IS BILATERAL QUADRICEPS INHIBITION IN UNILATERAL ANTERIOR KNEE PAIN ATTRIBUTABLE TO GAMMA LOOP DYSFUNCTION?

by

© Tony Ingram

A thesis submitted to the

School of Graduate Studies

in partial fulfillment of the requirements for the degree of

Master of Science

School of Human Kinetics and Recreation

Memorial University of Newfoundland

May 2014

St. John's, Newfoundland and Labrador

ABSTRACT

A growing body of literature is revealing that unilateral knee pathology can cause bilateral quadriceps inhibition. The mechanisms by which these bilateral deficits occur are poorly understood. Research on knee ligament injury and osteoarthritis appears to indicate a link between traumatic disruption of sensory structures in the knee and a dysfunction of the gamma loop. Disruption of sensory structures appears to reduce afferent feedback to the gamma loop, and an intact gamma loop is necessary to achieve full muscle activation bilaterally. However, bilateral quadriceps inhibition is also seen in unilateral anterior knee pain conditions in which there is no obvious damage to the sensory structures of the knee. The purpose of this study was to determine the existence of gamma loop dysfunction in individuals with unilateral anterior knee pain to investigate its role as a mechanism for bilateral deficits.

ACKNOWLEDGEMENTS

I'd like to thank my supervisor Dr. Jeannette Byrne for the guidance throughout the program. Thank you to my friends and family for the encouragement. And thank you to my wife Sarah for the support and patience.

Table of Contents

List of Tables

List of Figures

List of Abbreviations and Symbols

ACL.....	Anterior Cruciate Ligament
AKP.....	Anterior Knee Pain
AMI.....	Arthrogenic Muscle Inhibition
ANOVA.....	Analysis of Variance
CPG.....	Central Pattern Generator
EMG.....	Electromyography
Hz.....	Hertz
iEMG.....	Integrated Electromyography
ITT.....	Interpolated Twitch Technique
Kg.....	Kilograms
MVIC.....	Maximum Voluntary Isometric Contraction
N.....	Newtons
NPRS.....	Numerical Pain Rating Scale
PFPS.....	Patellofemoral Pain Syndrome
TSK.....	Tampa Scale of Kinesiophobia
%VA.....	Percent Voluntary Activation

CHAPTER 1

LITERATURE REVIEW

1.1 Introduction and Literature Review

Previous research has shown that injury to one limb can cause bilateral changes (Byrne, Gage, & Prentice, 2002; Milner, 2008; Hart, Pietrosimone, Hertel, & Ingersoll, 2010; Wikstrom, Naik, Lodha, & Cauraugh, 2010). For instance, bilateral quadriceps force deficits are observed following unilateral anterior cruciate ligament (ACL) injury (Konishi, Konishi, & Fukubayashi, 2003; Konishi, Aihara, Sakai, Ogawa, & Fukubayashi, 2007). Why deficits cross from injured to healthy limbs is poorly understood. There appears to be a link between traumatic disruption of local sensory structures and gamma loop dysfunction.

Prolonged vibration to the quadriceps tendon leads to bilateral knee extension force deficits in healthy individuals (Jackson & Turner, 2003). These deficits are attributed to a temporary dysfunction of the gamma loop caused by attenuated Ia afferent feedback after vibration (Konishi et al., 2003). An intact gamma loop is required for maximal quadriceps activation (Hagbarth, Kunesch, Nordin, Schmidt, & Wallin, 1986). When prolonged vibration is applied to the tendons of those with previous injury, such as ACL injury, no additional force deficits are observed (Konishi et al., 2003). This implies gamma-loop dysfunction is already present in such populations. Previous researchers have concluded that damage to sensory structures is responsible for gamma loop dysfunction in injured populations, leading to bilateral force deficits (Rice, McNair, & Lewis, 2011; Konishi et al., 2007).

However, unilateral anterior knee pain (AKP) can occur in the absence of observable damage to the knee joint (Mann et al., 2007), yet similarly leads to bilateral

quadriceps inhibition (Drover, Forand, & Herzog, 2004; Suter, McMorland, Herzog, & Bray, 1999; Thomee, Grimby, Svantesson, & Osterberg, 1996). No study has investigated the effects of prolonged tendon vibration in individuals with AKP, and thus it is unknown whether this population exhibits gamma loop dysfunction. The purpose of the current study was to investigate the effects of prolonged vibration to the quadriceps tendon of individuals with unilateral AKP to fill this gap in the literature, and to further the understanding of mechanisms of bilateral deficits in unilateral pathology.

Before proceeding with a description of the proposed experimental design, a discussion of relevant background information is in order. First, a discussion of normal muscle activation, followed by knee joint afferents and their affects on muscle activation. Then we will review joint pathology related muscle inhibition and the present evidence that supports the conjecture that it is caused by alterations of sensory receptor activity. This will be followed by a discussion of potential mechanisms of bilateral muscle inhibition. Finally, the pathophysiology of AKP will be discussed, which will explain why this is a unique case that may provide further insight.

1.2 Motoneurons and Muscle Activation

Normal muscle activation is a multi factorial phenomenon. Movement is typically initiated consciously and unconsciously through the central nervous system. However, peripheral mechanisms of muscle activation exist through the action of spinal circuits, such as reflexes. The fundamental importance of reflexes has been known for over one hundred years. Reflexes may be modulated significantly by descending input from the central nervous system, but do not require these inputs. The most obvious evidence of this

is the observation that reflexes exist when descending input is removed (Sherrington, 1910). Furthermore, locomotion in animals is possible when both descending input as well as sensory input is removed (Brown, 1911).

This review will discuss the role of peripheral mechanisms of muscle activation through a discussion of simple reflexes present at the knee joint. First, this review will discuss the basics of muscle activation through a description of motoneurons and their known types. Next, the review will provide a brief description of the major knee joint afferent receptors and their possible effects on motoneuron activation through various reflexes.

1.2.1 Motoneurons

Motoneurons are broadly categorized as either 'upper' or 'lower' motoneurons. 'Upper' motoneurons originate in the motor cortex and project to 'lower' motoneurons that innervate muscle. Upper motoneurons are also known as pyramidal cells. For the purposes of this section only lower motoneurons will be discussed.

Motoneurons innervate muscle fibres acting as the final common pathway involved in the activation of muscle contraction (Sherrington, 1910). The cell bodies are located in the ventral horn of the spinal cord with their axonal projections travelling through the anterior roots of spinal nerves. These projections make their excitatory post-synaptic connection to muscle fibres through the release of acetylcholine at the neuromuscular junction. At least seven different types of motoneurons are known to exist (Manuel & Zytnicki, 2011). The three main categories of motoneurons are: α-

motoneurons, γ-motoneurons, and β-motoneurons (Figure 1.1). Each category has their own subtypes reflecting the function of the muscle fibres they innervate.

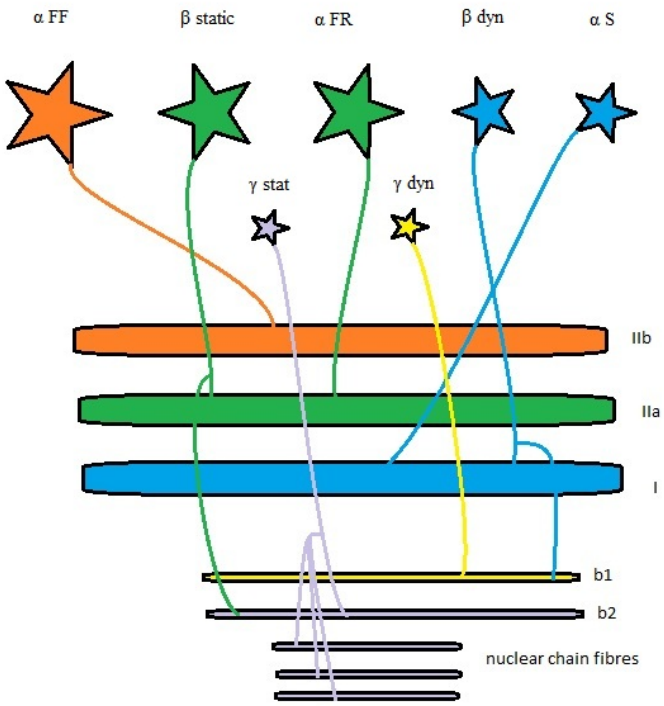

Figure 1.1 Schematic Diagram of motoneuron types and their innervation patterns. Adapted from Manual & Zytnicki, 2011. Abbreviations: α FF, fast fatiguing α-motoneuron; α FR, fast fatigue resistant α-motoneuron; α S, slow fatiguing α-motoneuron; β static, static β-motoneuron; β dyn, dynamic β-motoneuron; γ stat, static γ-motoneuron; γ dyn, dynamic γ-motoneuron; I, type I muscle fibres; IIa, type IIa muscle fibres; IIb, type IIb muscle fibres. b1, bag_1 nuclear bag fibre; b2, bag_2 nuclear bag fibre.

1.2.1.1 α-motoneurons

The most common type of motoneuron is the α-motoneuron. α-motoneurons innervate the extrafusal muscle fibres of skeletal muscle. In this way, α-motoneurons act

as the prime mechanism of joint movement through torque producing muscle contraction (Manuel & Zytnicki, 2011). Each α-motoneuron innervates multiple extrafusal muscle fibres, with the term 'motor unit' referring to the α-motoneuron and the muscle fibres it innervates.

