruitment strategies, the broad range of literature describing the effects of pain on muscle contractions has the unanimous finding of reduced muscle strength from the painful muscle, or that which moves a painful joint (Henriksen et al., 2011; Ireland, Willson, Ballantyne, & McClay Davis, 2003; Reinking et al., 1996). The pain adaptation model postulates that nociceptive afferent input from a painful joint or muscle converges upon spinal interneurons causing inhibition of motoneurons to the painful muscle or that which moves the painful joint (Lund, Donga, Widmer, & Stohler, 1991). However existing research has indicated that motor inhibitory pathways may be mediated at both spinal and supraspinal levels (Le Pera et al., 2001; Martin, Weerakkody, Gandevia, & Taylor,
2008; Valeriani et al., 1999), which could explain why the motor effects of nociception are not always uniform and not confined to the local area of pain.

**Alterations in the Central Nervous System**

Neuroplastic changes in the CNS are thought to occur following nociceptive afferent input. This neuroplasticity of the CNS may contribute to the changes in muscular activity and morphology evident as the altered movement patterns observed during pain (Le Pera et al., 2001; Schabrun & Hodges, 2012). Environmental and sensory stimuli have been seen to evoke rapid plastic changes in the CNS in human and primate studies as soon as three weeks following tissue injury (Henderson, Bandler, Gandevia, & Macefield, 2006; Merzenich et al., 1983; Wall, Xu, & Wang, 2002). These include changes to normal excitation and inhibitory processes, atrophy of normal structures, and the formation of new synapses (Wall et al., 2002).

Such neuroplastic changes in the CNS have the potential to cause long-term alterations in motor performance. Quadriceps muscle inhibition has been observed to persist long after an initial injury, despite no evidence of further joint damage (Becker et al., 2004). While it is not known whether other factors have the potential to trigger neuroplastic changes, existing evidence indicates that neuroplasticity of the CNS can be triggered by nociceptive afferent input (Le Pera et al., 2001; Schabrun & Hodges, 2012), which may help to explain the persistence of quadriceps muscle inhibition.

**Potential Neural Pathways for Contralateral Inhibition**

Stimulation of nociceptive joint afferents may alter the excitability of various neural pathways that could be involved in mediating contralateral quadriceps inhibition. A number of potential spinal reflex and/or supraspinal pathways have been implicated in quadriceps inhibition of the ipsilateral limb and have been reviewed elsewhere (Rice & McNair, 2010). The following section builds on this work to consider the potential neural mechanisms underlying quadriceps muscle inhibition of the
contralateral limb, and particularly, how joint nociception may affect these pathways.

**Supraspinal pathways**

Nociceptive stimulation has been shown to induce changes in excitability of the motor cortex (Kirveskari, Vartiainen, Gockel, & Forss, 2010; Le Pera et al., 2001; Martin et al., 2008), and modify muscular representation within the motor cortex (Sanes & Donoghue, 2000; Schabrun & Hodges, 2012; Tsao et al., 2008), in studies that use both clinical and experimental pain procedures. However, limitations in the ability to study the activity of the brain during nociceptive stimulation means that still very little is known about the supraspinal mechanisms that integrate nociceptive information (Sterling et al., 2003; Valeriani et al., 1999).

Presently, non-invasive exploration of cerebral motor cortex activity is possible via transcranial magnetic or electrical stimulation techniques, or monitoring changes in regional cerebral blood flow. Using these techniques, changes in neuronal activity have been detected in various cerebral areas during noxious cutaneous, intramuscular and/or joint stimulation. Areas with consistent significant detectable changes in neuronal activity during nociceptive stimulation include the contralateral primary and secondary somatosensory cortices, primary motor cortex, anterior insula, anterior cingulate cortex and thalamus (Apkarian, Bushnell, Treede, & Zubieta, 2005; Bingel et al., 2004; Coghill et al., 1994).

Evidence of nociception leading to muscle inhibition at the motor cortex level has been provided using experimental pain models in the upper limb (Le Pera et al., 2001; Schabrun & Hodges, 2012). In such studies, painful stimulation has been shown to reduce motor evoked potential (MEP) amplitude, and increase short-interval intracortical inhibition (SICI), (Valeriani et al., 2001). Though these findings suggest that cortical mechanisms may contribute to quadriceps muscle inhibition there is little evidence to infer that acute lower limb pain also evokes inhibition at
the level of the motor cortex. Surprisingly, the effects of acute knee pain upon motor cortex excitability and SICI differ greatly from the observations of acute pain in the upper limb. Rice, Graven-Nielsen, Lewis, McNair, and Dalbeth (2015), found that experimental knee pain caused an increase in quadriceps muscle MEP amplitude, with no significant changes in SICI. These findings are consistent with observations of individuals with knee joint pathology (Héroux & Tremblay, 2006; Kittelson, Thomas, Kluger, & Stevens-Lapsley, 2014; On, Uludag, Taskiran, & Ertekin, 2004) where quadriceps corticospinal excitability is typically increased, rather than decreased.

A potential explanation for contralateral quadriceps muscle inhibition, coinciding with findings of increased quadriceps MEP amplitude following nociceptive stimulation, lies in the theory of interhemispheric inhibition. Interhemispheric inhibition refers to the neurophysiological mechanism of one hemisphere of the brain inhibiting the other. This phenomenon has been observed when suppression of the contralateral motor cortex occurs following stimulation of the ipsilateral motor cortex (Di Lazzaro et al., 1999; Valeriani et al., 2001).

