

The Effect of Experimental Quadriceps Muscle Pain on Nociceptive and Non-nociceptive Somatosensation

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THESIS

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LIST OF ABBREVIATIONS

ADL	Activity of daily living
CM	Carpometacarpal
DOMS	Delayed onset muscle soreness
EEG	Electroencephalogram
fMRI	Functional magnetic resonance imaging
MP	Metacarpophalangeal
OA	Osteoarthritis
rANOVA	Repeated-measures Analysis of Variance
RF	Rectus Femoris
TDPM	Threshold to Detection of Passive Motion
TA	Tibialis Anterior
VAS	Visual Analog Scale
VM	Vastus Medialis
VPT	Vibratory Perception Threshold

SUMMARY

Purpose: Both hyperalgesia and hypoesthesia have been reported in individuals with chronic pain. Although previous studies have investigated clinical characteristics of chronic pain in either people with chronic musculoskeletal pain or healthy people, less is known on the effect of persistent pain on somatosensation. Specifically, while hypoesthesia in terms of proprioceptive deficits and vibration perception deficits have been reported in different chronic pain populations, a direct relationship between pain and hypoesthesia has not been demonstrated. Further, if pain does give rise to somatosensory deficits, the effect on balance is unclear. The purpose of this study is to examine the effect of experimentally induced quadriceps muscle pain on nociceptive and non-nociceptive somatosensation and to investigate whether changes in measures of hypoesthesia correlate following induction of pain.

Methods: In ten healthy individuals, quadriceps pain was induced via delayed onset muscle soreness, which was produced using an eccentric exercise protocol. The dominant limb served as the experimental side and the non-dominant limb served as a control. Measurements which included pressure pain threshold (PPT), proprioception, measured via threshold to detect passive movement (TDPM), vibration perception threshold (VPT), subjective report of pain measured via visual analog scale (VAS) and Y-balance test were performed at baseline, immediately following the eccentric exercise and two days post-exercise.

Results: Compared with baseline measures, a significant difference was found in

SUMMARY(continued)

all measures of hyperalgesia, as by PPT ($p<0.05$), and in measures of hypoesthesia including TDPM ($p<0.05$) and VPT ($p<0.05$) at the experimental knee post-exercise. PPT measures were also significantly reduced at the vastus medialis muscle ($p<0.05$), the tibialis anterior muscle ($p<0.05$) and the webspace between the 1st and 2nd metacarpals of the contralateral hand ($p<0.05$) at two days post-exercise. Measures of TDPM ($p=0.19$) and VPT ($p=0.74$) on the contralateral knee were not significantly different as compared to baseline. Changes on the Y-balance composite score were not significantly different, both immediately and 2 days post exercise protocol. Change scores for measures of hypoesthesia, ie, proprioception and VPT, were moderately correlated ($r=0.439$), however this relationship was not significant ($p=0.106$). A positive correlation between subjective report of pain (VAS) and VPT ($r=0.67$, $p=0.014$) was found, but not with TDPM ($r=0.048$, $p=0.44$).

Conclusion: This study found that experimentally induced quadriceps pain resulted in widespread hyperalgesia and hypoesthesia locally at the painful limb, as measured by knee proprioception and VPT at the knee. Pain induced hypoesthesia may occur through central inhibitory mechanisms. A moderate but non-significant relationship was found between change scores of hypoesthesia, indicating that the two modalities, while distinct, may be affected via similar mechanisms.

I: INTRODUCTION

A. Background

Chronic musculoskeletal pain is one of the principal contributors to lifetime disability, and often diminishes quality of life (Stubbs et al., 2014). Clinically, chronic musculoskeletal pain is characterized by heightened levels and larger areas of pain, as well as tenderness of musculoskeletal tissues which has been referred to as hyperalgesia (Sluka, 1996). Hyperalgesia has been defined as an increased response to a painful stimulus, (International Association for the Study of Pain, 2014) and has been reported clinically in individuals with chronic musculoskeletal disorders such as knee osteoarthritis (OA) (Arendt-Nielson et al., 2010; Kavchak et al., 2012), low back pain (Gieseke et al., 2004) and temporomandibular disorder (Hollins et al., 1996). Hypoesthesia, defined as a diminished sensitivity to a given stimulus (International Association for the Study of Pain, 2014), has also been reported in individuals with chronic musculoskeletal conditions (Courtney and Rine, 2006; Felson et al., 2009; Shakoor et al., 2008; Shakoor et al., 2014; Shanahan et al., 2015). Two commonly investigated sensory modalities are proprioception and vibration perception threshold. Deficits in these sensory modalities has been attributed to local damage of neural structures in peripheral tissues. However, experimental and

clinical studies have suggested that these abnormal findings may possibly be related to altered central processing (Apkarian, et al., 1994; Geber et al., 2008; Hollins et al., 2001). Specifically, studies have suggest a spinal (Geber et al., 2008) or supraspinal level (Apkarian et al., 1994) mechanism underlying these changes, indicating that pain may inhibit non-nociceptive afferent input from contiguous tissues. While these somatosensory findings have been demonstrated in patient populations (Apkarian et al., 1994; Kavchak et al., 2011; Hollins et al., 2001), the underlying neurophysiologic mechanism behind these findings remains obscure. If clinical findings of hypoesthesia can be attributed to central pain mechanisms, it is not known which sensory modalities might be affected and if they would be affected in a systematic manner. Further, it is not known whether these somatosensory deficits may lead to altered postural control. Greater understanding of pain induced functional deficits may improve rehabilitative strategies in chronic pain populations.

B. Purpose of Study

The purpose of this study was to examine the effect of experimentally induced quadriceps muscle pain on nociceptive and non-nociceptive somatosensation and to investigate whether changes in measures of hypoesthesia correlate following induction of pain. Specifically, measures of PPT, proprioception, vibration acuity were performed for the purpose of understanding nociceptive mechanisms associated with musculoskeletal pain. Also the effect of these impairments on dynamic standing balance was also examined.

C. Hypothesis

I. Induction of delayed onset muscle soreness of unilateral quadriceps via an eccentric exercise protocol will result in widespread hyperalgesia indicated by diminished pressure pain thresholds at bilateral limbs and at the contralateral hand.

Ia. Induction of delayed onset muscle soreness of unilateral quadriceps via an eccentric exercise protocol will result in hypoesthesia, demonstrated by increased proprioception at the knee, measured via threshold to detection of passive movement, and increased vibration perception threshold at the patella.

Ib. Measures of change in hypoesthesia, specifically proprioception and vibration perception, will be correlated.

D. Rational

Although many previous studies have investigated clinical characteristics of pain in chronic musculoskeletal pain populations, less is known on how experimental muscle pain may affect measures of pressure pain threshold (PPT), vibration perception threshold, proprioception acuity and balance. Chronic pain mechanisms underlying clinical nociceptive changes (hyperalgesia) and non-nociceptive changes (proprioceptive and vibratory deficits) remain unclear. A deeper understanding of how chronic pain develops can contribute to prevention and more effective management strategies.

II: LITERATURE REVIEW

A. The Prevalence of Chronic Musculoskeletal Pain

One of the largest contributors to lifetime disability is chronic musculoskeletal disease (e.g, osteoarthritis, chronic neck pain, low back pain) and one common symptom of chronic musculoskeletal dysfunction is persistent musculoskeletal pain (Haas et al., 2015; Stubbs et al., 2014; Vascopoulos and Lema, 2010). Musculoskeletal disorders comprise a major socioeconomic burden on health systems in North America and Europe (Jay et al., 2014; Stubbs et al., 2014). Musculoskeletal pain remains one of the most common reasons (Gaskin and Richard, 2012; Stubbs et al., 2014) that older adults (Stubbs et al., 2014) and the working population (Jay et al., 2014) seek medical attention. The epidemiological significance of chronic pain after surgery is enormous. The prevalence of chronic pain can range from 10.1% to 55.2% of the population (Vascopoulos and Lema, 2010). The financial impact of chronic musculoskeletal pain is also enormous. For example, in 2010 it was estimated that the costs associated with chronic pain in the United States were between 560 and 635 billion dollars per year (Gaskin and Richard, 2012). Chronic musculoskeletal pain is associated with mobility limitations, functional decline, increased risk of injury and

decrease in health-related quality of life (Haas et al., 2015; Jay et al., 2014; Stubbs et al., 2014). Clearly, chronic pain is a serious public health burden (Dzau and Pizzo, 2014).

B. Transition From Acute to Chronic Pain

The transition from acute to chronic pain occurs in discrete pathophysiological steps involving multiple neurophysiologic mechanisms (Voscopoulos and Lema, 2010). Prolonged experience of noxious somatic input can result in neuroplastic changes of the nociceptive pathways. Woolf et al. (2004) discussed several primary types of pain: nociceptive pain, defined as a transient pain in response to a noxious stimulus, inflammatory pain, characterized by spontaneous pain and hypersensitivity to pain in response to tissue damage and inflammation, and neuropathic pain, which is typified by spontaneous pain and hypersensitivity to pain in association with damage or disease of the nervous system. Musculoskeletal pain that persists beyond 3 months has been defined as chronic pain (Woolf, 2011). Various studies have proposed nociceptive mechanisms associated with this transition.