α-motoneurons can be further subdivided into three types. The properties of these motoneurons reflect the physiological function of the muscle fibres they innervate (Burke, Levine, Tsairis, & Zajac, 1973). S-type (referring to slow fatiguing, or 'SO-type' for 'slow oxidative') α-motoneurons innervate Type I (slow fatiguing) muscle fibres. Likewise, FR-type (fast fatigue resistant) α-motoneurons innervate Type IIa muscle fibres. And finally, FF-Type (fast fatiguing) α-motoneurons innervate Type IIb muscle fibres. FF-Type α-motoneurons innervate the largest number of muscle fibres in their motor units, while S-type α-motoneurons innervate the smallest number of fibres. S-type α-motoneurons also demonstrate a slower axonal conduction velocity than those of FR α-motoneurons, and FF α-motoneurons display the fastest axonal conduction.

1.2.1.2 γ-motoneurons

γ-motoneurons are part of the 'fusimotor' system (Manuel & Zytnicki, 2011). Activation of a γ-motoneuron by itself does not produce joint movement. Innervating the intrafusal muscle fibres of the muscle spindle organ, γ-motoneurons control the gain of the 'stretch reflex' (see the description of muscle spindle function in Part II). It does so by activating the ends of the intrafusal (bag and nuclear chain) fibres, effectively changing the baseline tension detected by the Ia and II afferent fibres innervating the middle portion of the intrafusal fibres. For example, if a muscle is relatively relaxed, so too will

be the intrafusal fibres. Therefore the baseline tension in intrafusal fibres will be similar to the extrafusal fibres, and changes in tension caused by stretch of the entire muscle will be detected by the muscle spindle afferents. However, if the muscle was active due to α-motoneuron activation of the extrafusal muscle fibres, γ-motoneurons would then proportionally activate the intrafusal fibres such that the muscle spindle afferents would remain able to detect a change in length appropriately.

Two subtypes of γ-motoneurons exist: dynamic and static (Manuel & Zytnicki, 2011). Dynamic γ-motoneurons innervate only the bag_1 nuclear bag fibre, where static γ-motoneurons innervate the bag_2 nuclear bag fibre as well as the nuclear chain fibres. Static γ-motoneurons adjust the static sensitivity of the secondary endings (II afferents), encoding change in muscle length. Dynamic γ-motoneurons adjust the dynamic sensitivity of the primary ending (Ia afferent), encoding both rate and amount of length change.

1.2.1.3 β-motoneurons

The least studied of the three main categories of motoneurons are the β-motoneurons (Manuel & Zytnicki, 2011). β-motoneurons are interesting in that they innervate both extrafusal and intrafusal muscle fibres. Like γ-motoneurons, β-motoneurons are divided into two subtypes: dynamic and static. Dynamic β-motoneurons innervate the bag1 intrafusal fibre of the muscle spindle, while also innervating type I (slow fatiguing) extrafusal fibres (Manuel & Zytnicki, 2011). Static β-motoneurons innervate the bag2 and nuclear chain intrafusal fibres while also innervating type IIa/IIb extrafusal fibres. Manuel and Zytnicki (2011) presented in their review that the function

of β-motoneurons have really only been speculated upon, as relatively little is known about their role in muscle function. Dynamic β-motoneurons cause an increase in dynamic sensitivity of muscle spindles while simultaneously contracting type I muscle fibres, therefore may have a role in adjusting posture and balance. Static β-motoneurons cause concurrent increase in static sensitivity while contracting type IIa/IIb fibres and as such are hypothesized to play a role in preventing the slowing or stopping of rapid movements.

1.2.2 Knee Joint Afferent Receptors Affecting Motoneurons

There are several types of afferent receptors found in the structures of the knee joint (Solomonow, & Krogsgaard, 2001). Receptors can be found in the ligaments, joint capsule, menisci, articular surfaces, periosteum, tendons, muscles crossing the joint, and the skin. Major receptor types include, but are not limited to, free nerve endings, Ruffini endings, Pacinian corpuscles, Golgi organs, and muscle spindles (Table 1.1). Although sensory receptors can respond to a variety of stimuli, the receptors of interest found in the knee most often respond to a mechanical stimulus. As joint afferents may have different effects in different parts of the body, this paper will discuss only the major mechanoreceptors found in the area of the knee joint.

Table 1.1 Receptor types found in various structures of the knee joint. Rows refer to receptor types, columns refer to knee structures, and check boxes indicate whether receptor types have been identified in a particular structure. Adapted from Solomonow & Krogsgaard (2001).

Receptor Type	Muscle	Tendon	Capsule	Menisci	Ligament	Articular Surface
Muscle Spindle	☑					
Golgi Organ		☑	☑	☑	☑	
Pacinian Corpuscle				☑	☑	
Ruffini Ending				☑	☑	
Free Nerve Endings					☑	☑

Difficulty arises in accurately determining how each receptor type affects motoneuron activation. Motoneurons receive many different inputs from supraspinal structures, spinal interneurons, and sensory inputs responsible for mono and polysynaptic reflexes (Manuel & Zytnicki, 2011). Another issue is that while each type of receptor responds best to particular mechanical stimuli, their activation is not exclusively dependent on a particular stimulus. Rather than modality specific activation, it is thought that stimuli are encoded through ensemble (or population) encoding (Sjölander, Johansson, & Djupsjöbacka, 2002). Different neurons fire at different frequencies depending on the stimulus, and can even respond equally to two different stimuli. However, when multiple neurons are stimulated, the overall pattern represents a particular stimulus. Other factors create additional difficulty in determining the effect of a receptor

type on muscle activation. Many studies investigate the differences between injured and healthy structures. However, it is difficult to isolate damage of a particular structure (for example, a ligament) as surrounding structures can also be effected (Sjölander et al., 2002). Even in cases of isolated ligament damage, laxity may alter the biomechanics of the surrounding structures, therefore altering the activity of receptors and motoneurons. These limitations should be kept in mind for the following discussion of receptor types and their possible roles in muscle activation.

1.2.2.1 Free Nerve Endings

Free nerve endings are nerve endings terminating in the periphery without a non-neural component. These receptors are relatively unspecialized, responding to both mechanical deformation as well as chemical stimulation (Solomonow & Krogsgaard, 2001). They are polymodal, being able to detect temperature, mechanical stimuli such as touch, pressure, and stretch, and finally nociception (colloquially known as pain receptors). It should be noted, however, that nociception is neither necessary nor sufficient to produce the perception of pain. Nociceptors may simply be high threshold sensory receptors (Basbaum, Bautista, Scherrer, & Julius, 2009), thus signalling potential tissue damage that may or may not lead to the experience of pain (Apkarian, Baliki, & Geha, 2009). Free nerve endings may be fast or slow adapting, depending on their function. Generally speaking, free nerve endings are most likely involved in sensing pressure in the joint capsule near its end range of motion.

Free nerve endings can directly cause muscle activation through a polysynaptic reflex (Solomonow & Krogsgaard, 2001). This 'flexor withdrawal' reflex causes

excitation of flexor muscle groups in the ipsilateral limb as well as inhibition of the extensor groups. Simultaneously, the opposite occurs in the contralateral limb, known as the 'crossed extensor reflex'. The effect is a quick lifting of the foot and single leg stance to avoid further damage by the potentially damaging stimulus. This reflex occurs before conscious perception of pain, illustrating that voluntary movement is not required for this response to occur (Chan & Dallaire, 1989).

1.2.2.2 Pacinian Corpuscles and Ruffini Endings

Pacinian corpuscles are nerve endings with a thinly encapsulated terminal ending (Solomonow, & Krogsgaard, 2001). They are sensitive to small changes in mechanical pressure on their capsule head. These receptors are 'fast-adapting', which causes them to discharge only during the application or removal or pressure; they only fire when the stimulus is changing. In skin, they are known to detect pressure and vibration. In joint capsules, the Pacinian corpuscle signals acceleration and deceleration of joint angle change.

Ruffini endings consist of several endings from a single neuron, each thinly encapsulated (Solomonow & Krogsgaard, 2001). These receptors respond to low thresholds of mechanical pressure. They are slow-adapting, which causes them to continue discharging longer after stimulation, and are therefore thought to signal a change as well as a new baseline of the tissues status. They are therefore both dynamic and static in nature.

Both Pacinian corpuscles and Ruffini endings may be involved in the 'ligamento-muscular protective' reflex (Solomonow & Krogsgaard, 2001). An example is the 'ACL-

hamstrings reflex loop', where a high force stretch of the ligament leads to the contraction of the hamstrings. However, Sjölander et al. (2002) postulates that this is not so much a protective reflex, as much as it is a feedback mechanism for the control of skilled movement. Sjölander et al. (2002) proposes that high force activates free nerve endings, causing the hamstrings to contract due to the previously mentioned flexor withdrawal reflex. Sjölander et al. (2002) further elaborates that low threshold ligament receptors such as the Pacinian corpuscles and Ruffini endings only cause significant changes in muscle EMG activity when these muscles are already activated, such as during locomotion (Dyhre-Poulsen & Krogsgaard, 2000). Finally, the actions of these reflexes do not occur quickly enough to protect a joint from damage except during slow movements (Sjölander et al., 2002). Whether protective or simply involved in coordinated movement, ligamento-muscular reflexes are present in many ligaments throughout the body (Hagert, 2010).