For example, in stroke patients, interhemispheric inhibition has been demonstrated to contribute to changes in motor performance. Use of transcranial magnetic stimulation has revealed that a loss of interhemispheric inhibition from the primary motor cortex of the lesioned hemisphere in stroke patients may be partially responsible for an abnormal decrease in SICI of the non-lesioned contralateral primary motor cortex (Bütefisch, Weßling, Netz, Seitz, & Hömberg, 2008). Decreased SICI in the non-lesioned primary motor cortex facilitates motor recruitment, which may in turn increase interhemispheric inhibition from the non-lesioned hemisphere to the lesioned hemisphere. Furthermore, inhibition of sensory output from the non-paretic hand of stroke patients using cutaneous anaesthesia has been shown to reduce the inhibitory drive from the non-lesioned hemisphere to the lesioned hemisphere leading to improved transient movements in the contralateral paretic hand (Floel, Hummel, Duque, Knecht, & Cohen, 2008), suggesting that interhemispheric inhibition from the non-lesioned motor cortex to the lesioned motor cortex directly affects motor performance.
Similarly, interhemispheric inhibition may partially explain the bilateral quadriceps muscle inhibition observed in the presence of unilateral knee joint pathology. If, as observed, nociceptive input from the knee joint results in increased quadriceps corticospinal excitability of the ipsilateral limb (Rice et al., 2015), this may lead to inhibition of quadriceps corticospinal excitability of the contralateral limb by an increase in interhemispheric inhibition.

**Spinal reflex pathways**

**Group I Non-Reciprocal (Ib) Inhibitory Pathway**

Group I non-reciprocal (Ib) interneurons predominantly receive input from Ib afferent fibres originating in the Golgi tendon organ (Lundberg, Malmgren, & Schomburg, 1978), but also from peripheral afferent receptors including group II, and potentially group III and IV joint afferents (Harrison & Jankowska, 1985; Lundberg et al., 1978). Group II afferents facilitate Ib inhibitory interneurons via disynaptic and trisynaptic excitatory pathways (Harrison & Jankowska, 1985; Lundberg et al., 1978). Facilitation of Ib interneurons reduces the excitability of quadriceps motoneurons and thus inhibits muscle contraction (Lundberg et al., 1978). Due to the effect of swelling on group II joint afferents, the Ib inhibitory pathway may be one way by which joint effusion contributes to muscle inhibition, however this has only been observed ipsilaterally. Though it is not known whether group III and IV joint afferents facilitate Ib inhibitory interneurons in humans, this relationship has been seen in the cat (Harrison & Jankowska, 1985), suggesting that joint nociceptors may also facilitate Ib inhibition of the quadriceps motoneuron pool. It is not known whether Ib inhibition could contribute to quadriceps weakness in the contralateral as well as ipsilateral limbs.

**Gamma Loop**
The gamma (γ-) loop spinal reflex pathway is essential for normal muscle function. γ-motoneurons innervate primary muscle spindles enabling transmission of excitatory impulses to the α-motoneuron pool via Ia afferents, that are essential to enable full activation of muscles during voluntary contractions (Rice & McNair, 2010). In accordance with bilateral observations of muscle inhibition, γ-loop dysfunction has been shown to occur bilaterally in cases of unilateral anterior cruciate ligament rupture (Konishi, Aihara, Sakai, Ogawa, & Fukubayashi, 2007) and may therefore contribute to quadriceps weakness in the contralateral limb. The mechanisms underlying γ-loop dysfunction are poorly understood but may be caused by insufficient Ia afferent transmission to the motoneuron pool (Konishi et al., 2002), or increased discharge of group IV nociceptive afferents (Scott, Ferrell, & Baxendale, 1994). Thus, γ-loop dysfunction is one way in which increased nociceptive output from the knee may lead to quadriceps muscle weakness.

The Nociceptive Flexion Reflex

The nociceptive flexion reflex is a pathway with multiple synapses that facilitates a flexion response and inhibits extension (Leroux, Bélanger, & Boucher, 1995; Rice & McNair, 2010; Sterling, Jull, & Wright, 2001) and is suggested to be partially responsible for quadriceps muscle inhibition (Young, 1993). Nociceptive flexion reflex thresholds are significantly lower in subjects with joint pain (Leroux et al., 1995), and osteoarthritis (Courtney, Lewek, Witte, Chmell, & Hornby, 2009) than in those without, inferring that facilitation of the nociceptive flexion reflex pathway occurs from nociceptive joint afferent input.

Altered joint afferent output may affect the excitability of the nociceptive flexion reflex. Animal models of arthritis have shown a large increase in flexion reflex excitability with the subsequent injection of local anaesthetic into the knee joint resulted in a reduction of the flexion reflex excitability back to the level of control values (Baxendale & Ferrell, 1981; Ferrell et al., 1988). Furthermore, recent findings in humans have shown that knee joint aspiration and corticosteroid injection can
reduce flexion reflex excitability in individuals with chronic arthritis (Rice et al, 2015). Although it is not known exactly which interneurons are involved in mediating the nociceptive flexion reflex, wide dynamic range (WDR) neurons are suggested to play a large role in its mediation (You, Colpaert, & Arendt-Nielsen, 2008; You, Dahl Morch, Chen, & Arendt-Nielsen, 2003). WDR neurons receive input from a variety of peripheral afferents including articular receptors (Rice & McNair, 2010). Articular inflammation following joint damage has been shown to cause a large amount of input from group III and group IV afferents to be transmitted to the WDR neurons resulting in their hyper-excitability, expanded receptive fields, and progressively decreasing activation threshold causing enhanced responsiveness to innocuous and noxious stimuli, a process known as central sensitization (Neugebauer & Schaible, 1990).