1. Acute musculoskeletal pain: Nociception

The sensory experience of acute pain is mediated by the nociceptive system which is a specialized high-threshold sensory system (Woolf, 2011). This system

ascends from the periphery through the spinal cord, brain stem, and thalamus to the cerebral cortex, where sensory input is perceived and interpreted (Latremoliere and Woolf, 2009). Nociception, the neural process of encoding noxious stimuli (International Association for the Study of Pain, 2014), is initiated by stimuli that activate the peripheral terminals of nociceptors (Woolf et al., 2004). Nociceptive neurons have three functions: detection of damaging stimuli (transduction); passage of the sensory input from peripheral to spinal cord (conduction); and synaptic transfer of the sensory input to neurons in dorsal horn (transmission) (Kidd and Urban, 2001). Nociceptors have unmyelinated (group IV fibers) or thinly myelinated (group III fibers) axons (McCleskey and Gold, 1999). Transfer of input from nociceptors to neurons in the dorsal horn that project to supraspinal levels is mediated by direct monosynaptic contact or via multiple interneurons, some of which are excitatory and some inhibitory (Kidd and Urban, 2001; Woolf et al., 2004).

When tissue damage occurs, inflammatory mediators, such as prostaglandins, bradykinin, substance P, and histamine are released at the site of injury, which leads to activation of nociceptors (Kidd and Urban, 2001). In the early stages of inflammation due to tissue injury, these mediators change the sensitivity of receptors, i.e., peripheral sensitization, leading to hyperalgesia (Kidd and Urban, 2001; Woolf et al., 2004;

Voscopoulos and Lema, 2010).

2. Peripheral sensitization

Following injury, peripheral sensitization may occur at the site of injury which increases excitability and reduces the threshold of nociceptor response (Woolf et al., 2004). Because of this diminished threshold of nociceptors in the injured musculoskeletal tissues, hyperalgesia, defined as a heightened pain sensitivity, occurs (Kidd and Urban, 2001; Woolf et al., 2004; Voscopoulos and Lema, 2010). Clinically, algometry measurements such as pressure pain threshold (PPT) have been commonly used (Fernandez-Carnero, Fernandez-de-las-Penas et al., 2008) to identify sensitization of musculoskeletal tissues (Kilo et al., 1994).

3. Central sensitization

a. Hyperalgesia

Sustained or repetitive activation of primary nociceptive afferents (group III and IV fibers) produces substantial changes in neurophysiologic pathways (Kidd and Urban, 2001; Woolf, 2007; Latremoliere and Woolf, 2009). With persistent noxious input and inflammation in the periphery, long-lasting changes in spinal excitability may be induced via activation of spinal and/or supraspinal neurons, the dorsal

horn to thalamus, brainstem and cortex. This has been referred to as central sensitization (Kidd and Urban, 2001; Woolf, 2007). Central sensitization is believed to underlie the transition to the chronic pain state (Latremoliere and Woolf, 2009; Courtney et al., 2010; Woolf, 2007; Woolf, 2011). With central sensitization, nociceptive afferents in the dorsal horn become hyperexcitable due to persistent input from peripheral noxious input (Ji et al., 2003; Latremoliere and Woolf, 2009; Voscopoulos and Lema, 2010). In other words, central sensitization amplifies and facilitates the synaptic transfer from nociceptive terminal to dorsal horn neurons (Woolf et al., 2004). With central sensitization, regional expansion of hyperalgesia may occur due to spatial summation of neural input and activation of previously ineffective dorsal horn synaptic connections (Graven-Nielsen et al., 2003, Gibson et al., 2006). Furthermore, bilateral hyperalgesia in unilateral repetitive pain relating to central segmental sensitization also may occur (Fernandez-Carnero et al., 2008; Sluka et al., 2001).

With progression of pain and progression of central sensitization, diffuse pain sensitivity in multiple body parts outside the region of injury may occur (Ji et al., 2003). Clinically it presents as widespread pain (hyperalgesia) (Latremoliere and Woolf, 2009; Woolf, 2007; Woolf, 2011; Courtney et al., 2010) which is also mediated by both

facilitatory and inhibitory mechanisms (Schaible et al., 2009).

Hyperalgesia is commonly observed in people with chronic pain and quantitative sensory testing is an objective means of examining for this sensory change (Arendt-Nielsen et al., 2010; Rolke et al., 2006). Quantitative measurement of hyperalgesia using pressure pain threshold (PPT) in musculoskeletal tissues is reliable and recommended for clinical and experimental use (Vanderweeen et al., 1996). Lower PPT at sites far from the location of injury or dysfunction has been demonstrated in various musculoskeletal disorders and is indicative of central sensitization. In addition, PPT has been suggested in the differentiation of regional versus widespread central sensitization of nociceptive pathways (Courtney et al., 2010).

In clinical studies, hyperalgesia has been found in patients with painful articular disorders (Shakoor et al., 2008), knee OA (Imamura et al., 2008; Kavchak et al., 2012), and other chronic musculoskeletal pain (Fernandez-Carnero et al., 2009; Geber et al., 2008). Other studies have demonstrated bilaterally reduced PPT outside of the site of injury in patients with chronic neck pain (Curatolo et al., 2001), unilateral lateral epicondylalgia (Fernández-Carnero et al., 2008), unilateral shoulder pain (Ge et al., 2008) and low back pain (O'Neill et al., 2007). It has been suggested that hyperalgesia found in chronic

musculoskeletal disorders may be centrally mediated (Ramiro-Gonzalez et al., 2012).

b. Hypoesthesia

The ability to detect a vibratory stimulus is mediated by the non-nociceptive afferents (i.e, Group II ($A\beta$) fibers) with specialized low-threshold sensory receptors located in cutaneous tissues (Gilman, 2002; Purves et al., 2012), although studies have suggested that receptors in muscle and tendon may transmit this sensation (Fallon and Macefield, 2007). This cutaneous mechanosensory system ascends from the periphery through the dorsal columns in the spinal, caudal medulla where the afferents cross from ipsilateral to contralateral pathways, and the thalamus to the primary somatosensory and secondary somatosensory cortex (Purves et al., 2012).

Central sensitization may alter the function of non-nociceptive Group II ($A\beta$) fibers. In the presence of noxious stimuli, non-nociceptive input may be inhibited (Geber et al., 2008; Apkarian et al., 1994). Hypoesthesia to mechanical and vibration stimuli has been found concurrently with hyperalgesia (Kavchak et al., 2011; Shakoor et al., 2008) and researchers have proposed central mechanisms to be the underlying origin of this phenomenon (Apkarian et al., 1994; Geber et al., 2008).

Geber et al. (2008), using unilateral experimental pain, induced via intradermal

injection of capsaicin and intradermal nociceptive electrical stimulation, demonstrated tactile hypoesthesia in the regions of pin-prick hyperalgesia after the nociceptive stimulation. They proposed that these neurophysiologic changes occurred at a spinal rather than supraspinal level. Specifically, A δ fiber excitation would presynaptically inhibit non-nociceptive processing conveyed by A β fibers (Geber et al., 2008). Alternatively, Apkarian et al. (1994) using experimentally induced pain, demonstrated an increased vibratory threshold (diminished vibratory sense) adjacent to the painful area, purportedly due to cortical level inhibition by the nociceptive input. They referred to this phenomenon as a ‘reverse pain gate’ or ‘touchgate’ where pain was inhibiting non-nociceptive somatosensation instead of the reverse.

While vibratory mechanoreceptors perceive external stimuli, proprioceptors distinguish input generated from within the body. Proprioception is transmitted to the central nervous system through afferent input from cutaneous receptors in the skin, muscles, joint tissues, ligaments, and tendons. Muscle spindles (group Ia, II fibers) are believed to be the most important contributor to proprioception (Gandevia and McCloskey, 1976). Proprioceptive afferents ascend from the periphery, through the spinal cord via synapse with Clarke’s nucleus, to the cerebellum and thalamus, and from there to the somatosensory

cortex (Roijezon et al., 2015).

Altered proprioceptive acuity may be another example of pain-related hypoesthesia, however this notion has been minimally investigated. Proprioception involves not only conscious or unconscious awareness of joint position (joint position sense) but also kinesthesia (sense of movement) (Gandevia and McCloskey, 1976). Joint position sense examines accuracy in repositioning a joint to a predetermined target angle (Benjaminse et al., 1994; Malmstrom, Westergren et al., 2013), whereas measures of kinesthesia examine the ability to perceive passive joint movement by measuring the threshold to detection of passive motion (TDPM) (Courtney et al., 2013; Proske and Gandevia, 2009). Although both are proprioceptive senses, the two senses are believed to be neurophysiologically separate (Proske and Gandevia, 2009). Individuals with chronic musculoskeletal conditions often demonstrate deterioration of proprioceptive acuity in both senses (Courtney and Rine, 2006; Hassan et al., 2001).

Clinically it has been reported that chronic pain is correlated with decreased proprioceptive acuity in either modality of joint position sense or TDPM in people with knee OA (Felson et al., 2009; Shanahan et al., 2015), hip OA (Shakoor et al., 2014) and anterior cruciate ligament deficiency (Courtney et al., 2006). Felson et al. (2009) and

Shanahan et al. (2015) demonstrated diminished acuity at the affected knee while Shakoor et al. (2014) found diminished proprioceptive acuity on both isilateral and contralateral knee in individuals with unilateral hip OA.

C. Effect of Chronic Pain on Balance

Previous studies have reported that chronic pain is associated with several negative health outcomes, including loss of balance and falls (Eggermont et al., 2014). Eggermont et, al. (2014) found that individuals with knee OA demonstrated impaired balance. Kavchak et al. (2012) found a correlation between reduced PPT and perceived instability during a step task in persons with knee OA. Furthermore, Felson et al.(2009) found that pain was related to reduced proprioceptive acuity and loss of physical function in persons with knee OA.

As described above, chronic pain has been associated with diminished proprioceptive acuity. Proprioception and accompanying neuromuscular control mechanisms provide an important component for maintenance of posture and balance (Lephart et al., 1998). Thus, chronic pain conditions likely influence the ability to balance.