1.2.2.3 Muscle Spindles (Ia and II afferents)

Muscle spindles receptors are the sensory receptor of the fusimotor system. Spindles are found in the muscles crossing over the knee joint. They consist of intrafusal (inside the spindle) muscle fibres arranged in series with the extrafusal muscles (Proske & Gandevia, 2012; Ellaway, Taylor, Durbaba, & Rawlinson, 2002; Granit, 1975). These intrafusal muscle fibres are innervated in the mid portion by sensory afferents, the Ia and II sensory fibres. The outer portions of these intrafusal fibres are innervated by γ-motoneurons. Intrafusal muscle fibres include nuclear bag1 and bag2 fibres, as well as

nuclear chain fibres (for more detailed functional analysis of innervation patterns see the description of γ-motoneurons in Part I).

When a muscle spindle is stretched, Ia (primary) and II (secondary) sensory fibres are stimulated and cause the 'stretch reflex' (Proske & Gandevia, 2012; Ellaway et al., 2002; Granit, 1975). Type Ia afferents respond to both static and dynamic stimuli in that they encode a change in muscle length as well as the rate at which it changes. Type II afferents only respond to static changes in muscle length. The stretch reflex involves a monosynaptic reflex where the stimulated afferents within the spindle fire upon the α-motoneuron of the same muscle. In this way, when a muscle is suddenly stretched, it contracts to prevent further elongation. To prevent this reflex during voluntary contraction, γ-motoneurons and β-motoneurons fire along with the α-motoneuron to keep the intrafusal muscle tension similar to that of the extrafusal muscle. This concurrent firing thereby causes the stretch reflex to only normally become activated when external force is applied to a muscle. Furthermore, γ-motoneurons and β-motoneurons are also thought to adjust the sensitivity of the stretch reflex during different functional tasks.

1.2.2.4 Golgi Tendon and Joint Organs (Ib afferents)

Golgi organs are found both near the muscle-tendon junction of a tendon, as well as within the joint ligaments and capsules (Solomonow & Krogsgaard, 2001). Golgi organs are large, thinly encapsulated corpuscles. These receptors have high thresholds of activation by mechanical deformation and are generally slow adapting. Golgi organs found in tendons signal the amount of muscle tension or force in the tendon of the muscle they reside. Golgi organs that are found in joints are thought to signal joint angle.

Golgi organs are involved in a polysynaptic reflex through the stimulation of their Ib afferent receptors. When stimulated, Ib afferents synapse on interneurons in the spinal cord, which receive numerous inputs from local and descending afferents (Proske & Gandevia, 2012; Jami, 1988). While the organism is not in locomotion, Ib afferents synapse on inhibitory interneurons, thereby inhibiting the α-motoneuron of the same muscle. It has been proposed that this reflex is meant to decrease tension on a muscle as a protective reflex. However, when Ib afferents are stimulated during particular tasks, namely particular phases of locomotion, they elicit an excitatory effect on the α-motoneurons (Houk & Henneman, 1967). Therefore, the actions of Golgi tendon organs are state dependent. Rather than a previously proposed function of muscle strain protection, it is now thought that these reflexes are involved in regulation of coordinated movement (Proske & Gandevia, 2012; Chalmers, 2002).

1.2.2.5 Conclusion

Many more mechanisms exist in the control of muscle activation than simple reflexes. Besides their role in simple reflexes, each afferent discussed is known to make ascending projections to supraspinal structures (Solomonow & Krogsgaard, 2001). These ascending projections are the basis of conscious (cortical) and unconscious (cerebellar) propioception (Sjölander et al., 2002). Projections are also known to cross communicate to the contralateral side through spinal interneurons. Complex networks such as the central pattern generators (CPG's) known to exist in mammalian spinal cords may also influence movement (McCrea, 2008). And of course, motoneurons are activated and modulated via descending projections from supraspinal structures. Control of muscle

activation is thus far more complex and nuanced than can be explained through simple reflexes.

1.3 Arthrogenic Muscle Inhibition

Persistent weakness of the quadriceps is a ubiquitous consequence of pain or injury at the knee. This weakness is in part due to arthrogenic muscle inhibition (AMI), a neural inhibition of complete muscle activation associated with joint injury (Hart et al., 2010; Rice & McNair, 2010). AMI is thought to stem from joint pathology as it occurs in the absence of damage to the inhibited muscle or its innervating nerve (Hopkins & Ingersoll, 2000). AMI has been shown to be present in such knee joint pathologies as osteoarthritis (Rice et al., 2011), anterior cruciate ligament (ACL) rupture (Konishi et al., 2003), post-ACL repair (Konishi et al., 2007), and anterior knee pain (Drover et al., 2004; Suter, Herzog, De Souza, & Bray, 1998a; Suter, Herzog, & Bray, 1998b; Suter et al, 1999; Thomee et al., 1996). AMI is not exclusive to the knee, and has been reported in the hip (Freeman, Mascia, & McGill, 2012), ankle (Klykken, Pietrosimone, Kim, Ingersoll, & Hertel, 2011; McVey, Palmieri, Docherty, Zinder, & Ingersoll, 2005), and shoulder (Hsu, Boardman, Luo, & An, 2000; Voigt, Jakobsen, & Sinkjaer, 1998) joints as well.

Because of its pervasiveness, AMI is a clinical concern in the rehabilitation of knee joint pathology. Quadriceps strength can remain decreased despite resistance training, an issue often attributed to AMI (Hurley, Jones, Newham, 1994). While studies have demonstrated that AMI improves over time (Rice & McNair, 2010), others suggest that it does not, and can be present bilaterally up to four years after injury (Becker, Berth,

Nehring, Awiszus, 2004). Persistent quadriceps weakness may impair dynamic knee stability (Keays, Bullock-Saxton, Newcombe, & Keays, 2003) and physical functioning (Yoshida, Mizner, Ramsey, & Snyder-Mackler, 2008; Urbach & Awiszus, 2002), increase the risk of re-injury (Fyfe, Opar, Williams, & Shield, 2012), and contribute to the progression of osteoarthritis (Segal et al. 2009; Mikesky et al., 2006).

Numerous lines of evidence suggest that AMI may be due to altered afferent discharge from joint receptors. Factors that may influence afferent discharge include swelling, inflammation, joint laxity, and structural damage. Each of these factors can affect afferent discharge differently. Swelling appears to increase joint afferent discharge (Ferrell, 1987), possibly by stimulating pressure sensitive mechanoreceptors. Aspirating 150 mL of synovial fluid from an acutely injured knee can increase isometric knee extensor torque by approximately 85 to 400% (Reeves & Maffulli, 2008). Apart from contributing to swelling, chemical mediators of inflammation can increase afferent discharge by decreasing mechanical thresholds and increasing spontaneous discharge in joint afferents (Dunham, Kelly, & Donaldson, 2008; Schaible & Schmidt, 1988; Grigg, Schaible, & Schmidt, 1986). It has been shown that intra-articular corticosteroid injection can improve knee extension torque, presumably by reducing inflammation and normalizing afferent discharge (Geborek, Mansson, Wollheim, & Moritz, 1990). Joint laxity may increase afferent discharge by causing anomalously greater movement at the articular surfaces. For example, ACL transection tends to cause an increase in afferent discharge during joint movement in cats (Gomez-Barrena, Nunez, Ballesteros, Martinez-Moreno, & Munuera, 1999). Presumably due to restoration of normal joint kinematics, afferent discharge tends to normalize after the ACL is repaired with surgical

reconstruction. However, differences in afferent discharge can remain 9-18 months after surgical reconstruction (Gomez-Barrena et al., 2008).

Arthropathy does not always lead to an increase in afferent discharge. In the case of damage to the articular receptors themselves, afferent discharge apparently decreases (Konishi, Fukubayashi, & Takeshita, 2002; Hurley, 1997). Quadriceps inhibition is observed when local anaesthetic is injected into the knee of a healthy volunteer, but in a volunteer with ACL rupture no change in activation is observed, indicating pre-existing muscle inhibition (Konishi et al., 2002). Konishi et al. (2002) speculated that quadriceps inhibition was due to decreased afferent discharge secondary to ACL receptor damage. This is opposed to the increased afferent discharge found during movement of ligament lax knees, which would presumably originate from sensory receptors of the surrounding structures. Taken together, these factors indicate the necessity of normal joint afferent feedback for complete quadriceps activation.

AMI is also known to occur bilaterally, affecting the contralateral side to a similar magnitude as the injured side (Hart et al., 2010). Bilateral quadriceps inhibition has been found in such conditions as ACL rupture (Konishi et al., 2003), ACL reconstruction (Konishi et al., 2007), and anterior knee pain (Drover et al., 2004; Suter et al., 1999; Thomee et al., 1996). Hart et al. (2010) recently published a systematic review summarizing the percentage of quadriceps voluntary activation (%VA) for these three patient populations. Hart et al. (2010) also reported each group's prevalence of quadriceps activation failure, which was defined as an inability to reach more than 95 %VA which is regarded as normal. ACL deficiency led to %VA of 87.3 and 89.1, and a prevalence of 57.1% and 34.2% on the involved and uninvolved sides, respectively. ACL reconstruction

led to %VA of 86.5 and 84.0, with a prevalence of 24.2% and 8.3% for the involved and uninvolved sides, respectively. Anterior knee pain led to %VA of 78.6 and 77.7 for the involved and uninvolved sides, and a prevalence of 91% in either side. Based on the review by Hart et al. (2010), it appears that anterior knee pain leads to a greater magnitude as well as prevalence of bilateral AMI than ligament injuries.