The hypersensitivity of WDR neurons results in heightened responsiveness to stimuli from adjacent or even distal non-inflamed tissues as distant as the contralateral limb (Neugebauer & Schaible, 1990). An example of this expanded receptive field has been seen in animal studies where stimulation from both ipsilateral and contralateral toes in animals with induced osteoarthritis has been observed to increase the nociceptive flexion reflex excitability, demonstrating enhanced central excitability of the nociceptive flexion reflex pathway (Woolf & Wall, 1986). Hyper-excitability of the nociceptive flexion reflex pathway was also demonstrated in subjects with knee joint injury/pathology where the nociceptive flexion reflex was observed to cause simultaneous inhibition during knee extensor contraction (Baxendale and Ferrell, 1981). Leroux et al., (1995) demonstrated that the nociceptive flexion reflex modulates transmission along pathways to both distal muscles and contralateral muscles. This example of bilateral modulation has been considered to enable adjustment of the contralateral limb in order to maintain stability of the body (Baxendale & Ferrell, 1981; Leroux et al., 1995). Thus, it is possible that the nociceptive flexion reflex is involved in mediated quadriceps muscle inhibition of the both the ipsilateral and contralateral limbs.
Summary

Bilateral motor adaptations are frequently seen following musculoskeletal injury and in cases of joint pathology. Bilaterally reduced muscle strength has been consistently observed to affect the quadriceps muscles in cases of knee joint injury/pathology. Due to its load-bearing role in locomotion, substantial effort is placed into rehabilitation following damage to the knee joint. Classically, rehabilitation strategies have been directed at improving strength and stability of the injured knee joint, while the uninjured knee joint is used comparatively as a clinical baseline. However, bilateral observations of quadriceps strength deficits in cases of unilateral joint injury suggest that muscle inhibition also affects the contralateral limb, and so comparing muscle strength of the injured to uninjured side may substantially underestimate true muscle weakness. Furthermore, contralateral quadriceps weakness may increase the risk of joint injury and or degeneration in the uninjured knee, highlighting its potential clinical importance.

Presently, the underlying mechanisms of contralateral muscle weakness are poorly understood. Previous studies have explored the effects of swelling upon contralateral quadriceps muscle strength showing swelling to have no affect on the contralateral quadriceps, but the effects of inflammation and nociception on contralateral quadriceps muscle strength have not been explored. Increased nociceptive joint afferent activity has the potential to alter the excitability of various spinal and/or supraspinal pathways. Dysfunction of the gamma-loop spinal pathway has been observed to occur bilaterally in cases of unilateral knee joint injury but it is unclear whether nociception is involved. The nociceptive flexion reflex has been observed to affect motor output from many muscle groups, including those of the contralateral limb. The contralateral effects of the nociceptive flexion reflex suggest that exploration of this spinal pathway could provide further insight into the potential mechanisms contributing to contralateral quadriceps muscle inhibition.
References


Section Two: Manuscript
Introduction

Motor adaptations that often impede functional performance are consistently seen to follow musculoskeletal injury. These adaptations have been suggested to occur as a protective mechanism, preventing the injured structure from further injury (Ervilha, Farina, Arendt-Nielsen, & Graven-Nielsen, 2005; Hodges, 2011; Van Wilgen, Akkerman, Wieringa, & Dijkstra, 2003). However, motor adaptations have been observed bilaterally in cases of unilateral joint injury (Becker, Berth, Nehrig, & Awiszus, 2004; Suter, Herzog, De Souza, & Bray, 1998; Urbach & Awiszus, 2002; Wadsworth & Bullock-Saxton, 1997), suggesting that these motor changes may be dysfunctional.

At the knee joint in particular, bilateral quadriceps muscle weakness has been frequently observed across a variety of different injuries/pathologies despite joint damage/injury only occurring in one limb (Chmielewski, Stackhouse, Axe, & Snyder-Mackler, 2004; Hurley, Jones, & Newham, 1994; Machner, Pap, & Awiszus, 2002; Suter et al., 1998b; Urbach, Nebelung, Weiler, & Awiszus, 1999). Both ipsilateral and contralateral deficits in quadriceps maximum voluntary activation have been demonstrated using twitch-interpolation and/or burst superimposition techniques (Becker et al., 2004; Chmielewski et al., 2004; Suter, Herzog, & Bray, 1998a; Urbach & Awiszus, 2002), providing evidence that inactive muscle fibres remain despite conscious effort to produce a maximal muscle contraction. This infers that a neural inhibitory mechanism may be involved in both ipsilateral and contralateral quadriceps muscle weakness following unilateral injury of the knee joint.