D. Experimentally Induced Pain Models

Studying pain mechanisms in patient populations can be difficult due to disease co-morbidities which may bias experimental results. Because of this, pain mechanisms are

often investigated in animal models and in human models utilizing experimentally induced pain. Several models of experimentally induced pain have been used successfully. Each has advantages and limitations.

1. Electrical stimulation

Electrical stimulation has been used as a nonspecific method to induce pain by direct activation of nerve and muscle fibers for the purpose of examining central plasticity (Zimmermann et al., 2012). However, high currents are required to activate thinly and non-myelinated nociceptive fibers. Consequently, evoking pain results in unwanted activation of non-nociceptive nerves and muscle fibers. Muscle twitches and limb movement often accompany the stimulation (Zimmermann et al., 2008).

In one study (van den Broeke et al., 2011), healthy individuals received trains of 100 Hz stimuli (pulse width: 2 ms) for 1 sec. repeated 5 times at 10 sec intervals with an intensity of $20 \times$ detection threshold on the forearm 5cm distal to the cubital fossa. The contralateral arm served as a control. They found cortical changes on electroencephalogram (EEG), potentially indicating central plasticity. O'Neill et al. (2009) also used electrical stimulation to induce acute low back pain by inserting the electrodes into the facet joints. In the study, some subjects experienced local pain and others experienced wide range pain

including contralateral gluteal and inguinal pain. However PPT measures outside of local and referred pain areas did not change significantly before, during and after continuous experimental low back pain.

2. Injection of sensitizing agents

Another frequently used model consists in the injection of chemical irritants into the muscle tissue or/and fat pad, such as hypertonic saline, acid phosphate buffer, bradykinin or glutamate; these substances induce cramp like diffuse pain mimicking the chronic pain experienced by patients (Graven-Nielsen et al., 1997; Hirata et al., 2011; Joergensen et al., 2013). For example, Joergensen et al. (2013) induced pain by injection of hypertonic saline in the infrapatellar fat pad in healthy subjects. They found hyperalgesia, demonstrated via reduced PPT, at the infrapatellar fat pad and in muscles distant to the injection site. Hirata et al. (2011) induced muscle pain by injection of hypertonic saline into the vastus lateralis, vastus medialis, or biceps femoris muscle of the right leg. They found increased postural sway and displacement on movable platform during quiet standing and unexpected perturbation. They attributed this to pain causing impairment of sensorimotor mechanisms. It was proposed that persons suffering from leg pain may be more vulnerable to falls. One study elicited muscle pain hypersensitivity by experimental intramuscular

injection of bradykinin and serotonin into the tibialis anterior muscle in healthy individuals, however, muscular hyperalgesia to pressure was not detected up to 1 hour after injection (Babenko et al., 1999). Furthermore, another study showed that 1.0 M glutamate injected into the masseter muscle evokes pain and induces a marked reduction in PPTs of human. However, autonomic reactions also occurred which may influence brain imaging studies (Svensson et al., 2003).

3. Delayed onset muscle soreness

Pain from DOMS provides an effective, non-invasive model to study the central processing of inflammatory muscle pain (Zimmermann et al., 2012). Several authors have suggested that DOMS may be a simpler and safer method for induction of experimental pain (Chien et al., 2008; O'Neill et al., 2007). The typical time course of DOMS is characterized by pain and tenderness that peaks between 48 and 72 hours but can endure for up to 7 days post-exercise. It is one of the most common and recurrent forms of injury (Cheung et al., 2003). DOMS related muscle soreness is typically induced using exercise protocols consisting predominantly of eccentric activity such as downhill running and eccentric resistance exercise (Hedayatpour et al., 2008).

a. Delayed onset muscle soreness as a pain model inducing central sensitization

DOMS is classified as a muscle strain injury and presents with tenderness or stiffness to palpation and/or movement. The symptoms vary from muscle stiffness to severe pain restricting movement, induced by unfamiliar high-force muscle work such as high intensity of eccentric contraction exercise (Cheung et al. 2003).

Pain and the soreness may occur immediately after the high intensity exercise (Dannecker and Koltyn, 2014). The symptoms occur due to accumulation of metabolites within the muscle secondary to obstruction of blood flow during the exercise leading to inflammation (Koutris et al., 2013). Muscle damage leads to an immediate inflammatory pain from the release of inflammatory mediators from damaged muscle cells (Crane et al., 2012; Kidd and Urban, 2001).

Several studies have induced DOMS for the purpose of studying pain mechanisms which mainly focus on central and peripheral sensitization.. Zimmermann et al. (2012) showed that DOMS related pain induced bilateral activation in multiple brain regions such as sensory, motor and insular cortex which can lead to widespread pain. Functional magnetic resonance imaging (fMRI) was used to examine the patterns of cortical activation

arising during DOMS-related pain in the quadriceps muscle in the study. Many studies found evidence of widespread pressure hyperalgesia, reduced PPT, following DOMS of quadriceps (Zimmermann et al. 2012), trapezius (Nie et al., 2006; Nie et al., 2009) and elbow flexors (Hubscher et al., 2014). They found widespread pain bilaterally in people with unilateral experimental muscle pain by DOMS.

Also a few studies found that DOMS disturbed proprioceptive acuity specifically joint position sense (Paschalis et al., 2007; Serinken et al., 2013) or/and kinesthesia (Paschalis et al., 2007), which could potentially lead to increased risk of injury and perturbations in daily activities. Serinken et al (2013) found that DOMS on the upper extremities induces proprioceptive loss which lead to diminished shooting accuracy 48 hours after the eccentric exercise in wheelchair basketball players.

Thus, DOMS is an experimental pain model which induces hyperalgesia related to central sensitization and diminished proprioceptive acuity. It results in loss of balance, decreased activities of daily living, and increased risk of further injury (Broadbent et al., 2010; Han et al., 2014; Hedayatpour et al., 2008; Paschalis et al., 2007).

II. METHODS

A. Participants

Ten healthy young adults (mean (SD) age: 24.7(4.2) years) took part in the study. The subjects had no previous experience of knee injury, denied any pain nor had taken any pain-relieving medications drugs or anti-inflammatory drugs in the month prior to the study. The participants were blinded to the results during the testing period with no information provided concerning the postulated hypothesis. The study was reviewed and approved by the Institutional Review Board (IRB) of the University of Illinois at Chicago. Each participant signed a written informed consent prior to testing.

Assessment of experimental measures was performed serially at baseline, immediately following the eccentric exercise protocol and two days post-exercise. Participants were allowed to warm up 8 minutes on a stationary bicycle and then performed an eccentric exercise protocol on their dominant leg (Paschalis et al. 2007). There were three data points of the all outcome measurements in this study.

B. Eccentric Exercise Protocol

The subjects were seated on a Biodex System 3 isokinetic dynamometer (Biodex Medical Systems, Shirley, NY, USA) with the body stabilized by straps over the thighs,

waist, and chest and the lateral epicondyle of the femur aligned with the axis of rotation. In order to induce DOMS, 10 sets of 10 maximum eccentric quadriceps contractions of the dominant knee were performed at 60°/s with the range of motion set to 10° of knee extension and 90° knee flexion and the isokinetic dynamometer in continuous passive mode (Lund et al., 1998; Paschalis et al., 2007; Tufano et al., 2012). The dynamometer passively extended the limb between each eccentric action of the knee extensors. One minute of rest was allotted between sets.

Prior to each exercise session, subjects performed a warm-up consisting of 8-min cycling on a cycle ergometer (Monark, Vansbro, Sweden) at 70 rpm and 50 W as previously described (Paschalis et al., 2007).

C. Muscle Pain Intensity Measurement

Visual analog scale (VAS) (Wewers and Lowe, 1990) was used to assess the perceived pain intensity before, immediately after, and two days post-exercise. VAS has excellent reliability used for people with pain (Bijur et al., 2001; Boonstra et al., 2008). The subjects were asked to rate the maximum pain intensity of the quadriceps on both sides during their regular activities of daily living (Hubscher et al., 2014). Following the eccentric exercise protocol, subjects were allowed to walk for 60 seconds to allow them to

gage the intensity of their quadriceps muscle pain.

D. Pressure Pain Threshold

PPT has excellent inter-rater reliability in healthy humans (Chesterton et al., 2007).

PPT were assessed using a pressure algometer (WAGNER INSTRUMENTS, CT) at 7 locations, bilaterally over the belly of the rectus femoris, vastus medialis, tibialis anterior muscles and the contralateral hand (between 1st and 2nd carpometacarpal joint with the muscles relaxed (See Figure 1). The algometer consisted of a 1-cm² rubber tip, mounted on a force transducer. Measurements of PPT were performed twice for each location (Joergensen et al., 2013). The test order was rectus femoris on experimental (DOMS) side, rectus femoris on contralateral side, vastus medialis on experimental side, vastus medialis on contralateral side, tibialis anterior on experimental side, tibialis anterior on contralateral side, and hand on contralateral side. The algometer was applied perpendicular to the tissue being assessed. PPT was taken as the amount of pressure required to elicit a sensation of pain distinct from pressure (Chesterton et al., 2007). The subjects were instructed to say “now” at the moment the sensation of pressure becomes pain; at this point the algometer pressure was immediately released. Subjects were educated pre-PPT testing on their arm by the experimenter to clarify the procedure prior to actual testing. The mean of the two trials

was averaged for data analysis (Hollins et al., 2001).