It should be noted, however, that the methodological quality of the research reviewed by Hart et al. (2010) was generally of poor quality, with PEDro scores ranging from 2 to 6. With respect to anterior knee pain, the Drover et al. (2004), Suter et al. (1999), and Thomee et al. (1996) studies received PEDro scores of 3, 5, and 5, respectively (Hart et al., 2010). None of these three studies blinded investigators to the involved leg, and the first two did not include a control group. Therefore, the greater magnitude and prevalence of AMI in AKP compared to other pathology may be overstated.

1.4 Potential Mechanisms of Bilateral Inhibition

The existence of contralateral effects raises interesting questions about the physiology of AMI. Namely, what are the potential mechanisms of bilateral muscle inhibition? Understanding how AMI might affect the contralateral limb is a primary goal of the proposed research. Therefore, a detailed review of possible mechanisms of contralateral inhibition will follow. Much research has been done on the contralateral effects of training (Carroll, Herbert, Munn, Lee, & Gandevia, 2006; Lee & Carroll, 2007). However, the literature concerning contralateral effects of injury, such as AMI, has been

explored in less detail (Hart et al., 2010). Therefore, many of the reviewed mechanisms are borrowed from either exercise physiology or pathology related research.

Though impossible to definitively separate, mechanisms that influence contralateral muscle activation can be thought of as 'peripheral', 'spinal', or 'supraspinal' (Rice & McNair, 2010). For the purposes of this research, locations will be defined based on where changes might occur. 'Peripheral' mechanisms refer to local changes in sensory receptors that may consequently affect motoneuron activation. Peripheral mechanisms may affect contralateral motoneurons through spinal reflexes or by altering supraspinal influence. 'Spinal' mechanisms involve changes that occur within the circuitry of the spinal cord. These mechanisms are heavily influenced by supraspinal structures as well as sensory afferent information, and can include such things as central pattern generators (CPGs) (McCrea, 2008), as well as simpler reflexes whose spinal connectivity can be altered in pathology. Finally, 'supraspinal' mechanisms are alterations in conscious and unconscious activity above the level of the spinal cord. Again, these supraspinal mechanisms may be influenced or initiated elsewhere, but the changes occur within supraspinal structures. Examples of 'supraspinal' mechanisms include altered arthrogenic corticomotor excitability (Heroux & Trenblay, 2006).

1.4.1 Peripheral Mechanisms

1.4.1.1 Flexor Withdrawl and Crossed Extensor Reflex

One of the most widely known peripheral reflexes that can effect contralateral muscle activation is the flexor withdrawal and crossed extensor reflex (Sherrington, 1910). This 'simple' reflex involves the withdrawal of the lower extremity upon nociceptive

stimuli, with concurrent extensor muscle activation in the opposite limb for support. This reflex is modulated by body position (Paquet, Tam, & Hui-Chan, 1996) and can be altered pharmacologically (Frigon, Johnson, & Heckman, 2012). Muscle activation from this reflex is temporary and immediate, occurring before conscious perception, and therefore most likely crossing contralaterally at the level of the spinal cord through interneurons (Chan & Dallaire, 1989). While such a reflex may exist elsewhere, it is typically described to result from nociceptive input from cutaneous nociceptors in the foot. Due to the temporary effects, as well as cutaneous origin, it is unlikely to be involved in chronic contralateral AMI. AMI does not involve an obvious source of continuous acute nociception. However, similar mechanisms may be involved.

1.4.1.2 γ loop dysfunction

Interestingly, prolonged vibration to the infrapatellar tendon of healthy individuals causes a bilateral decrease in voluntary quadriceps activation (Jackson & Turner, 2003). The authors originally speculated that contralateral effects were due to alterations in the crossed extensor reflex (Jackson & Turner, 2003). However, this bilateral inhibition is now thought to occur due to alterations in the γ loop (Konishi et al., 2002; Konishi et al., 2003). As discussed, the γ loop is a spinal reflex where γ-motoneurons innervate muscle spindles, which in turn provide feedback to the homonymous α-motoneuron pool through Ia afferent fibers (Manuel & Zytnicki, 2011). Prolonged vibration may attenuate Ia afferent feedback (Shinohara, 2005) through neurotransmitter depletion (Curtis & Eccles, 1960), heightened discharge threshold of Ia fibers (Hayward, Nielsen, Heckman, & Hutton, 1986), or pre-synaptic inhibition of Ia terminals (Hultborn, Meunier, Pierrot-

Deseilligny, & Shindo, 1987). By decreasing Ia afferent feedback, activation or 'gain' of γ-motoneurons may be decreased. Because the intrafusal muscle fibres are no longer taut, they do not detect force properly, thus decreasing afferent (Ia) feedback. Adequate Ia feedback seems to be necessary for the recruitment of high-threshold alpha motor units (Kouzaki, Shinohara, & Fukunaga, 2000; Bongiovanni, Hagbarth, & Stjernberg, 1990; Hagbarth et al., 1986). Therefore, attenuation of this γ loop, termed 'γ loop dysfunction', may cause quadriceps femoris weakness. Konishi (2003) speculated that γ loop dysfunction may explain the bilateral deficit for two reasons. First, the affected side may send inhibitory signals to the contralateral side via interneurons in the spinal cord. Second, feedback from mechanoreceptors in the affected limb may be transmitted supraspinally, resulting in descending inhibition bilaterally. Neither of these speculations have since been confirmed.

When prolonged vibration is applied to the infrapatellar tendon of individuals with knee joint pathology, no additional muscle inhibition is observed. It has been proposed that this phenomenon indicates a pre-existing γ loop dysfunction. This has been shown in individuals with knee osteoarthritis (Rice et al., 2011), ACL rupture (Konishi et al., 2003), and post-ACL repair (Konishi et al., 2007). γ loop dysfunction is thought to be due to damage to the sensory receptors of the knee joint that contribute to Ia afferent feedback. γ loop dysfunction has been shown to affect both the ipsilateral as well as contralateral sides of injury (Konishi et al., 2007). These findings suggest that γ loop dysfunction may be a significant contributor of bilateral quadriceps AMI when the knee joint is damaged. While AMI is indeed multifactorial, γ loop dysfunction provides a possible mechanism explaining bilateral inhibition.

The precise anatomy and physiology of γ loop dysfunction has not been elucidated. Konishi et al. (2007) proposed the altered sensory information travels first to the upper central nervous system before returning to the γ-motor units to have their effect on the γ loop. However, as shown by the crossed extensor reflex discussed above, neuronal circuits can cross at the level of the spinal cord. In any event, the exact physiology of γ loop dysfunction is yet to be determined.

1.4.2 Spinal Mechanisms

Spinal mechanisms refer to physiological pathways affecting muscle activation where any changes occur primarily within spinal cord networks. Spinal networks are generally under descending control of the brain, and influenced substantially by sensory stimuli (McCrea, 2008). However, all other things equal, changes can occur in a spinal network that may alter the effect of these descending signals and sensory stimuli. The flagship example of a spinal network that can affect muscle activation bilaterally is a Central Pattern Generator (CPG) (McCrea, 2008).

1.4.2.1 Central Pattern Generators

CPG's have been extensively studied in invertebrates and rodents due to their simpler nervous systems compared to humans (McCrea, 2008; Hooper, 2000). It is not definitive whether humans innately have CPGs or if they may be developed from experience (Molinari, 2009). Hooper (2000) postulated that humans may not have such stereotyped neural networks due to the extensive sophistication and voluntary control of human movement. However, infants can be demonstrated to have a step reflex resembling walking with sensory input to the feet (Yang et al., 2004). Whether born with CPGs

innately or gained from experience, it is generally accepted that they exist in humans to some degree (Tassinari et al., 2005; Dimitrijevic, Gerasimenko, & Pinter, 1998).

CPGs respond to descending pathways and sensory stimuli with high fidelity (McCrea, 2008). CPG's generate patterns through a variety of mechanisms; rhythmicity of motoneuron firing can be established through the arrangement of a network, as well as through the properties of the neurons involved in the network themselves (McCrea, 2008). The action of CPG's can be altered such that they may be utilized when learning new rhythmic movements such as swimming, dancing, and other skills. Similarly, it is thought that pathology can alter pattern generation. Investigations are being done on the role of CPGs in Spinal Cord Injury (Rossignol & Frigon, 2011), Stroke (Teismann et al., 2011), Parkinson's disease (De Nunzio, Grasso, Nardone, Godi, & Schieppati, 2010), and Amyotrophic Lateral Sclerosis (Aydogu, Tanriverdi, & Ertekin, 2011).

Alterations of CPG networks may be one explanation of bilateral effects of unilateral injury. Invertebrate studies have shown that alterations in any one neuron in a CPG can alter the entire pattern (Hooper, 2000). Because of the high level of adaptability CPG's exhibit, small deficits often adjust patterns in a way that can maintain the most effective movement possible (McCrea, 2008; Yang, Stephens, & Vishram, 1998). It may be possible that these adjustments, while maintaining effective pattern generation, cause a change in motoneuron firing in the opposite limb.