To date, the causal mechanisms of contralateral quadriceps muscle inhibition are poorly understood. With respect to ipsilateral quadriceps inhibition, it has been suggested that changes in sensory output from the damaged joint may alter the excitability of spinal reflex and/or supraspinal pathways, leading to an ongoing muscle activation deficit. Knee joint injury may lead to damage to articular receptors and thus decreasing sensory output from the joint. A loss of sensory output has been
demonstrated by investigating the effect of local anaesthetic on injured versus uninjured knee joints. When injected with an anaesthetic, ipsilateral quadriceps EMG activity of an uninjured knee joint diminishes, while quadriceps EMG of an injured knee joint is unchanged, indicative of damage to joint receptors and thus reduced sensory output (Konishi, Fukubayashi, & Takeshita, 2002; Konishi, Suzuki, Hirose, & Fukubayashi, 2003). In contrast to this, increased sensory output has also been linked to quadriceps activation deficits after knee joint injury/pathology. Factors such as joint laxity, swelling, inflammation and nociception have been associated with increased sensory output from damaged knee joints (Grigg, Schaible, & Schmidt, 1986; Schaible & Schmidt, 1983, 1988). Immediate activation deficits of the ipsilateral quadriceps have been seen in experimental models of both swelling (McNair, Marshall, & Maguire, 1996; Palmieri et al., 2003; Rice, McNair, Lewis, & Dalbeth, 2014), and pain (Henriksen, Rosager, Aaboe, Graven-Nielsen, & Bliddal, 2011). Palmieri et al. (2003) demonstrated how experimental unilateral joint effusion led to a reduced H-reflex in the ipsilateral vastus medialis, however no change in the H-reflex of the contralateral vastus medialis occurred. Though the effects of nociception have not yet been explored on the contralateral limb.

Nociceptive afferents may alter the excitability of sensorimotor pathways potentially involved in mediating contralateral muscle weakness. Supraspinal changes, such as various alterations in motor cortex excitability, have been observed directly following nociceptive stimulation (Kirveskari, Vartiainen, Gockel, & Forss, 2010; Le Pera et al., 2001; Martin, Weerakkody, Gandevia, & Taylor, 2008; Schabrun & Hodges, 2012), but have not been directly associated with contralateral muscle inhibition. Three spinal pathways have been attributed to quadriceps muscle inhibition including the group I non-reciprocal (Ib) inhibitory pathway, the gamma (γ-) loop spinal reflex pathway, and the nociceptive flexion reflex (NFR) pathway (David A. Rice & McNair, 2010). γ-loop dysfunction has been observed to occur bilaterally despite unilateral knee joint injury (Konishi et al., 2002; Konishi et al., 2003), and may be caused by an increase in nociceptor activity from the damaged joint (Scott, Ferrell, & Baxendale, 1994), though this relationship remains unclear. The NFR pathway however, has been seen to be affected by nociceptive stimulation of both
ipsilateral and contralateral toes in animals (Woolf & Wall, 1986), and appears to modulate transmission of bilateral motor pathways regardless of unilateral stimulation (Baxendale & Ferrell, 1981). This is hypothesized to be due to central sensitization following increased nociceptive afferent output (Neugebauer & Schaible, 1990). The NFR is also seen to be greater in subjects with anterior knee pain than in those without pain (Leroux, Bélanger, & Boucher, 1995), suggesting facilitation of the NFR pathway due to nociceptive afferent output.

Contralateral quadriceps inhibition has thus far only been reported in clinical contexts, so it is not clear what the causal factors are. Existing evidence suggests that swelling does not stimulate contralateral motor changes but that some neural mechanisms extend bilaterally. Nociception appears to have widespread effects on motor function. However, the effects of nociception on the contralateral limb have not been adequately explored. Using an experimental pain model, the effects of isolated nociception on contralateral muscle activity can be explored, and may inform future intervention and rehabilitation strategies for improving quadriceps strengthening.

**Methods**

**Participants**

Fourteen healthy volunteers (four females, ten males) participated in the study (mean age 25 years ± 3.807, range 21-31 years). Participants were excluded if they had any diagnosed spinal or neurological disorders, had suffered any previous significant trauma to the lower limb and/or trunk with any current musculoskeletal or neural symptoms, were experiencing pain (1/10 or higher on the numeric rating scale (NRS)) anywhere in the body on the day of testing, or had a Pain Catastrophizing Scale score of 30 or greater. The study was granted ethical approval from the Unitec Institute of Technology and Auckland University of Technology.
ethics committees, in accordance with the principles outlined in the Declaration of Helsinki (2013). All participants provided written, informed consent.

**Protocol**

Participants attended two sessions a minimum of 72 hours apart. During one of the sessions, experimental knee pain was induced by injecting hypertonic saline into the infrapatellar fat pad of the resting leg. In the other session, a non-painful control injection of isotonic saline was administered to the resting leg. Torque and NFR values were obtained from the active leg. A simple randomisation table was used to determine which injection (hypertonic or isotonic) was given on the first day of testing and which leg would be actively tested. For both sessions, the sequence of dependent variables were collected from the contralateral leg before and immediately after the injection.

**Experimental Knee Pain**

Hypertonic saline injection is reported to closely mimic the deep, diffuse quality associated with musculoskeletal pain (Capra & Ro, 2004), and has demonstrated reliable intra-individual reliability (Graven-Nielsen, 2006). In this study, experimental knee joint pain was induced by injecting 0.5ml of 5.8% hypertonic saline into the infrapatellar fat pad. Injections were administered using a 1-mL plastic syringe with a 25-gauge disposable needle. Injections were from a medial approach, with the needle inserted ~1cm at a 45 degree angle in a posterolateral direction into the infrapatellar fat pad. All injections were performed under sterile conditions. For the control condition, a 0.5mL injection of isotonic (0.9%) saline was administered using the same procedure.