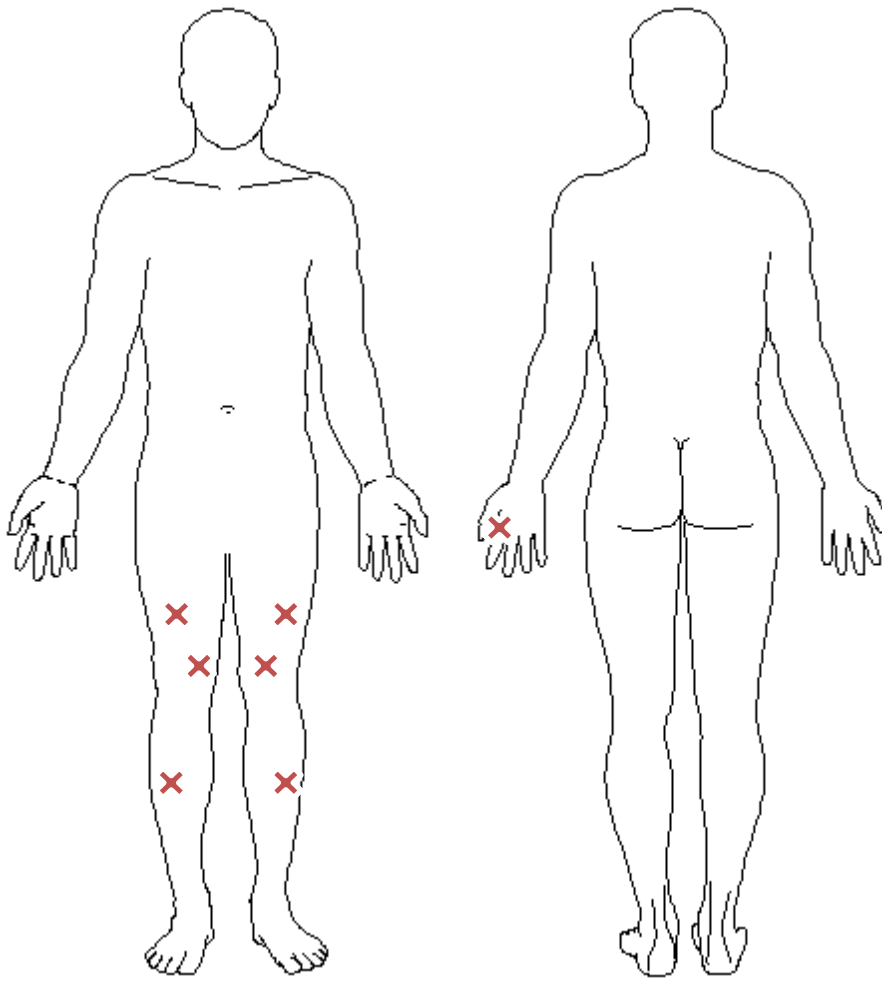


Figure 1. Pressure pain threshold measurement sites

E. Proprioceptive Acuity

Proprioception was examined using TDPM. This method has been shown to be reliable and has been previously used (Barrack et al., 1989; Courtney et al., 2006; Courtney et al., 2013). Individuals in the study were tested in the seated position (hip flexed at 70°, knee flexed at 45°, ankle in neutral) on the Biodex System 3 (Biodex Medical Systems Inc, Shirley, NY). A specially made device, utilizing a motor and pulley system, moved the limb passively into either flexion or extension at a slow rate (0.5°/sec) after a random delay (Figure 2). The direction of movement and limb to be tested was randomly assigned. The subject was provided a handheld switch and was instructed to push the switch upon detecting change of joint position. An air splint inflated to 20 mm Hg was placed on the foot to minimize cutaneous input. The subject was blindfolded and listened to white noise to minimize visual and auditory inputs respectively. Before every trial the subject was asked to co-contract the knee for 10 seconds to minimize the effects of thixotropy which can alter TDPM (Wise et al., 1996). A pretest trial was followed by three actual trials, the mean of which was used for data analysis. The amount of linear movement of the pulley (x) was documented and used to obtain the angle of threshold to detection of motion (Θ in degrees) using the formula $\Theta = \tan^{-1}(x/r)$ where r= shank length.

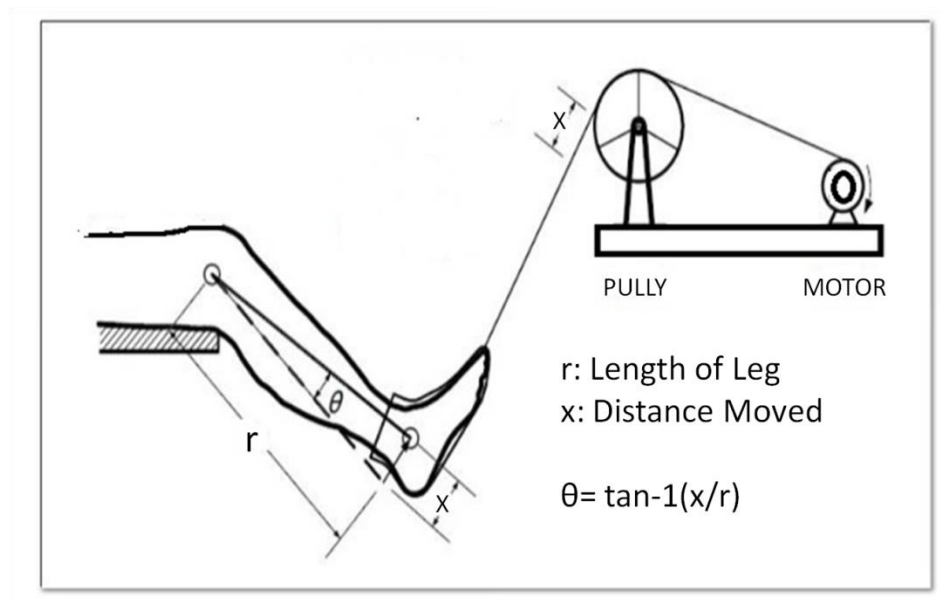


Figure 2. Proprioception testing device

F. Vibratory Acuity

Vibratory perception threshold was assessed bilaterally using a Biothesiometer (Bio-Medical, OH) applied at the center of the patella. Excellent intra-rater and test-retest reliability has been reported using this method (van Deursen et al., 2001). The vibratory tip (13 mm cylinder) oscillates at a frequency of 100 Hz at the site of application (Shakoor et al., 2008) and vibration was increased 1 volt per second at the site until the subject reported sensation (Shakoor et al 2008). Three trials of this measurement were taken at each location.

G. Dynamic Balance Testing

The Y balance test examines dynamic unilateral balance and consists of reaching in three independent directions (anterior, posteromedial, and posterolateral) while standing on the opposite leg (Butler et al., 2013). It has excellent inter-rater and test-retest reliability (Shaffer et al., 2013). The three testing lines extend from the center point with 135 degrees between anterior and posteromedial line and anterior and posterolateral line respectively (Butler et al.2013)(See Figure 3). Prior to testing, subjects were instructed to extend the contralateral limb as far as possible and touch lightly on each line with the tip of toe without shifting body weight. Instructions were given to maintain abdomen and toes of

stance leg in forward position during testing and to avoid raising the heel of the stance leg during testing. All subjects were barefoot during the performance of the test. The ankle joint of the supporting leg was aligned on the center point. Three tests in each direction were performed. The specific testing order was right anterior, left anterior, right posteromedial, left posteromedial, right posterolateral, and left posterolateral (Plisky et al. 2009). The greatest successful reach for each direction was recorded. From these data, the composite reach distance (composite score) was calculated by summing the maximum reach distance for the three reach directions on a given limb and dividing by three times the limb length prior to multiplying by 100 in order to reference the composite reach as a percentage of leg length (% LL) for analysis (Butler et al., 2013; Plisky et al., 2009).

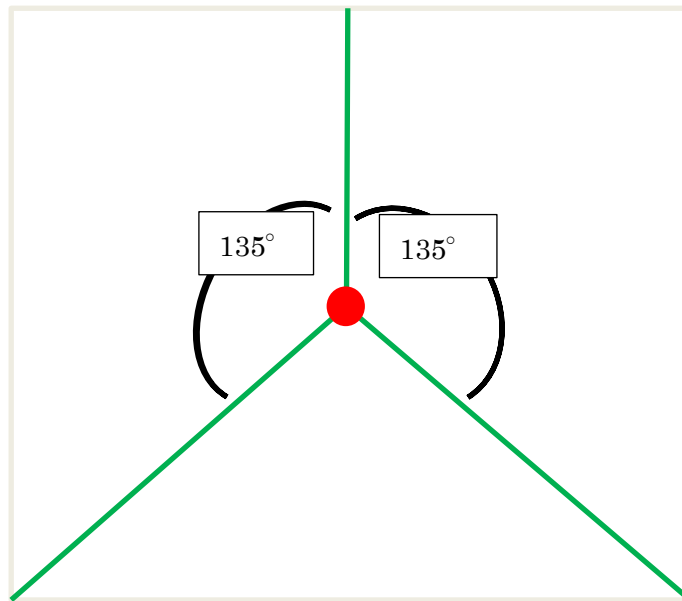


Figure 3. Y-balance test lines

H. Statistical analysis

All Statistical analyses were performed using SAS 9.3 software (SAS Institute Inc. NC USA). The univariate procedure was used for all variables to check normality of the data. The time effect of DOMS, which examined significant changes from baseline, on VAS, PPT, proprioception, vibration and Y-balance test in each group was assessed using univariate repeated-measures analysis of variance (rANOVA) and when a significant time effect was obtained, then paired t-test was performed in order to determine which exact data point, immediately after or two days post-exercise, was significant. Furthermore, Pearson's correlations coefficients(r) were calculated to determine correlations between VAS, TDPM, VPT and Y-balance composite score.

III. RESULTS

A. Subject Characteristics

Ten healthy subjects participated in this study. Demographics are shown in Table1.