However, alterations in CPG's seem unlikely to cause contralateral AMI for at least two reasons. First, these alterations likely have more of an effect on pattern generation and less of an effect on maximum voluntary contraction where AMI is most apparent. Second, CPG's exist for each side of the body and can act independently of each

other (Brown, 1911). If each side interacts, cross over likely occurs supraspinally, and thus offers no more explanatory power than γ loop dysfunction. Thus, while providing another example of how muscle activation is modulated, altered CPG's are not often considered a mechanism for contralateral AMI.

1.4.3 Supraspinal Mechanisms

Supraspinal mechanisms refer to changes in brain and brain stem activity that can influence muscle activation after joint injury. Insights into the possible supraspinal mechanisms involved in contralateral AMI may be garnered from such phenomenon as the cross-education effect in training, the central governor theory of fatigue, chronic pain research, corticomotor excitability research, and the potential role of the Red Nucleus. We will now proceed with a discussion of each topic, and how they may provide insight into the nature of contralateral AMI.

1.4.3.1 Reverse 'Cross-education Effect'

While investigating possible physiological mechanisms of contralateral muscle inhibition after injury, one may consider the pathways involved being similar to that of the 'cross over effect' of exercise. This 'cross over effect' refers to the observation of increased physical performance in the contralateral side of a training stimulus (Carroll et al., 2006; Lee & Carroll, 2007). The 'cross over effect' is thought to be an example of a central mechanism of strengthening (Gabriel, Kamen, & Frost, 2006). While still possible, a review of the literature suggests it may not be due to an increase in muscle activation, but that of motor learning, i.e. an effect on coordination (Folland & Williams, 2007). This effect improves physical performance on the opposite side through improved technique

and coordination of stabilizer muscles involved in the task. Therefore, the idea of a 'reverse cross-over effect' is an unlikely mechanism of arthrogenic muscle inhibition, although similar mechanisms may apply.

1.4.3.2 Central Governor Theory

Another intriguing line of thought comes from 'central governor theory'. Central governor theory states that the nervous system is responsible for the perception of muscle fatigue to discourage excessive exertion that may disrupt homeostasis (Noakes, Gibson, & Lambert, 2005; Noakes, 2011). Muscle fatigue is multifactoral (Knicker, Renshaw, Oldham, & Cairns, 2011) and the central governor theory is debated (Marcora, 2008; Weir, Beck, Cramer, & Housh, 2006). Nonetheless, similar pathways or mechanisms may be at work in inhibiting muscle activation after injury as that of inhibition due to fatigue, especially when the inhibition is not accompanied by pain. Central mechanisms may decrease muscle activation as a protective measure due to previous experience (Noakes, 2011). One might postulate that this protective measure may affect both the contralateral side as well as the ipsilateral side of previous injury. However, contralateral arthrogenic muscle inhibition has been studied primarily within the context of strength, and not muscle endurance. Central governor theory may be another mechanism altering corticomotor excitability, which will be discussed later. Further study is required in this area of research before any link to arthrogenic muscle inhibition can be made.

1.4.3.3 Chronic Pain

Research indicates that pain can lead to inhibited muscle activation (Dube & Mercier, 2011), even in locations at a distance from the painful area (Verbunt et al., 2005).

Central mechanisms associated with the persistence of chronic pain may help explain the bilateral effects of unilateral pathology, and will be reviewed in more detail during the discussion of anterior knee pain below. Chronic pain is known to lead to bilateral arthrogenic muscle inhibition (Hart et al., 2010). In their review of quadriceps activation following knee injuries, Hart et al. (2010) found that not only did anterior cruciate ligament deficiency (ACLd) and repair (ACLr) lead to long standing (> 12 months) bilateral quadriceps inhibition, but so did chronic anterior knee pain. Furthermore, chronic anterior knee pain caused greater deficits in maximum voluntary contraction than that of the ACLd and ACLr deficits. Although they were of moderate to poor quality when assessed with the Physiotherapy Evidence Database (PEDro) score (Hart et al., 2010), these studies reveal pain as a potential mechanism explaining bilateral arthrogenic muscle inhibition.

1.4.3.4 Corticomotor Excitability

Heroux & Trenblay (2006) argued that peripheral mechanisms cannot fully account for arthrogenic muscle inhibition, and therefore investigated corticomotor excitability in individuals with previous ACL injury. Using transcranial magnetic stimulation (TMS), their experiment revealed decreased resting motor thresholds (RMTs) on the injured side of ACL injured patients compared to controls. The decrease in RMTs was taken by the authors to indicate an increase in corticomotor excitability. It was proposed that this increased excitation was caused by decreased sensory feedback from the damaged ligament. Decreased feedback may lead to increased corticomotor excitability to help protect the injured ligament from damage, forcing a more voluntary

mode of control of muscle activation over a more semi-automatic control. However, this seems to be the only study of its kind, and these further hypotheses have yet to be tested. Furthermore, one cannot truly estimate corticomotor excitability through motor evoked potentials with TMS, as it does not distinguish between spinal and supraspinal excitability, which requires additional methodology to elucidate (Taylor & Gandevia, 2004). It may be that the increase in corticomotor excitability may be an attempt to overcome quadriceps inhibition at the spinal level. Finally, there were some methodological issues with this study that make application of results problematic. For instance, the TMS coil used during this study was changed halfway through the study, causing roughly half the participants to be tested with different equipment.

Altered corticomotor excitability may be a mechanism through which all 'central' mechanisms converge. This is similar to the fact that all influences of muscle activation ultimately have their effect on α-motoneurons, the final neurons involved in activating skeletal muscle. When fatigue, pain, or lack of sensory feedback cause a change in muscle activation, they may each have their effect through corticomotor activation. Of course, other pathways exist through which muscle activation can be influenced by brain changes. One possible pathway could be inhibition of corticospinal descending pathways. Another possibility is that proposed by Konishi, et al. (2007) where changes in the brain likely modulate γ loop gain continuously. By decreasing spindle gain, muscle activation may proceed fairly normally, yet the strongest contractions are inhibited to protect from possible re-injury. Thus, the brain may be involved in mechanisms that appear to be 'peripheral'.

1.4.3.5 Red Nucleus and The γ Loop

Another mechanism that may help to explain the contralateral component of bilateral AMI is neuroplasticity of the Red Nucleus and its influence on the γ loop. The Red Nucleus is a rostral midbrain structure that receives input from the contralateral cerebellum and ipsilateral motor cortex, and sends efferent projections through the rubrospinal tract (Hicks & Onodera, 2012). These projections appear to synapse with γ-motoneurons (Johansson, 1988). The Red Nucleus is thought to work together with the Cerebellum to modulate the fusimotor system during motor adaptation by facilitating predictive compensations during ongoing motor commands and error feedback learning (Scheidt et al., 2012).

The Red Nucleus is also involved in pain in at least two important ways. First, it is thought to be involved in coordinating motor response to nociception (Matsumoto & Walker, 1991). Second, it has been shown to be involved in the development of neuropathic pain by modulation of pro-inflammatory cytokines (Wang, Zeng, Han, Fan, & Wang, 2012; Li et al., 2008). This illustrates the neuroplasticity of the Red Nucleus during pathology. Thus, it is possible that alterations in Red Nucleus activity are important in the modulation of bilateral γ loop function, and as such, bilateral AMI during knee joint pathology.

1.4.3.6 Conclusion

Bilateral AMI is likely a multifactoral phenomenon. Attributing only one of the possible mechanisms discussed in this review would be ignoring any evidence for others. While it may be possible that all factors essentially converge into one mechanism, such as

γ loop dysfunction, the possibility remains that there may be numerous sufficient mechanisms, but no single mechanism that's necessary. Further studies need to be carried out to determine whether the fundamental mechanism of bilateral AMI following joint pathology is indeed γ loop dysfunction.

Regardless of its multifactoral nature, the most promising theory explaining bilateral AMI appears to be γ loop dysfunction. As previously discussed, it is speculated that the γ loop is altered due to damage to the afferent sensory receptors of the injured joint. While it may seem clear that dysfunction of the γ loop is involved, that is it caused by damage to the sensory receptors becomes contentious when considering AMI in the case of anterior knee pain.

1.5 Anterior Knee Pain

Anterior knee pain (AKP) is characterized by pain at or around the patellofemoral joint (Mann et al., 2007). AKP is commonly used interchangeably with patellofemoral pain syndrome (PFPS) (Thomee, Augustsson, & Karlsson, 1999). AKP is used to define non-specific knee pain that cannot be attributed to intra-articular pathology, peripatellar tendonitis or bursitis, plica syndromes, Sinding- Larsen-Johannson disease, Osgood-Schlatter disease, neuromas, or other clear pathology (Thomee et al., 1999). AKP is particularly prevalent in young active females, and may be higher in those involved in particular activities. For instance, while AKP has been shown to affect 12 to 13% of females aged 18 to 35 (Roush & Curtis Bay, 2012), it appears to affect 23.6% of female dancers aged 8 to 20 (Steinberg et al., 2012).

There exists very little consensus on the nature of AKP. Currently, AKP is difficult to predict (Foss, Hornsby, Edwards, Myer, & Hewett, 2012; Pappas & Wong-Tom, 2012; Lankhorst, Bierma-Zeinstra, & van Middelkoop, 2012), and lacks reliable clinical tests and screens (Nunes, Stapait, Kirsten, de Noronha, & Santos 2013; Cook, Mabry, Reiman, & Hegedus, 2012). The pathogenesis of AKP is unclear, often presenting insidiously with no history of trauma or radiographic changes (Mann et al. 2007). AKP syndrome is likely multifactoral, involving complex interactions between anatomical and environmental factors (Collado & Fredericson, 2010), and possibly neuroimmune factors (Jensen, Kvale, & Baerheim, 2008; Dye, 2005). It's possible that its pathophysiology may be similar to other chronic pain conditions, whereby maladaptive changes in the nervous system are responsible for heightened sensitivity to pain (Apkarian et al., 2009; Bausbaum et al., 2009).