Following withdrawal of the needle, knee pain intensity associated with each injection was rated every 60 seconds using a NRS from 0-10, where 0 = “no pain” and 10 = “worst pain imaginable.” Scale measurements that associate numerical values
to pain intensity are frequently used by clinicians and researchers to quantify the pain experience (Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011; Strong, 1999). Commonly used scales include the Visual Analogue Scale (VAS), Numerical Rating Scale (NRS), and the Faces Pain Scale-Revised (Ferreira-Valente et al., 2011). Of these, the NRS is reported to have higher ease of use, compliance and superior responsiveness (Hjermstad et al., 2011).

Maximal Voluntary Contractions

Participants were seated in an isokinetic dynamometer (Biodex System 3, Biodex Medical Systems, Shirley, New York, USA) with the tested leg securely fastened at 30° knee flexion, 85° hip flexion, and straps placed over the waist, chest and thigh to stabilise the body during contractions. The axis of rotation of the Biodex was aligned with the lateral epicondyle of the femur and the lever arm of the dynamometer was secured to the tibia, just proximal to the medial malleolus. This positioning was used for all testing procedures.

Following a warm-up of 3 sub-maximal contractions (approximately 25%, 50% and 75% of perceived maximum effort) and 1 maximal effort contraction, participants waited 1 minute and were then instructed to perform an isometric MVC of the quadriceps as “hard and fast” as possible and to hold the contraction for 5 seconds. This was repeated three times with a 1-minute rest in between contractions to minimise muscle fatigue. Strong verbal encouragement and visual feedback from the Biodex monitor were provided to the participant to promote a maximum voluntary effort in each trial.

During each quadriceps MVC, surface electromyography (EMG) signals were collected from vastus medialis (VM), vastus lateralis (VL), biceps femoris (BF) and the medial hamstring (MH) muscles using bipolar disposable AgCl electrodes (Norotrode20, Myotronics Inc, Kent, USA) positioned according to established guidelines (Merletti & Hermens, 2000). Prior to electrode placement, the skin was
shaved, abraded and cleaned with alcohol to reduce signal impedance. A unipolar AgCl ground electrode (3M Red Dot) was placed on the proximal portion of the ipsilateral tibia. EMG signals were amplified (x1000), filtered (10-1000 Hz) (AMT8, Bortec Biomedical, Alberta, Canada), and sampled at 2000 Hz (Micro 1401, Cambridge Electronic Design, Cambridge, UK).

Data Analysis

Peak torque and maximum rate of torque development (MRTD) were chosen as reliable measures of muscle activation following evidence of their reproducibility, which has been determined in previous investigations by calculating intraclass correlation coefficient and standard error of measurements values. Both peak torque and MRTD demonstrated good intraclass correlation coefficient and low standard error of measurements values during knee extension (Larsson, Karlsson, Eriksson, & Gerdle, 2002; Larsson et al., 1999). A recent investigation suggests that reliable peak torque measures may be achieved using a minimum of two repetitions of knee extension providing that a rest period of 30-60s between MVCs is provided (Hill, 2014). Using Signal software (Signal 4, Cambridge Electronic Design, Cambridge, UK) the peak torque during each MVC was determined using a cursor routine. MRTD during the first 250ms of each quadriceps MVC was determined using overlapping windows of 0.5ms. For both peak torque and MRTD, the values obtained were averaged across all 3 contractions at each measurement interval and used in subsequent analysis.

Differences in EMG signals taken from different subjects, or the same subjects on different days can occur due to differences in skin surface preparation, electrode placement or the amount of mechanical artifacts contributing to electrical noise. For this reason, EMG signals are normalised to the percentage of each subject’s maximal voluntary contraction for each muscle and changes in EMG are often compared quantitatively as a percentage (Türker, 1993). Normalisation is a frequently used and accepted method for reducing variability in EMG (Soderberg, Cook, Rider, &
The root mean square (RMS) amplitude of the EMG signals from each muscle was calculated during a 1-second window corresponding to maximum quadriceps torque production during each MVC. To obtain a measure of overall quadriceps EMG amplitude the RMS amplitude of VM and VL was averaged at each contraction. Similarly, hamstrings EMG amplitude was obtained by averaging BF and MH RMS amplitude. For both quadriceps and hamstrings EMG, the average RMS amplitude across all 3 MVCs was calculated and used in subsequent analysis.

**Statistical Analysis**

Statistical analysis was run using SPSS v.22 software. Shapiro-Wilk tests were used to determine whether the dependent variables were normally distributed in order to indicate whether parametric testing could be used. One-sample t-tests were used to analyze whether the percentage change (from baseline to post-injection) in quadriceps peak torque, MRTD, quadriceps RMS amplitude, and inhibition of the ongoing VM EMG differed from zero in each condition (hypertonic, isotonic).

Hamstrings EMG data were not normally distributed so a one-sample Wilcoxon signed rank test was used to determine whether the percentage change (baseline to post-injection) in hamstrings RMS amplitude was different from zero in each condition (hypertonic, isotonic). Pearson product moment correlations were utilised to determine the relationships between peak knee pain intensity and the change in quadriceps peak torque, quadriceps MRTD, quadriceps EMG and hamstrings EMG respectively.

**Results**

**Experimental Knee Pain**

The average duration of knee pain following hypertonic saline injection was 13.09 minutes ± 4.66 and average peak knee pain intensity was 4.6 ± 1.59. One participant
reported knee pain following isotonic saline injection of 2 minutes duration and pain intensity of 1 on the 0-10 NRS. No other participants reported pain following the isotonic saline injection.