Table I. SUBJECT CHARACTERISTICS	
	Mean (SD)
Age	24.7(4.2)
Gender (%Female)	30%
Dominant Knee (%Right)	80%
BMI	23.03(3.25)

B. Subjective Report of Quadriceps Pain

Univariate repeated-measures analysis of variance (rANOVA) revealed that the pain induced in the quadriceps on the experimental limb was significantly different after exercise ($F=27.90$, $p<0.001$). Post hoc testing using paired t-test indicated a significant increase both immediately after exercise ($p<0.001$) and 2 days post-exercise ($p<0.001$) when compared to baseline measures (Figure 4). Subjective report of quadriceps pain on the contralateral limb increased but not significantly over time ($F=1.47$ $p=0.25$).

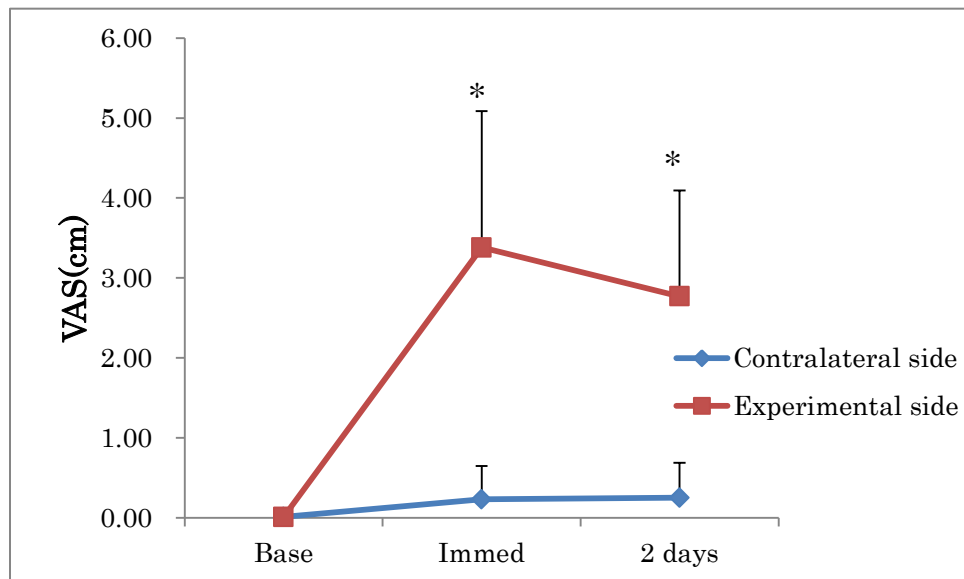


Figure 4. The effect of the eccentric exercise protocol on subjective report of pain (mean \pm SD)

*significant increase compared to baseline ($p < 0.05$) on experimental side (paired t-test)
 -rANOVA: Time effect on experimental side and contralateral side: $p < 0.0001$ ($F = 27.90$)
 and $p = 0.25$ ($F = 1.47$)

C. Pressure Pain Threshold

Univariate repeated-measures analysis of variance (rANOVA) revealed significantly decreased PPT at all experimental limb sites, RF ($F=6.01$, $p=0.02$), VM ($F=15.03$, $p=0.0001$) and TA ($F=6.65$, $p=0.01$), and also significantly decreased PPT on the contralateral side in VM ($F=8.97$, $p=0.01$), TA ($F=4.9$, $p=0.03$) and hand ($F=44.66$, $p<0.0001$). Using paired t tests, significant differences were demonstrated at each test site compared to baseline (Figures 5-8).

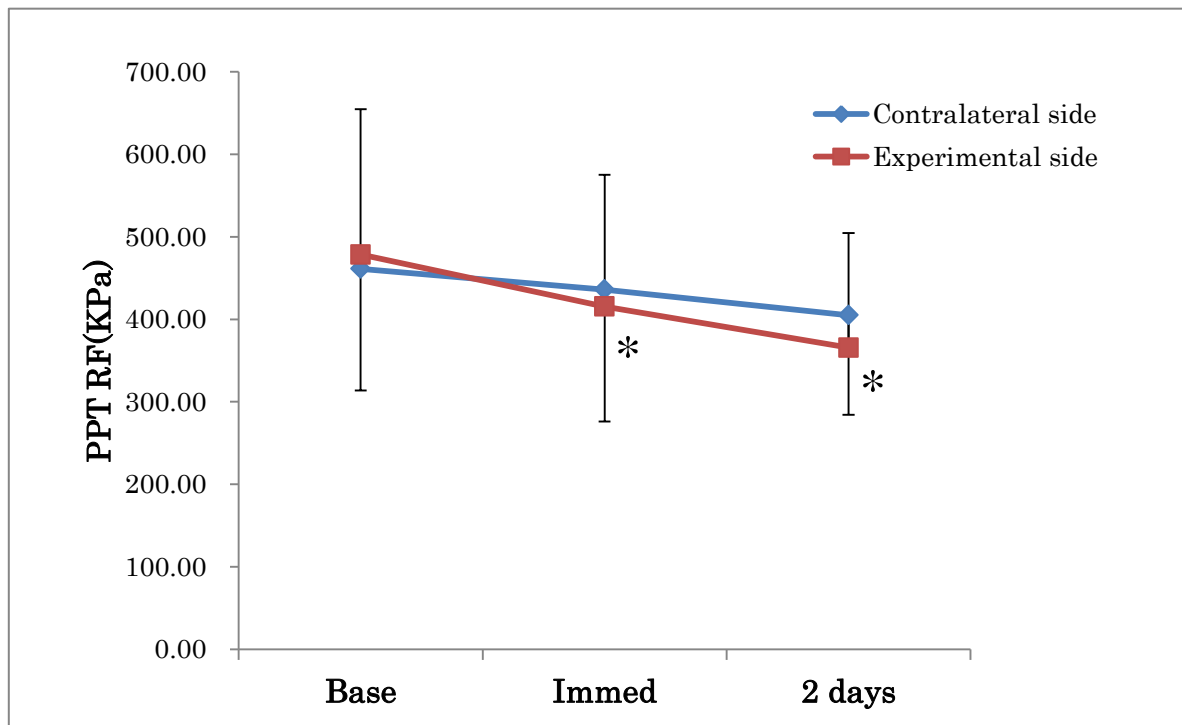


Figure 5. Effect of experimentally induced pain on PPT at rectus femoris (mean \pm SD)

*significantly different from baseline value ($p < 0.05$) on the experimental limb (paired t-test)

-rANOVA: Time effect on experimental side and contralateral side: $p = 0.02$ ($F = 6.01$) and $p = 0.18$ ($F = 1.9$)

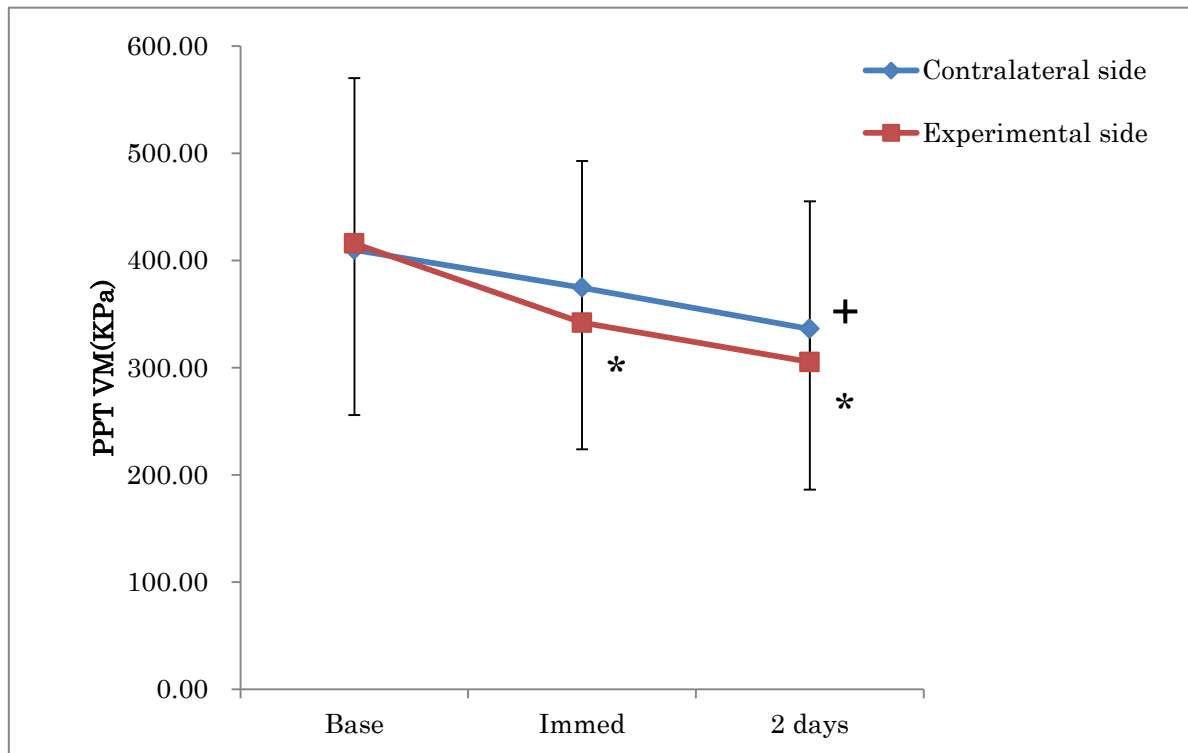


Figure 6. Effect of experimentally induced pain on PPT of vastus medialis
(mean±SD)

*significantly different from baseline value ($p < 0.05$) on experimental side (paired t -test)
+significantly different from baseline value ($p < 0.05$) in contralateral side (paired t test)
-rANOVA: Time effect on experimental side and contralateral side: $p = 0.0001$ ($F = 15.03$)
and $p = 0.01$ ($F = 8.97$)