As discussed previously, AKP has been shown to result in bilateral AMI of the knee extensors (Drover et al. 2004; Suter et al., 1998a; Suter et al., 1999; Thomee et al. 1996). Other examples of knee pathology such as ACL rupture, ACL repair, and osteoarthritis have shown similar bilateral effects, and it has been suggested that these bilateral effects involve γ loop dysfunction (Rice et al., 2011; Rice & McNair, 2010). Furthermore, it is thought that this γ loop dysfunction is due to altered afferent discharge, secondary to damage to the sensory receptors. However, bilateral AMI can be present in patients with AKP that is not attributable to sensory receptor damage. If these AKP patients exhibit γ loop dysfunction, it suggests another mechanism for this dysfunction other than sensory receptor damage.

For instance, bilateral AMI may be set in motion by pain related neuroplastic changes that may also affect the γ loop. This is plausible for two reasons. First, pain itself has been shown to inhibit muscle activation in a variety of situations, independent of overt tissue damage (Schabrun, & Hodges, 2012; Dube & Mercier, 2011; Verbunt et al., 2005; Graven-Nielsen, Lund, Arendt-Nielsen, Danneskiold-Samsoe, & Bliddal, 2002; Le Pera et al., 2001). Secondly, chronic pain is often characterised by neuroplastic changes that result in increased sensitivity and spontaneity of pain perception (Bonezzi, Demartini, & Buonocore, 2012; Apkarian et al., 2009; Moseley, 2007).

Neuroplastic changes include such phenomena as peripheral sensitization, central sensitization, and cortical reorganization. Peripheral sensitization refers to decreased thresholds of nociceptive sensory receptors (Basbaum et al., 2009), while central sensitization refers to changes in spinal and supraspinal nociceptive circuitry (Woolf, 2011; Latremoliere & Woolf, 2009). Peripheral and central sensitization are both thought to be mediated by neuro-immune interactions (Calvo, Dawes, & Bennett, 2012; Ren & Dubner, 2010). Through disinhibition and neural sprouting, central sensitization leads to nociception via normally non-noxious stimuli (Woolf, 2011; Latremoliere & Woolf, 2009). Furthermore, chronic pain has also been associated with reorganization of the sensory cortex (Yang et al., 1994) as well as other brain structures (Henry, Chiodo, & Yang, 2011). These cortical changes appear to be especially relevant; the degree of reorganization is highly correlated with the magnitude of pain intensity (Flor et al., 1995), and corticostriatal functional connectivity has been shown to predict the transition from acute to chronic back pain (Baliki et al., 2012). Overall, these neuroplastic changes

resemble the mechanisms of memory, with chronic pain being characterized as a sort of "pain memory" by some prominent authors (Yi & Zhang, 2011; Apkarian et al., 2009).

With such complex neuroplastic sequelae involved, it is not unreasonable to speculate that chronic muscle inhibition is set in motion by pain. Indeed, knee joint pathology ubiquitously involves a painful experience, either acutely as in ACL injury, or chronically as in osteoarthritis. That the γ loop may be affected by such spinal or supraspinal changes even in the absence of direct sensory receptor trauma is of interest to researchers and clinicians alike.

1.6 References

Apkarian, A. V., Baliki, M. N., & Geha, P. Y. (2009). Towards a theory of chronic pain. *Progress in Neurobiology, 87*(2), 81-97. doi:10.1016/j.pneurobio.2008.09.018

Aydogdu, I., Tanriverdi, Z., & Ertekin, C. (2011). Dysfunction of bulbar central pattern generator in ALS patients with dysphagia during sequential deglutition. *Clinical Neurophysiology, 122*(6), 1219-1228. doi:10.1016/j.clinph.2010.11.002

Baliki, M. N., Petre, B., Torbey, S., Herrmann, K. M., Huang, L., Schnitzer, T. J., Apkarian, A. V. (2012). Corticostriatal functional connectivity predicts transition to chronic back pain. *Nature Neuroscience, 15*(8), 1117-1119. doi:10.1038/nn.3153

Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell, 139*(2), 267-284. doi:10.1016/j.cell.2009.09.028

Becker, R., Berth, A., Nehring, M., & Awiszus, F. (2004). Neuromuscular quadriceps dysfunction prior to osteoarthritis of the knee. *Journal of Orthopaedic Research, 22*(4) doi:10.1016/j.orthres.2003.11.004

Bonezzi, C., Demartini, L., & Buonocore, M. (2012). Chronic pain: Not only a matter of time. *Minerva Anestesiologica, 78*(6), 704-711.

Bongiovanni, L., Hagbarth, K., & Stjernberg, L. (1990). Prolonged muscle vibration reducing motor output in maximal voluntary contractions in man. *Journal of Physiology-London, 423*, 15-26.

Brown, T. G. (1911). The intrinsic factors in the act of progression in the mammal. *Proc. R. Soc. Lond. B, 84*(572), 308-319. doi:10.1098/rspb.1911.0077

Burke, R. E., Levine, D. N., Tsairis, P., & Zajac, F. E.,3rd. (1973). Physiological types and histochemical profiles in motor units of the cat gastrocnemius. *The Journal of Physiology, 234*(3), 723-748.

Byrne, J. M., Gage, W. H., & Prentice, S. D. (2002). Bilateral lower limb strategies used during a step-up task in individuals who have undergone unilateral total knee arthroplasty. *Clinical Biomechanics, 17*(8), 580-585.

Calvo, M., Dawes, J. M., & Bennett, D. L. (2012). The role of the immune system in the generation of neuropathic pain. *Lancet Neurology, 11*(7), 629-642. doi:10.1016/S1474-4422(12)70134-5

Carroll, T. J., Herbert, R. D., Munn, J., Lee, M., & Gandevia, S. C. (2006). Contralateral effects of unilateral strength training: Evidence and possible mechanisms RID C-3513-2008 RID D-5009-2011. *Journal of Applied Physiology, 101*(5), 1514-1522. doi:10.1152/japplphysiol.00531.2006

Chalmers, G. (2002). Do golgi tendon organs really inhibit muscle activity at high force levels to save muscles from injury, and adapt with strength training? *Sports Biomechanics / International Society of Biomechanics in Sports, 1*(2), 239-249. doi:10.1080/14763140208522800

Chan, C., & Dallaire, M. (1989). Subjective pain sensation is linearly correlated with the flexion reflex in man. *Brain Research, 479*(1), 145-150. doi:10.1016/0006-8993(89)91344-9

Collado, H., & Fredericson, M. (2010). Patellofemoral pain syndrome. *Clinics in Sports Medicine, 29*(3), 379-+. doi:10.1016/j.csm.2010.03.012

Cook, C., Mabry, L., Reiman, M. P., & Hegedus, E. J. (2012). Best tests/clinical findings for screening and diagnosis of patellofemoral pain syndrome: A systematic review. *Physiotherapy, 98*(2), 93-100. doi:10.1016/j.physio.2011.09.001

Curtis, D. R., & Eccles, J. C. (1960). Synaptic action during and after repetitive stimulation. *Journal of Physiology-London, 150*(2), 374-398.

De Nunzio, A. M., Grasso, M., Nardone, A., Godi, M., & Schieppati, M. (2010). Alternate rhythmic vibratory stimulation of trunk muscles affects walking cadence and velocity in parkinson's disease. *Clinical Neurophysiology, 121*(2), 240-247. doi:10.1016/j.clinph.2009.10.018

Dimitrijevic, M., Gerasimenko, Y., & Pinter, M. (1998). Evidence for a spinal central pattern generator in humans. *Neuronal Mechanisms for Generating Locomotor Activity, 860*, 360-376. doi:10.1111/j.1749-6632.1998.tb09062.x

Drover, J. M., Forand, D. R., & Herzog, W. (2004). Influence of active release technique on quadriceps inhibition and strength: A pilot study. *Journal of Manipulative and Physiological Therapeutics, 27*(6), 408-413. doi:10.1016/j.jmpt.2004.05.006

Dube, J. A., & Mercier, C. (2011). Effect of pain and pain expectation on primary motor cortex excitability. *Clinical Neurophysiology, 122*(11), 2318-2323. doi:10.1016/j.clinph.2011.03.026

Dunham, J. P., Kelly, S., & Donaldson, L. F. (2008). Inflammation reduces mechanical thresholds in a population of transient receptor potential channel A1-expressing nociceptors in the rat. *European Journal of Neuroscience, 27*(12), 3151-3160. doi:10.1111/j.1460-9568.2008.06256.x

Dye, S. F. (2005). The pathophysiology of patellofemoral pain - A tissue homeostasis perspective. *Clinical Orthopaedics and Related Research,* (436) doi:10.1097/01.blo.0000172303.74414.7d

Dyhre-Poulsen, P., & Krogsgaard, M. (2000). Muscular reflexes elicited by electrical stimulation of the anterior cruciate ligament in humans. *Journal of Applied Physiology, 89*(6), 2191-2195.