**Peak Torque**

A significant reduction in contralateral quadriceps peak torque (t= -5.347, p< 0.001) was observed following hypertonic saline injection (see Figure 1). There was no significant change in contralateral quadriceps peak torque following isotonic injection (t= 1.149, p = 0.273). A moderate negative correlation was found between the change in peak torque and peak pain intensity (Pearson product-moment correlation coefficient = -0.683), with higher pain intensity being associated with a greater decline in quadriceps peak torque in the contralateral limb.

**Maximum Rate of Torque Development**

Maximum rate of torque development (MRTD) was significantly reduced in the contralateral quadriceps following hypertonic injection (t= -5.427, p< 0.001) (see Figure 2). No significant change to MRTD was observed following isotonic injection (t= -1.837, p= 0.089). A moderate negative correlation was found between the change in MRTD and peak pain intensity (Pearson product-moment correlation coefficient = -0.643), with higher knee pain intensity being associated with a greater decline in MRTD in the contralateral quadriceps.

**Quadriceps EMG**

Quadriceps EMG amplitude was significantly reduced following hypertonic injection (t= -2.591, p= 0.02) (see Figure 3). Quadriceps EMG amplitude did not change significantly following isotonic (t= -0.362, p= 0.723) injection.
Hamstrings EMG

No significant changes in hamstrings EMG were found following hypertonic (p = 0.07) or isotonic (p = 0.730) injections compared to baseline (see Figure 4).

Figure 1. Percentage change in knee extensor peak torque (Nm) following injection into the infrapatellar fat pad of the opposite limb with either isotonic (control) or hypertonic (pain) saline. Data are means and standard error of the means. * = significant change compared to zero (p < 0.05)

Figure 2. Percentage change in knee extensor rate of torque development (Nm) following injection into the infrapatellar fat pad of the opposite limb with either isotonic (control) or hypertonic (pain) saline. Data are means and standard error of the means. * = significant change compared to zero (p < 0.05)
Discussion

The findings of the present study suggest that increased nociceptive output from the knee joint contributes to contralateral quadriceps muscle inhibition. Experimental
knee pain via hypertonic saline injection induced a significant reduction in contralateral quadriceps peak torque and MRTD, which was not seen following isotonic saline injection. A reduction in quadriceps EMG activity was observed following contralateral knee pain suggesting that inhibition of quadriceps muscle activation led to reduced knee extensor peak torque and rate of torque development. Increased antagonist activity is unlikely to have contributed to changes in knee extensor peak torque and rate of torque development, as hamstrings EMG activity did not increase during post-injection quadriceps MVCs. Negative correlation between peak torque and peak pain rating and MRTD and peak pain rating infer a significant relationship between pain intensity and quadriceps torque production exists. These findings indicate that nociceptive stimulation produces an inhibitory response at spinal and/or supraspinal levels.

There are several potential mechanisms that may be involved in mediating contralateral quadriceps inhibition following experimental knee pain. Changes in motor cortex excitability have been consistently seen to occur following nociception (Kirveskari et al., 2010; Le Pera et al., 2001; Martin et al., 2008). Nociceptive output from the knee joint specifically has been demonstrated to increase ipsilateral quadriceps motor evoked potentials (MEPs) (Rice, Graven-Nielsen, Lewis, McNair, & Dalbeth, 2015), an observation consistent with decreased MEPs seen in knee joint pathology (Héroux & Tremblay, 2006; Kittelson, Thomas, Kluger, & Stevens-Lapsley, 2014; On, Uludag, Taskiran, & Ertekin, 2004). This increase in MEPs could have the potential to trigger a deficit in the MEPs of the contralateral quadriceps via interhemispheric inhibition (Di Lazzaro et al., 1999; Valeriani et al., 2001), though more research is required to support this notion. At a spinal level, nociception may be linked to reflex pathways such as the γ-loop and the NFR. γ-loop dysfunction has been observed to cause bilateral effects despite unilateral stimulation (Konishi, Aihara, Sakai, Ogawa, & Fukubayashi, 2007). While it is not presently proven, there is a potential for γ-loop dysfunction to occur from enhanced nociceptor activity in a damaged joint (Scott et al., 1994). Unilateral nociceptive stimulation has also been shown to cause enhanced NFR responses in both ipsilateral and contralateral limbs (Leroux et al., 1995; Woolf & Wall, 1986), so it is also likely that the NFR may be
involved in contralateral quadriceps inhibition. Further investigation is required to
determine which mechanisms are involved in contralateral muscle inhibition.

The results of this study support the findings of bilateral quadriceps muscle
inhibition observed in cases of unilateral knee joint damage (Becker et al., 2004;
Chmielewski et al., 2004; Suter et al., 1998; Urbach & Awiszus, 2002; Urbach,
Nebelung, Becker, & Awiszus, 2001; Urbach et al., 1999). The persistence of bilateral
quadriceps muscle inhibition beyond the pain experience in these studies suggest
that nociceptive-induced neuroplastic changes in the central nervous system may
also occur leading to long-term changes in motor excitability. In support of this,
Henriksen et al. (2007), found that reduced EMG activity of VM and VL muscles
following nociceptive stimulation persisted for up to 20 minutes beyond the
presence of pain.