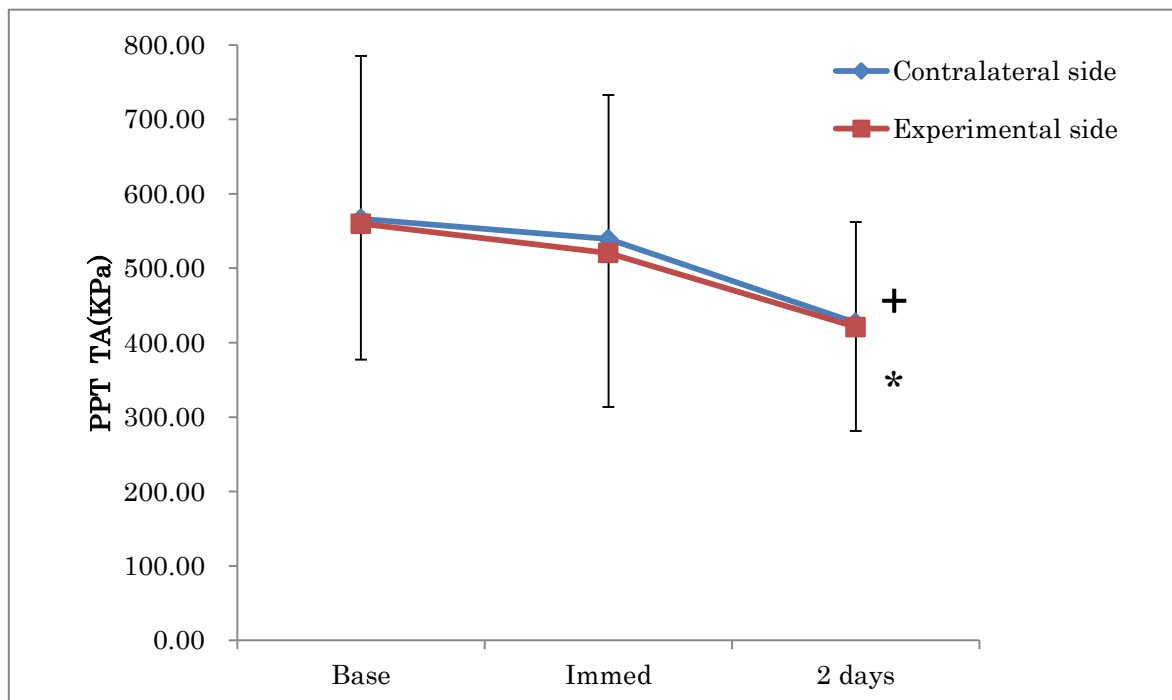


Figure 7. Effect of experimentally induced pain on PPT of tibialis anterior (mean \pm SD)

*significantly different from baseline value($p < 0.05$) in experimental side(paired t-test)
 +significantly different from baseline value($p < 0.05$) in contralateral side(paired t-test)
 -rANOVA: Time effect on experimental side and contralateral side: $p = 0.01$ ($F = 6.65$) and
 $p = 0.03$ ($F = 4.9$)

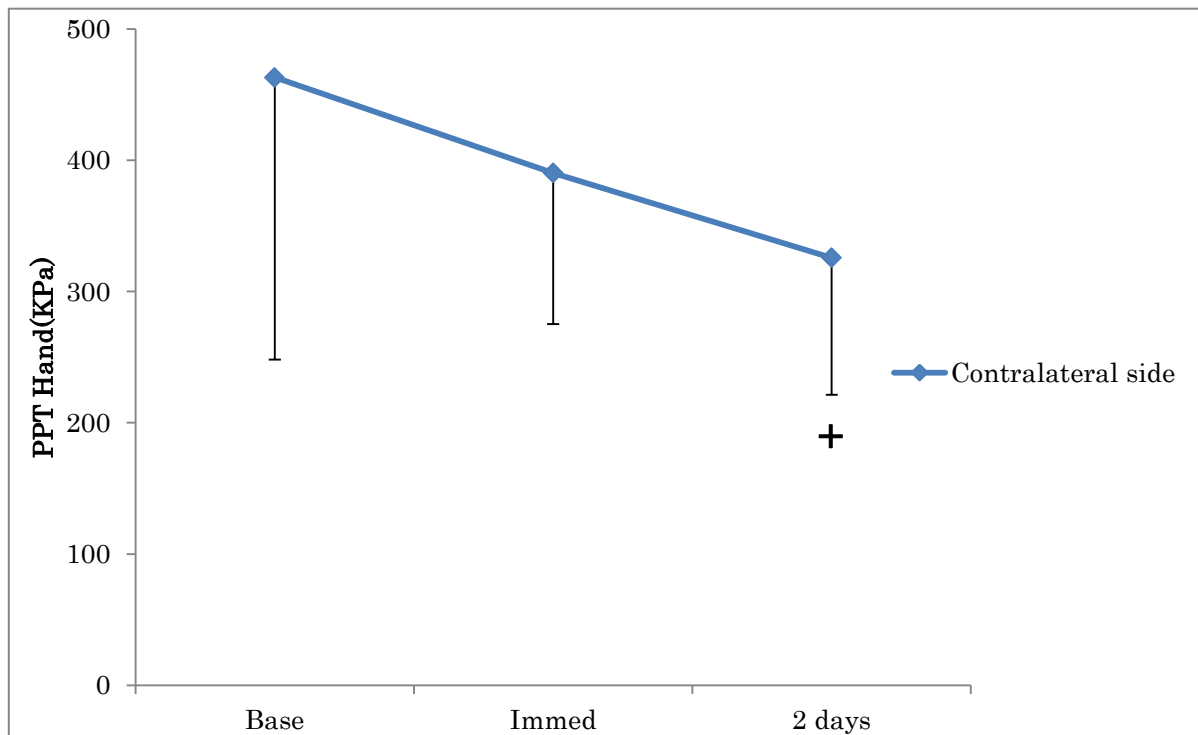


Figure 8. Effect of experimentally induced pain on PPT at the hand (mean \pm SD)

+significantly different from baseline value ($p < 0.05$) on the contralateral side (paired t-test)
 -rANOVA; Time effect contralateral side: $p < 0.0001$ ($F = 44.66$)

D. Proprioception Acuity

Univariate repeated-measures analysis of variance (rANOVA) revealed that a proprioceptive acuity, measured by TDPM, was significantly different at the experimental knee post-exercise ($F=12.35$, $p=0.0007$). Post hoc testing using paired t-test indicated a significant difference (Figure 9) both between baseline and immediately post-exercise ($p=0.02$) and at 2 days post-exercise ($p=0.0008$). However, TDPM at the contralateral knee did not change significantly over time ($F=2.01$, $p=0.18$).

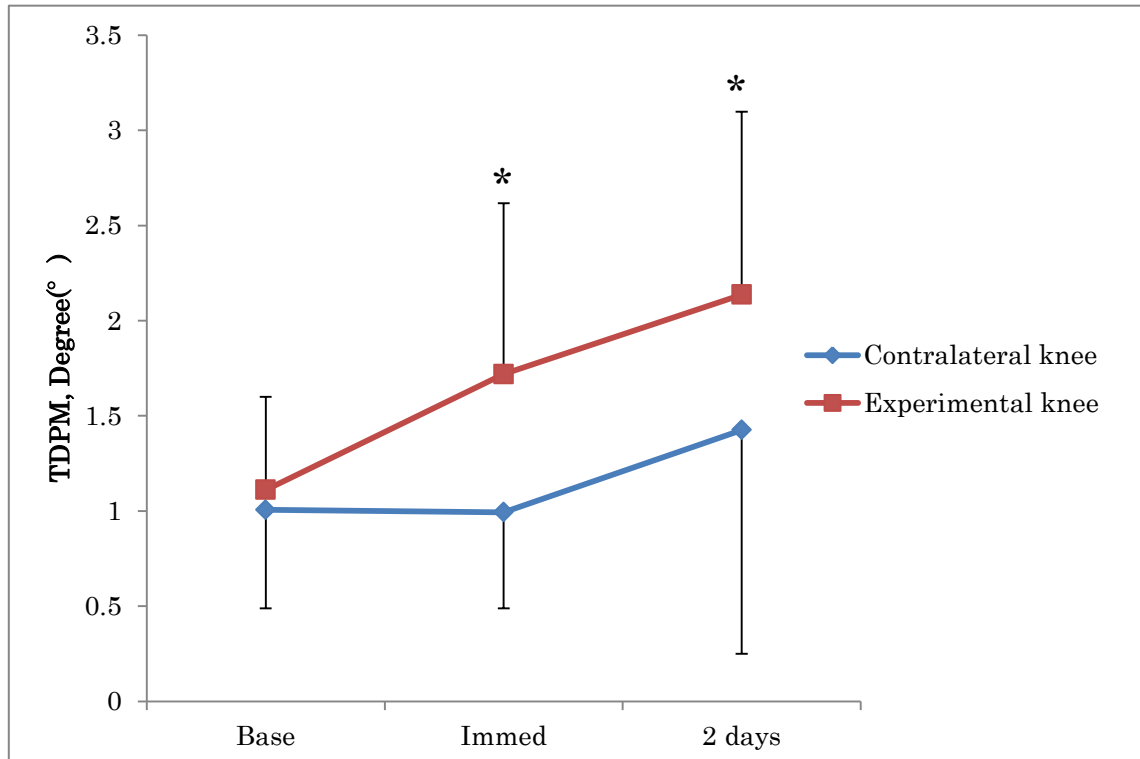


Figure 9. Effect of experimental induced pain on proprioception (mean±SD)

*significantly different compared to baseline ($p < 0.05$) at the experimental knee (paired t-test)

-rANOVA: Time effect on experimental knee and contralateral knee: $p = 0.0007$ ($F = 12.35$) and $p = 0.18$ ($F = 2.01$)

E. Vibration Acuity

Univariate repeated-measures analysis of variance (rANOVA) revealed a significantly diminished vibration perception as measured by VPT at the experimental knee after exercise ($F=13.22$, $p=0.002$) (Figure 10). Using paired t-test, a significant difference was demonstrated between baseline and immediately post-exercise ($p=0.003$) and 2 days post-exercise ($p<0.0001$). However, VPT at the contralateral knee did not change significantly over time ($F=0.25$, $p=0.74$).