Ellaway, P., Taylor, A., Durbaba, R., & Rawlinson, S. (2002). Role of the fusimotor system in locomotion. *Sensorimotor Control of Movement and Posture, 508,* 335-342.

Ferrell, W. R. (1987). The effect of acute joint distension on mechanoreceptor discharge in the knee of the cat. *Quarterly Journal of Experimental Physiology (Cambridge, England), 72*(4), 493-499.

Flor, H., Elbert, T., Knecht, S., Wienbruch, C., Pantev, C., Birbaumer, N., . . . Taub, E. (1995). Phantom-limb pain as a perceptual correlate of cortical reorganization following arm amputation. *Nature, 375*(6531), 482-484. doi:10.1038/375482a0

Folland, J. P., & Williams, A. G. (2007). The adaptations to strength training - morphological and neurological contributions to increased strength RID B-6817-2008. *Sports Medicine, 37*(2), 145-168. doi:10.2165/00007256-200737020-00004

Foss, K. D. B., Hornsby, M., Edwards, N. M., Myer, G. D., & Hewett, T. E. (2012). Is body composition associated with an increased risk of developing anterior knee pain in adolescent female athletes? *Physician and Sportsmedicine, 40*(1), 13-19. doi:10.3810/psm.2012.02.1947

Freeman, S., Mascia, A., & McGill, S. (2012). Arthrogenic neuromusculature inhibition: A foundational investigation of existence in the hip joint. *Clinical Biomechanics (Bristol, Avon),* doi:10.1016/j.clinbiomech.2012.11.014; 10.1016

Frigon, A., Johnson, M. D., & Heckman, C. J. (2012). Differential modulation of crossed and uncrossed reflex pathways by clonidine in adult cats following complete spinal cord injury. *The Journal of Physiology, 590*(Pt 4), 973-989. doi:10.1113/jphysiol.2011.222208

Fyfe, J. J., Opar, D. A., Williams, M. D., & Shield, A. J. (2013). The role of neuromuscular inhibition in hamstring strain injury recurrence. *Journal of Electromyography and Kinesiology, 23*(3), 523-530. doi:10.1016/j.jelekin.2012.12.006

Gabriel, D., Kamen, G., & Frost, G. (2006). Neural adaptations to resistive exercise - mechanisms and recommendations for training practices. *Sports Medicine, 36*(2), 133-149. doi:10.2165/00007256-200636020-00004

Geborek, P., Mansson, B., Wollheim, F., & Mortiz, U. (1990). Intraarticular corticosteroid injection into rheumatoid-arthritis knees improves extensor muscles strength. *Rheumatology International, 9*(6), 265-270. doi:10.1007/BF00541322

Gomez-Barrena, E., Nunez, A., Ballesteros, R., Martinez-Moreno, E., & Munuera, L. (1999). Anterior cruciate ligament reconstruction affects proprioception in the cat's knee. *Acta Orthopaedica Scandinavica, 70*(2), 185-193. doi:10.3109/17453679909011260

Gomez-Barrena, E., Bonsfills, N., Martin, J. G., Ballesteros-Masso, R., Foruria, A., & Nunez-Molina, A. (2008). Insufficient recovery of neuromuscular activity around the knee after experimental anterior cruciate ligament reconstruction. *Acta Orthopaedica, 79*(1), 39-47. doi:10.1080/17453670710014743

Granit, R. (1975). Functional role of muscle-spindles - facts and hypotheses. *Brain, 98*(Dec), 531-556. doi:10.1093/brain/98.4.531

Graven-Nielsen, T., Lund, H., Arendt-Nielsen, L., Danneskiold-Samsoe, B., & Bliddal, H. (2002). Inhibition of maximal voluntary contraction force by experimental muscle pain: A centrally mediated mechanism. *Muscle & Nerve, 26*(5), 708-712. doi:10.1002/mus.10225

Grigg, P., Schaible, H., & Schmidt, R. (1986). Mechanical sensitivity of group-iii and group-iv afferents from posterior articular nerve in normal and inflamed cat knee. *Journal of Neurophysiology, 55*(4), 635-643.

Hagbarth, K. E., Kunesch, E. J., Nordin, M., Schmidt, R., & Wallin, E. U. (1986). Gamma loop contributing to maximal voluntary contractions in man. *The Journal of Physiology, 380*, 575-591.

Hagert, E. (2010). Proprioception of the wrist joint: A review of current concepts and possible implications on the rehabilitation of the wrist. *Journal of Hand Therapy, 23*(1), 2-16. doi:10.1016/j.jht.2009.09.008

Hart, J. M., Pietrosimone, B., Hertel, J., & Ingersoll, C. D. (2010). Quadriceps activation following knee injuries: A systematic review. *Journal of Athletic Training, 45*(1), 87-97.

Hayward, L. F., Nielsen, R. P., Heckman, C. J., & Hutton, R. S. (1986). Tendon vibration-induced inhibition of human and cat triceps surae group I reflexes: Evidence of selective ib afferent fibre activation. *Experimental Neurology, 94*(2), 333-347. doi:10.1016/0014-4886(86)90107-X

Henry, D. E., Chiodo, A. E., & Yang, W. (2011). Central nervous system reorganization in a variety of chronic pain states: A review. *PM & R : The Journal of Injury, Function, and Rehabilitation, 3*(12), 1116-1125. doi:10.1016/j.pmrj.2011.05.018

Heroux, M. E., & Trenblay, F. (2006). Corticomotor excitability associated with unilateral knee dysfunction secondary to anterior cruciate ligament injury. *Knee Surgery Sports Traumatology Arthroscopy, 14*(9), 823-833. doi:10.1007/s00167-006-0063-4

Hicks, T. P., & Onodera, S. (2012). The mammalian red nucleus and its role in motor systems, including the emergence of bipedalism and language. *Progress in Neurobiology, 96*(2), 165-175. doi:10.1016/j.pneurobio.2011.12.002; 10.1016

Hooper, S. (2000). Central pattern generators. *Current Biology, 10*(5), R176-R177. doi:10.1016/S0960-9822(00)00367-5

Hopkins, J., & Ingersoll, C. (2000). Arthrogenic muscle inhibition: A limiting factor in joint rehabilitation. *Journal of Sport Rehabilitation, 9*(2), 135-159.

Houk, J., & Henneman, E. (1967). Responses of golgi tendon organs to active contractions of soleus muscle of cat. *Journal of Neurophysiology, 30*(3), 466-&.

Hsu, H. C., Boardman, N. D.,3rd, Luo, Z. P., & An, K. N. (2000). Tendon-defect and muscle-unloaded models for relating a rotator cuff tear to glenohumeral stability. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 18*(6), 952-958. doi:10.1002/jor.1100180615

Hultborn, H., Meunier, S., Pierrot-Deseilligny, E., & Shindo, M. (1987). Changes in presynaptic inhibition of ia fibers at the onset of voluntary contraction in man. *Journal of Physiology-London, 389*, 757-772.

Hurley, M. V. (1997). The effects of joint damage on muscle function, proprioception and rehabilitation. *Manual Therapy, 2*(1), 11-17. doi:10.1054/math.1997.0281

Hurley, M. V., Jones, D. W., & Newham, D. J. (1994). Arthrogenic quadriceps inhibition and rehabilitation of patients with extensive traumatic knee injuries (vol 86, pg 309, 1994). *Clinical Science, 86*(6)

Jackson, S. W., & Turner, D. L. (2003). Prolonged muscle vibration reduces maximal voluntary knee extension performance in both the ipsilateral and the contralateral limb in man. *European Journal of Applied Physiology, 88*(4-5), 380-386. doi:10.1007/s00421-002-0701-6

Jami, L. (1988). Functional-properties of golgi tendon organs. *Archives Internationales De Physiologie De Biochimie Et De Biophysique, 96*(4), A363-A378.

Jensen, R., Kvale, A., & Baerheim, A. (2008). Is pain in patellofemoral pain syndrome neuropathic? *Clinical Journal of Pain, 24*(5) doi:10.1097/AJP.0b013e3181658170

Johansson, H. (1988). Rubrospinal and rubrobulbospinal influences on dynamic and static gamma-motoneurones. *Behavioural Brain Research, 28*(1-2), 97-107.

Keays, S. L., Bullock-Saxton, J. E., Newcombe, P., & Keays, A. C. (2003). The relationship between knee strength and functional stability before and after anterior cruciate ligament reconstruction. *Journal of Orthopaedic Research, 21*(2), PII S0736-0266(02)00160-2. doi:10.1016/S0736-0266(02)00160-2

Klykken, L. W., Pietrosimone, B. G., Kim, K. M., Ingersoll, C. D., & Hertel, J. (2011). Motor-neuron pool excitability of the lower leg muscles after acute lateral ankle sprain. *Journal of Athletic Training, 46*(3), 263-269.

Knicker, A. J., Renshaw, I., Oldham, A. R. H., & Cairns, S. P. (2011). Interactive processes link the multiple symptoms of fatigue in sport competition. *Sports Medicine, 41*(4), 307-328.