Limitations

A possible limitation of the present study was that ipsilateral quadriceps muscle
activity was not measured and so comparison of strength deficits between
extremities could not be made. It has been unanimously demonstrated that
nociceptive stimulation of the knee joint causes ipsilateral quadriceps muscle
inhibition but the level of deficit appears to be unique to the individual. Testing the
ipsilateral limb of each participant may have provided information as to the
comparative extent of contralateral quadriceps muscle inhibition that occurs in the
presence of nociceptive stimulation. Regardless of this, the results of the present
study allow confident identification of contralateral quadriceps inhibition.

Experimental induction of knee pain in this study is another potential limitation.
Hypertonic saline injection produces a temporary nociceptive response of a deep
diffuse achy sensation not unlike musculoskeletal pain (Capra & Ro, 2004). However
the use of hypertonic saline to produce nociceptive stimulation may not accurately
replicate the pain experience that results from knee joint injury or pathology. In
order to closely replicate pain caused by injury or pathology of the knee joint, hypertonic saline was injected into the infrapatellar fat pad. This structure has been shown to be an important source of nociceptive input throughout a variety of different knee joint pathologies (Dye, Vaupel, & Dye, 1998; Hill et al., 2007; Tanaka, Sakahashi, Sato, Hirose, & Isima, 2003). This experimental pain method also enabled nociceptive activity to be isolated from other factors that commonly occur with knee joint injury/pathology such as swelling and joint damage. In this way it is known that the observed effects occurred as a result of nociceptive joint afferent input.

Clinical Implications

The findings of this study revealed contralateral motor effects following unilateral nociceptive knee joint afferent stimulation. Nociception frequently occurs with injury and/or pathology of a joint. Quadriceps muscle weakness has been seen to occur following knee joint injury/pathology and may compromise the stability of the knee joint leading to impeded functional performance and increased risk of further injury. Thus it is possible that contralateral quadriceps muscle inhibition in the absence of joint injury may have a negative effect on joint stability and increase the risk of injury to an uninjured joint. Furthermore, rehabilitation following knee injury or surgery often relies on the contralateral limb to provide a clinical baseline measure of quadriceps strength. The findings of this study suggest that by using the contralateral limb as a comparator, true muscle weakness of the injured limb may be significantly underestimated.

Conclusion

The evidence of contralateral quadriceps muscle weakness occurring as a result of unilateral knee joint nociception indicate that rehabilitation in cases of knee joint injury/pathology should be targeted at both the injured and uninjured limbs. Prolonged quadriceps weakness may compromise dynamic knee joint stability and
functional roles such as shock absorption during walking (Felson et al., 2007; Hurley, 1997; Jefferson, Collins, Whittle, Radin, & O’Connor, 1990; Liikavainio, Lyytinen, Tyrväinen, Sipilä, & Arokoski, 2008). Quadriceps weakness is also a known risk factor in the development and advancement of osteoarthritis (Segal et al., 2010). Consequently, contralateral quadriceps inhibition may increase the risk of injury to the uninjured knee joint. Thus we suggest that reducing nociceptive activity may be an important part of rehabilitation in knee joint injury/pathology, preventing the risk of injury and joint degeneration in the contralateral limb, as nociception alone produced contralateral quadriceps inhibition. Reducing nociceptive activity in the early stages of joint damage may help to restore muscle strength in both the injured and uninjured limbs and allow a more valid comparison of strength between limbs. This study made no conclusions regarding the neural mechanisms underlying contralateral muscle inhibition, however potential neural mechanisms have been suggested warranting further investigation of these.
References


Appendix

Appendix A: Ethics Approval

Tessa Little
1/43 Mc Breen Ave
Northcote
Auckland

25.9.14

Dear Tessa,

Your file number for this application: 2014-1064
Title: To what extent is contralateral limb strength affected by experimental pain?

Your application for ethics approval has been reviewed by the Unitec Research Ethics Committee (UREC) and has been approved for the following period:

Start date: 3.9.14
Finish date: 3.9.15

Please note that:

1. The above dates must be referred to on the information AND consent forms given to all participants.
2. You must inform UREC, in advance, of any ethically-relevant deviation in the project. This may require additional approval.

You may now commence your research according to the protocols approved by UREC.

We wish you every success with your project.

Yours sincerely,

Sara Donaghey
Acting Deputy Chair, UREC

cc: Jamie Mannion
Cynthia Almeida
Appendix B: Patient Information Sheet

RESEARCH INFORMATION FOR PARTICIPANTS

You are invited to participate in our research investigation. Please read carefully through this information sheet before you make a decision about volunteering.

Research question
To what extent is contralateral muscle strength affected by experimental pain?

Researcher
My name is Tessa Little and I am a Master of Osteopathy student at Unitec New Zealand. As part of this programme I am conducting a research project.

Purpose of the study
The purpose of this study is to identify the effect of experimentally induced knee pain of one limb on the strength characteristics of the thigh muscles in both limbs. The results of this study will assist in identifying the extent of central mechanisms on muscle inhibition during pain, provide a better understanding of functional and dynamic pain-related movement alterations and inform rehabilitation strategies.

What the study involves
Taking part in this study will require you to attend two sessions at AUT’s Akoranga campus. Each session will last approximately 1 hour. During the study you will be asked to sit in a machine (like a leg machine at the gym) that can measure the strength of your leg muscles. The electrical activity of your muscles will be recorded with adhesive electrodes (little stickers) following some light abrasion and a wipe with an alcohol wipe, which may sting a little. You will be asked to perform several contractions of various intensities (up to maximum effort) and types (pushing, pulling, resisting). The experimental condition consists of receiving a small injection of hypertonic saline (salty water) just below the patellar (knee cap). This is described in more detail below.