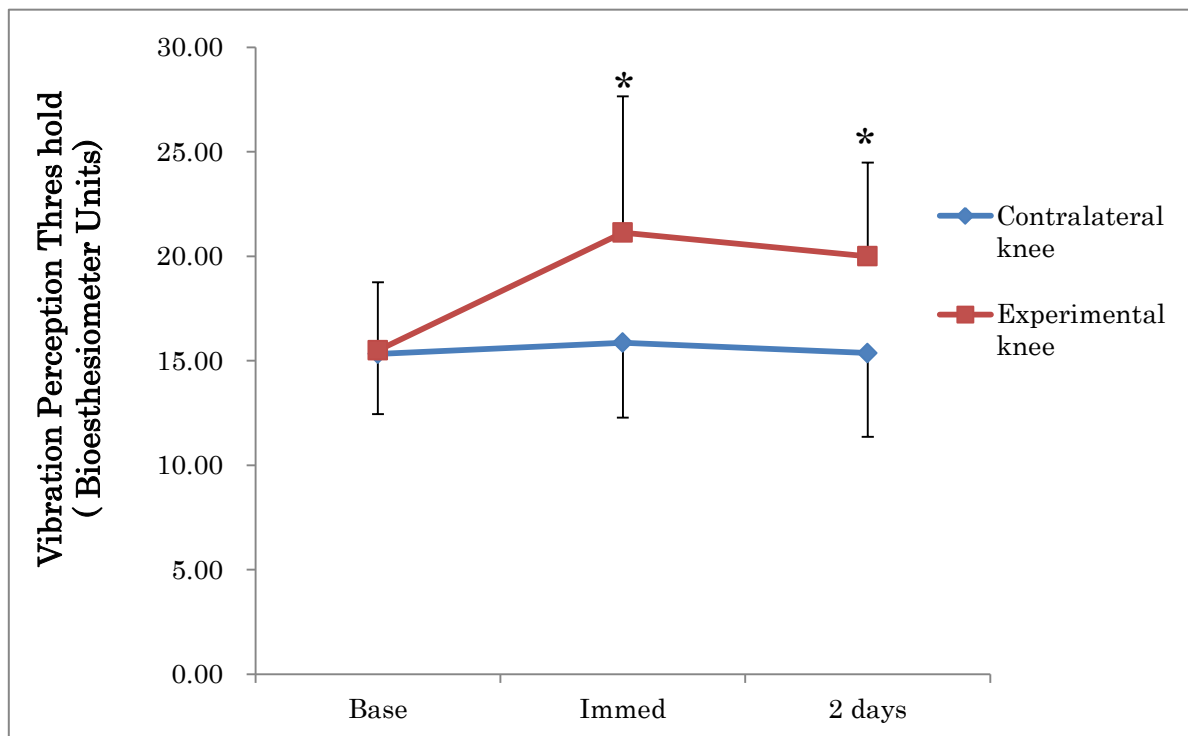


Figure 10. Effect of experimentally induced pain on vibration perception threshold (mean±SD)

*significantly different compared to baseline ($p < 0.05$) at the experimental knee (paired t-test)

-rANOVA: Time effect on experimental knee and contralateral knee: $p = 0.002$ ($F = 13.22$) and $p = 0.74$ ($F = 0.25$)

F. Y-balance Test (composite score)

Univariate repeated-measures analysis of variance (rANOVA) revealed that the Y-balance test composite score of either limb did not change significantly over time (experimental limb: $F=3.36$, $p=0.06$, contralateral limb: $F=1.02$, $p=0.37$) (Figure 11).

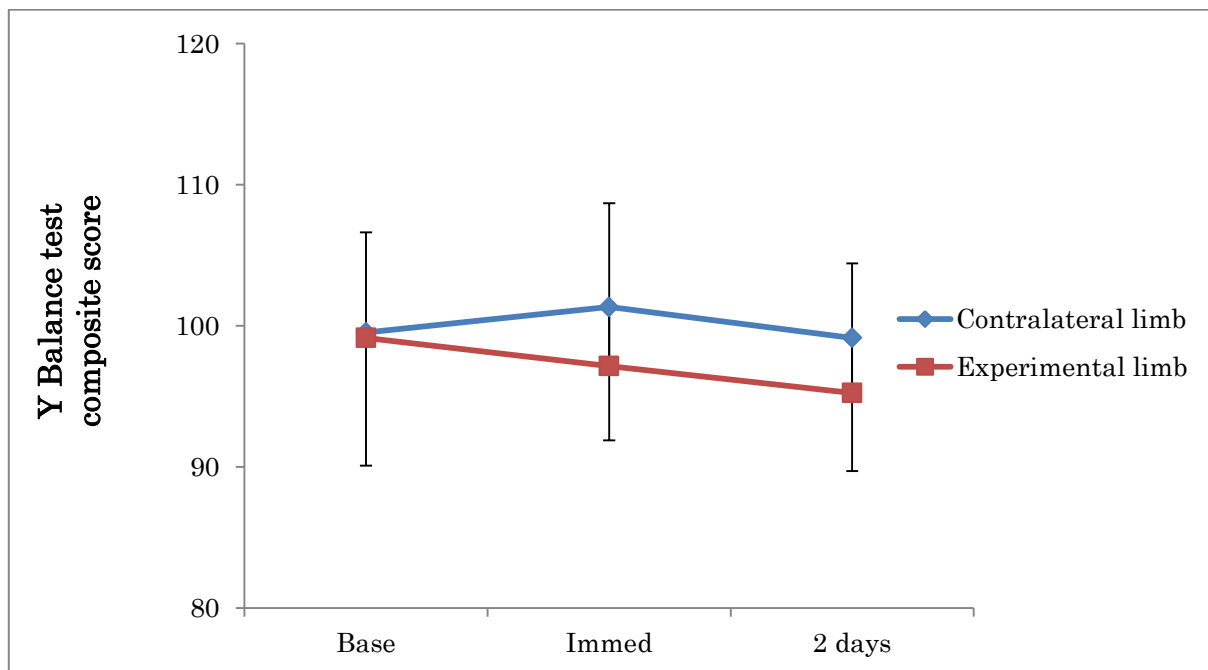


Figure 11. Effect of experimental induced pain on Y-balance composite score (mean±SD)

-rANOVA: Time effect on experimental side and contralateral side: $p=0.06$ ($F=3.36$) and $p=0.37$ ($F=1.02$)

G. Correlation Coefficients

Correlation coefficients for experimental side on two days post-exercise are presented in Table 2. A moderate to strong positive correlation was found between the changes in VAS and VPT ($r = 0.6789$, $p = 0.0143$) and a strong negative correlation was found between changes VAS and Y-balance composite score ($r = -0.79282$, $p = 0.0022$). Furthermore, a moderate positive correlations was observed between TDPM and VPT ($r = 0.4394$, $p = 0.1060$), indicating that a loss proprioceptive acuity may be associated with a diminished vibratory acuity.

Table II. CORRELATION COEFFICIENTS

	(1)	(2)	(3)	(4)
(1)VAS	1			
(2)Proprioception	0.04836 0.4491	1		
(3)Vibration Detection	0.67890 ^b 0.0143 *	0.43954 ^a 0.1060	1	
(4)Y-balance	-0.79282 ^c 0.0022 *	-0.19008 0.3053	-0.33671 0.177	1
Upper value: Correlation coefficients (r)				
Lower value: p-value (One tailed)				
^a : Moderate correlation (Dancey and Reidy's (2004) categorization)				
^b : Moderate to Strong correlation (Dancey and Reidy's (2004) categorization)				
^c : Strong correlation (Dancey and Reidy's (2004) categorization)				

IV: DISCUSSION

Induction of experimentally induced muscle pain via DOMS produced widespread hyperalgesia, demonstrated through diminished PPT at all test sites. Widespread diminished PPT has been demonstrated in several chronic pain conditions, including chronic tension type headache (Fernandez-de-las-Penas et al., 2008), unilateral epicondylalgia (Fernandez-Carnero et al., 2009) knee OA (Arendt-Neilsen et al., 2010) and low back pain (O'Neil et al., 2007). It is thought to be indicative of central sensitization of nociceptive pathways (Arendt-Neilsen et al., 2010). The use of this protocol allowed investigation of the effect of central sensitization on measures of hypoesthesia. This study demonstrated diminished proprioceptive acuity, measured via TDPM, and vibration perception, measured by VPT at the experimental knee post-exercise. Furthermore, this study found moderate but not significant ($p=0.106$) correlation between TDPM and VPT, indicating that these two modalities may be affected by nociceptive systems via similar mechanisms although it is likely the two sensory inputs are mediated by distinctly different pathways.

A. **The Effects of Muscle Pain on Nociceptive Sensation:Hyperalgesia**

Significant quadriceps pain measured using the VAS was induced in all subjects immediately (mean \pm SD: $3.3 \pm 0.41\text{cm}$) and two days post-exercise (mean \pm SD: $2.77\pm 0.43\text{cm}$) in this study. Reduced PPT was demonstrated at the site of induced pain and at remote testing sites. Similar studies (Hubscher et al., 2014; Nie et al., 2006; Tufano et al., 2012) evoked a similar degree of experimentally induced pain via high-force eccentric exercise, leading to a equivalent level of hyperalgesia.