About the experimental pain
The experimental pain condition can be expected to produce an intensity of approximately 5 or 6/10 and last for about 5 to 15 minutes. The perceptual characteristics are most commonly described as ‘aching’, ‘cramping’, and ‘dull’. It’s often likened to sore muscles after vigorous exercise. All participants will be monitored until pain subsides (usually this will be no longer than 30mins).

Adverse reactions are extremely rare and may consist of infection (as associated with any needle injection; risk will be managed by following World Health Organization (WHO) infection control practices), bruising or an undesirable level of pain. Excessive pain may be alleviated quickly by stretching and contracting the painful area. If you would like us to contact your GP prior to your participation, please provide their contact details below:

For immediate and after-hour concerns, you may contact an A&E clinic. The most local clinics that are open 24 hours are Ascot White Cross, contact number 5209555 and Henderson White Cross, contact number 8363336. Participants will be observed for 20 to 30 minutes following the injection, by which time the experimental pain should have almost completely subsided.

If required, counselling services are available at Unitec, Mt. Albert campus for all Maori and non-Maori Unitec students and staff. Contact number: 8154321, extension 7248. Maori consultation services are also available (Hare Paniora, Phone 8152854)
Your voluntary participation
Your participation in this study is entirely voluntary and you may withdraw at any time during the practical procedures. Data collected from your involvement in the study may be withdrawn up until 1 week following data collection.

Who may participate?
You are eligible to participate if you:
• Are aged between 18-30
• Speak and write English
• Have normal upper limb function
• Are a New Zealand citizen or permanent resident
• Are male or female

You are not eligible to participate if you:
• Have had previous significant trauma to upper/lower limbs and/or trunk with current symptoms
• Are diagnosed with any neurological disorders
• Use pain medications on the day or day prior to testing
• Have pain (2/10 or greater) anywhere in body on the day of testing
• Have Elevated Pain catastrophising as determined by the Pain Catastrophising Scale (PCS > 25%)
• Have any diagnosed spinal disorders

Please inform the researcher if any of the above pertains to you.

What we do with the data and results, and how we protect your privacy.
Personal information is collected and stored under the guidelines provided by the Privacy Act 1993 and the Health Information Privacy Code 1994. For information collection your identity will remain anonymous and you will simply have an identification number. If the information you provide is reported or published, this will be done in a way that does not identify you as its source. All the data recorded will be stored in password-locked computers and archived in a locked file room and will be stored for a minimum of 10 years. Access to this data will be limited to the researchers involved and yourself. This research project is not sponsored by any commercial company. This research project is part of Master of Osteopathy Programme.

Compensation for Adverse Reactions
Compensation may be available in the unlikely event of injury of negligence. As this procedure can be defined as a treatment, you may be eligible for compensation for treatment injury as described under Accident Compensation Act, 2001. Should you incur a physical injury as a result of your participation in this study, you may be covered by ACC under the Injury Prevention, Rehabilitation and Compensation Act 2002. You may or may not be entitled to ACC compensation, depending on several factors such as whether or not you are an earner. ACC will usually cover a proportion of income lost due to a physical injury, this does not cover mental injury unless as a direct result from a physical injury. ACC cover may affect your right to sue. Please contact your nearest ACC office for further information (0800 735 566) or visit their website: www.acc.co.nz

A summary of the final report will be available to you if you are interested.

Please contact me if you require further information about the study.

Principal investigator: Tessa Little
Phone: 021 0313570
Email: tessa.little@gmail.com

Supervisor: Jamie Mannion
Phone: 021 0629007
Email: jmannion@unitec.ac.nz

This study has been approved by the Unitec Research Ethics Committee (ref) from (X) to (X) and AUT Ethics Committee (ref) from (x) to (x). If you have any complaints or reservations about the ethical conduct of this research, you may contact the Committee through the UREC Secretary (Ph: 09 815 4321 ext.7284). Any issues you raise will be treated in confidence and investigated fully, and you will be informed of the outcome.
Appendix C: Pain Catastrophizing Scale

Everyone experiences painful situations at some point in their lives. Such experiences may include headaches, tooth pain, joint or muscle pain. People are often exposed to situations that may cause pain such as illness, injury, dental procedures or surgery.

We are interested in the types of thoughts and feelings that you have when you are in pain. Listed below are thirteen statements describing different thoughts and feelings that may be associated with pain. Using the following scale, please indicate the degree to which you have these thoughts and feelings when you are experiencing pain.

0 – not at all  1 – to a slight degree  2 – to a moderate degree  3 – to a great degree  4 – all the time

When I’m in pain …

1. I worry all the time about whether the pain will end.
2. I feel I can’t go on.
3. It’s terrible and I think it’s never going to get any better.
4. It’s awful and I feel that it overwhelms me.
5. I feel I can’t stand it anymore.
6. I become afraid that the pain will get worse.
7. I keep thinking of other painful events.
8. I anxiously want the pain to go away.
9. I can’t seem to keep it out of my mind.
10. I keep thinking about how much it hurts.
11. I keep thinking about how badly I want the pain to stop.
12. There’s nothing I can do to reduce the intensity of the pain.
13. I wonder whether something serious may happen.

…Total

Client No.: ________ Age: _____ Sex: M(____) F(____) Date: ______________

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