Eccentric exercise induced muscle damage causes an immediate inflammatory pain due to release of inflammatory mediators from damaged muscle cells. This results in sensitization of the nociceptors which innervate the quadriceps muscle (Kidd and Urban, 2001), a process referred to as peripheral sensitization (Kidd and Urban, 2001; Woolf et al., 2004; Voscopoulos and Lema, 2010). DOMS refers to the increased intensity and expanded area of muscle tenderness experienced typically 24-72 hours following this type of exercise protocol. The exercise protocol utilized in this study successfully induced DOMS and the result was an widespread expansion of muscle tenderness, ie, hyperalgesia, indicative of central sensitization.

Previous studies have found regional hyperalgesic responses outside the area of

induced pain, including distal ipsilateral sites (Babenko et al., 1999; Joergensen et al., 2013) and bilateral sites (Hubscher et al., 2014). Our findings of diminished PPTs at the hand supports the notion that the hyperalgesic response was widespread rather than regional, indicating potentially a more extensive central sensitization process, as has been found in several studies of various chronic musculoskeletal pain conditions (Chiarotto et al., 2013; Fernandez-Carnero et al., 2009; Fernandez-de-las-Penas et al., 2009).

B. The Effects of Muscle Pain on Non-Nociceptive Sensation:Hypoesthesia

This study also found significant hypoesthesia in both vibration perception threshold and proprioception in the experimental knee immediately and two days post-exercise.

1. Altered vibration acuity

Following induction of experimentally induced muscle pain, vibratory perception threshold was significantly diminished from baseline measures at the experimental knee immediately and two days post-exercise. In chronic pain patient populations where objective measures indicated central sensitization was present, hypoesthesia has been demonstrated concurrently with hyperalgesia, (Shakoor et al., 2008; Kavchak et al., 2011; Hollins et al., 2001). The ability to detect a vibratory stimulus is

thought to be mediated by mechanoreceptors in the skin (Gilman, 2002, Gandhi et al., 2011, Purves et al., 2012). Alternatively, it is known that receptors in muscle and tendon may also detect vibratory stimuli (Fallon and Macefield, 2007). Therefore, loss of vibratory acuity, as found in this study, might have occurred due to damaged receptors within the injured quadriceps muscle. However, because the vibratory stimulus in this study was applied at the center of the patella, it may be argued that first detection of the stimulus (i.e., threshold) would most likely occur by the receptors in closest proximity to the stimulating stylus, that is the cutaneous mechanoreceptors. No cutaneous damage occurred in this protocol. Therefore, it is possible that alterations in vibration detection are due to central neurosensory changes rather than peripheral.

Apkarian et al. (1994) demonstrated that heat pain induced an increase in vibrotactile threshold (ie, diminished vibratory acuity) and changes in pain sensitivity threshold (hyperalgesia). Their interpretation of this phenomenon was the existence of a neural mechanism (touch gate) which would inhibit vibrotactile perception in the vicinity of the noxious input. In the present study, testing sites for vibratory stimuli was limited to the patella on both limbs. Our findings support the findings of Apkarian et al. (1994) and others (Hollins et al., 2001), in that changes in vibratory threshold occurred only at the site of

induced pain but did not occur at remote sites, such as the contralateral limb. Assuming hypoesthesia was centrally mediated, this finding would support the notion that the inhibitory mechanism may be somatotopically organized (Bolanowski et al., 2000).

Thus, the changes in VPT found in the present study may occur due to central sensitization at spinal or/and supraspinal levels. Our findings of diminished proprioception following induced muscle pain may suggest that musculoskeletal pain may inhibit other non-nociceptive sensory modalities besides vibratory detection.

2. Altered proprioceptive acuity

This experiment found a proprioceptive deficit of the experimental knee immediately and two days post-exercise. Previous studies using experimentally induced muscle pain have also demonstrated proprioceptive deficits on the experimental limb when examining either joint position sense (Malmstrom et al., 2013; Paschalis et al., 2007; Serinken et al., 2013) or TDPM (Paschalis et al., 2007) as a measure of proprioception. Diminished proprioception may have occurred due to neuroplasticity at the receptor level (Capra et al., 2007). Capra et al. (2007) proposed that inflammatory mediators from muscle injury stimulate nociceptors (group III and IV afferents) and in turn activate gamma-motoneurons which provide input to intrafusal fibers in muscles, thereby

influencing muscle spindle sensitivity and proprioceptive acuity (proprioceptive deficits). Thus, proprioceptive deficits induced by abnormal nociceptive input may occur due to a peripheral mechanism.

Central sensitization is believed to be a component of chronic musculoskeletal pain, such as knee OA (Arendt-Nielsen et al., 2010; Kavchak et al., 2012). Knee OA has been associated with proprioceptive loss (Felson et al., 2009). Our finding of decreased proprioceptive acuity on the experimental limb is similar to previous clinical studies (Felson et al., 2009; Shanahan et al., 2015), which indicated greater deficits of proprioception on the ipsilateral limb in people with chronic pain, although deficits in the contralateral limb have been reported. Determining the mechanisms underlying proprioceptive impairment in patient populations with conditions such as knee OA or ACL rupture can be difficult due to co-morbid impairments such as muscle weakness (van der Esch et al., 2007). The muscle spindle is considered the main contributor to proprioception (Gandevia and McCloskey 1976). Thus, muscle damage secondary to eccentric exercise may also have caused damage or alteration of the muscle spindle and thereby negatively affected proprioceptive acuity. Alternatively, like other pain related somatosensory deficits (Shakoor et al., 2008; Kavchak et al., 2011; Hollins et al., 2001), proprioceptive acuity may

be inhibited by central pain mechanisms. The direct relationship between chronic pain and proprioceptive deficits remains unclear. Understanding the relationship between various sensory changes following experimentally induced pain may be valuable.

C. Possible Similar Mechanisms in Diminished Vibratory Perception and Proprioceptive Deficit due to Experimentally Induced Muscle Pain

It may be argued that experimentally induced muscle pain may have had an effect on muscle spindles, which are believed to be the primary mediator of proprioception (Gandevia and McCloskey, 1976), thereby altering proprioceptive acuity at the receptor level. However, this would not explain deficits found in vibratory acuity, receptors of which lie in cutaneous tissues (Gilman, 2002; Gandhi et al., 2011; Purves et al., 2012).

The present study demonstrated significant hypoesthesia in both modalities potentially due to experimentally induced muscle pain. A moderate correlation between change scores of proprioception and VPT was demonstrated, indicating that the decrease in proprioceptive acuity was associated with the decrease in vibratory acuity. It may demonstrate that the two modalities, while distinct, may be affected via similar nociceptive mechanisms. The relationship between VPT and proprioception was not statistically significant ($p=0.106$). Thus, our main hypothesis was not supported. Future studies with

larger sample sizes may be valuable.

D. Correlation Between Other Measures

This study demonstrated a significant moderate to strong correlation between pain and vibratory acuity as measured by VPT. Subjects with higher pain had a greater vibratory loss. Proprioception, however, was not significantly correlated with pain. A positive correlation was shown between VAS and TDPM.

Furthermore, this study also addressed Y-balance composite score correlation analysis, it reported the changes in ability to dynamic balance as measured by Y-balance test was significantly correlated with pain intensity. This is supported by previous studies which showed the negative correlation between chronic pain intensity and the ability to balance (Imamura et al., 2008; Kavchak et al., 2012). This study also demonstrated a weak correlation between dynamic balance and TDPM, and between dynamic balance and VPT. Previous research showed pain was correlated with proprioception (Felson et al. 2009; Shanahan et al., 2015) and with vibratory acuity (Shakoor et al., 2008; Hollins et al, 2011; Kavchak et al., 2012).

E. Dynamic Balance

Although all subjects had quadriceps pain on the experimental limb, their performance on the dynamic balance test did not change significantly. This may be because the Y-balance test was not sensitive enough to capture changes in this population. Y-balance test was actually invented to measure overall motor control involving entire lower limb function for the purpose of predicting risk of injury, especially in the athletic population (Butler et al., 2013). Future studies including a balance measure that more closely examines the role of proprioception in balance would be appropriate.

F. Limitations

A main limitation to this study was sample size and non-specific inclusion criteria. Similar studies which investigated the relationship between chronic pain and diminished vibratory acuity (Kavchak et al., 2012) and between chronic pain and proprioceptive acuity (Shakoor et al., 2014) had sixteen and sixty-two participants respectively. This study was underpowered and thus may not be an accurate assessment of the relationship between altered modalities of somatosensation. Secondly, this study may have recruited both trained and untrained subjects, and did not recruit all of the same gender subjects as similar previous studies (Paschalis et al., 2007; Serinken et al., 2013). This might increase the

variability in perceptual responses. Further study with larger size of sample and more specific inclusion criteria would provide more confidence in the results. It also would allow us to improve the ability to detect relationships between variables.

G. Conclusion

In healthy subjects, experimentally induced quadriceps pain via DOMS resulted in widespread hyperalgesia and hypoesthesia locally at the painful limb, as measured by knee proprioception and VPT at the knee. Local hyperalgesia immediately after the exercise may be due to peripheral and regional central sensitization. Widespread hyperalgesia observed two days post-exercise were possibly due to progressive central mediated changes in spinal or/and supraspinal level. Pain induced hypoesthesia may occur through central inhibitory mechanisms due to hyperexcitability of nociceptive pathways. Furthermore, a moderate relationship was found between change scores of hypoesthesia, indicating that the two modalities, while distinct, may be affected via similar mechanisms. Further study needs to be done to clarify central mediated chronic pain mechanisms which may inhibit innocuous sensory input.

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