Konishi, Y., Aihara, Y., Sakai, M., Ogawa, G., & Fukubayashi, T. (2007). Gamma loop dysfunction in the quadriceps femoris of patients who underwent anterior cruciate ligament reconstruction remains bilaterally. *Scandinavian Journal of Medicine & Science in Sports, 17*(4), 393-399. doi:10.1111/j.1600-0838.2006.00573.x

Konishi, Y., Fukubayashi, T., & Takeshita, D. (2002). Possible mechanism of quadriceps femoris weakness in patients with ruptured anterior cruciate ligament. *Medicine and Science in Sports and Exercise, 34*(9), 1414-1418. doi:10.1097/00005768-200209000-00003

Konishi, Y., Konishi, H., & Fukubayashi, T. (2003). Gamma loop dysfunction in quadriceps on the contralateral side in patients with ruptured ACL. *Medicine and Science in Sports and Exercise, 35*(6), 897-900. doi:10.1249/01.MSS.0000069754.07541.D2

Kouzaki, M., Shinohara, M., & Fukunaga, T. (2000). Decrease in maximal voluntary contraction by tonic vibration applied to a single synergist muscle in humans RID C-6635-2009. *Journal of Applied Physiology, 89*(4), 1420-1424.

Lankhorst, N. E., Bierma-Zeinstra, S. M., & van Middelkoop, M. (2012). Risk factors for patellofemoral pain syndrome: A systematic review. *The Journal of Orthopaedic and Sports Physical Therapy, 42*(2), 81-94. doi:10.2519/jospt.2012.3803

Latremoliere, A., & Woolf, C. J. (2009). Central sensitization: A generator of pain hypersensitivity by central neural plasticity. *The Journal of Pain : Official Journal of the American Pain Society, 10*(9), 895-926. doi:10.1016/j.jpain.2009.06.012

Le Pera, D., Graven-Nielsen, T., Valeriani, M., Oliviero, A., Di Lazzaro, V., Tonali, P. A., & Arendt-Nielsen, L. (2001). Inhibition of motor system excitability at cortical and spinal level by tonic muscle pain. *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology, 112*(9), 1633-1641.

Lee, M., & Carroll, T. J. (2007). Cross education - possible mechanisms for the contralateral effects of unilateral resistance training RID C-3513-2008. *Sports Medicine, 37*(1), 1-14. doi:10.2165/00007256-200737010-00001

Li, X., Wang, J., Wang, Z., Dong, C., Dong, X., Jing, Y.,Fan, G. (2008). Tumor necrosis factor-alpha of red nucleus involved in the development of neuropathic allodynia. *Brain Research Bulletin, 77*(5), 233-236. doi:10.1016/j.brainresbull.2008.08.025

Mann, G., Constantini, N., Hetsroni, I., Meidan, O., Dolev, E., Morgenstern, D., Nyska, M. (2007). Anterior knee-pain syndrome. *Adolescent Medicine: State of the Art Reviews, 18*(1)

Manuel, M., & Zytnicki, D. (2011). Alpha, beta and gamma motoneurons: Functional diversity in the motor system's final pathway. *Journal of Integrative Neuroscience, 10*(3), 243-276.

Marcora, S. M. (2008). Do we really need a central governor to explain brain regulation of exercise performance? RID C-5614-2009. *European Journal of Applied Physiology, 104*(5), 929-931. doi:10.1007/s00421-008-0818-3

Matsumoto, R. R., & Walker, J. M. (1991). Inhibition of rubral neurons by noxious and non-noxious pressure. *Brain Research, 556*(1), 78-84.

McCrea, D. A. (2008). Organization of mammalian locomotor rhythm and pattern generation. *Brain Research Reviews (2006), 57*(1), 134-146.

McVey, E. D., Palmieri, R. M., Docherty, C. L., Zinder, S. M., & Ingersoll, C. D. (2005). Arthrogenic muscle inhibition in the leg muscles of subjects exhibiting functional ankle instability. *Foot & Ankle International / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society, 26*(12), 1055-1061.

Mikesky, A. E., Mazzuca, S. A., Brandt, K. D., Perkins, S. M., Damush, T., & Lane, K. A. (2006). Effects of strength training on the incidence and progression of knee osteoarthritis. *Arthritis & Rheumatism-Arthritis Care & Research, 55*(5) doi:10.1002/art.22245

Milner, C. E. (2008). Interlimb asymmetry during walking following unilateral total knee arthroplasty. *Gait & Posture, 28*(1), 69-73. doi:10.1016/j.gaitpost.2007.10.002

Molinari, M. (2009). Plasticity properties of CPG circuits in humans: Impact on gait recovery RID A-9624-2010. *Brain Research Bulletin, 78*(1), 22-25. doi:10.1016/j.brainresbull.2008.02.030

Moseley, G. L. (2007). Reconceptualising pain according to modern pain science. *Physical Therapy Reviews, 12*(3), 169-178. doi:10.1179/108331907X223010

Noakes, T., Gibson, A., & Lambert, E. (2005). From catastrophe to complexity: A novel model of integrative central neural regulation of effort and fatigue during exercise in humans: Summary and conclusions RID E-7253-2011. *British Journal of Sports Medicine, 39*(2), 120-124. doi:10.1136/bjsm.2003.010330

Noakes, T. D. (2011). Time to move beyond a brainless exercise physiology: The evidence for complex regulation of human exercise performance RID E-7253-2011. *Applied Physiology Nutrition and Metabolism-Physiologie Appliquee Nutrition Et Metabolisme, 36*(1), 23-35. doi:10.1139/H10-082

Nunes, G. S., Stapait, E. L., Kirsten, M. H., de Noronha, M., & Santos, G. M. (2013). Clinical test for diagnosis of patellofemoral pain syndrome: Systematic review with meta-analysis. *Physical Therapy in Sport : Official Journal of the Association of Chartered Physiotherapists in Sports Medicine, 14*(1), 54-59. doi:10.1016/j.ptsp.2012.11.003

Pappas, E., & Wong-Tom, W. M. (2012). Prospective predictors of patellofemoral pain syndrome: A systematic review with meta-analysis. *Sports Health, 4*(2), 115-120. doi:10.1177/1941738111432097

Paquet, N., Tam, F., & Hui-Chan, C. W. (1996). Functional modulation of the human flexion and crossed extension reflexes by body position. *Neuroscience Letters, 209*(3), 215-217.

Proske, U., & Gandevia, S. C. (2012). The proprioceptive senses: Their roles in signaling body shape, body position and movement, and muscle force. *Physiological Reviews, 92*(4), 1651-1697. doi:10.1152/physrev.00048.2011

Reeves, N. D., & Maffulli, N. (2008). A case highlighting the influence of knee joint effusion on muscle inhibition and size. *Nature Clinical Practice Rheumatology, 4*(3), 153-158. doi:10.1038/ncprheum0709

Ren, K., & Dubner, R. (2010). Interactions between the immune and nervous systems in pain. *Nature Medicine, 16*(11), 1267-1276. doi:10.1038/nm.2234; 10.1038/nm.2234

Rice, D. A., McNair, P. J., & Lewis, G. N. (2011). Mechanisms of quadriceps muscle weakness in knee joint osteoarthritis: The effects of prolonged vibration on torque and muscle activation in osteoarthritic and healthy control subjects. *Arthritis Research & Therapy, 13*(5), R151. doi:10.1186/ar3467

Rice, D. A., & McNair, P. J. (2010). Quadriceps arthrogenic muscle inhibition: Neural mechanisms and treatment perspectives. *Seminars in Arthritis and Rheumatism, 40*(3), 250-266. doi:10.1016/j.semarthrit.2009.10.001

Rossignol, S., & Frigon, A. (2011). Recovery of locomotion after spinal cord injury: Some facts and mechanisms. *Annual Review of Neuroscience, Vol 34, 34*, 413-440. doi:10.1146/annurev-neuro-061010-113746

Roush, J. R., & Curtis Bay, R. (2012). Prevalence of anterior knee pain in 18-35 year-old females. *International Journal of Sports Physical Therapy, 7*(4), 396-401.

Schabrun, S. M., & Hodges, P. W. (2012). Muscle pain differentially modulates short interval intracortical inhibition and intracortical facilitation in primary motor cortex. *The Journal of Pain : Official Journal of the American Pain Society, 13*(2), 187-194. doi:10.1016/j.jpain.2011.10.013.

Schaible, H., & Schmidt, R. (1988). Time course of mechanosensitivity changes in articular afferents during a developing experimental arthritis. *Journal of Neurophysiology, 60*(6), 2180-2195.

Scheidt, R. A., Zimbelman, J. L., Salowitz, N. M., Suminski, A. J., Mosier, K. M., Houk, J., & Simo, L. (2012). Remembering forward: Neural correlates of memory and prediction in human motor adaptation. *Neuroimage, 59*(1), 582-600. doi:10.1016/j.neuroimage.2011.07.072; 10.1016.

Segal, N. A., Torner, J. C., Felson, D., Niu, J., Sharma, L., Lewis, C. E., & Nevitt, M. (2009). Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. *Arthritis & Rheumatism-Arthritis Care & Research, 61*(9) doi:10.1002/art.24541

Sherrington, C. S. (1910). Flexion-reflex of the limb, crossed extension-reflex, and reflex stepping and standing. *The Journal of Physiology, 40*(1-2), 28-121.

Shinohara, M. (2005). Effects of prolonged vibration on motor unit activity and motor performance. *Medicine and Science in Sports and Exercise, 37*(12), 2120-2125.

Sjölander, P., Håkan Johansson, & Mats Djupsjöbacka. (2002). Spinal and supraspinal effects of activity in ligament afferents. *Journal of Electromyography and Kinesiology : Official Journal of the International Society of Electrophysiological Kinesiology, 12*(3), 167-76.

Solomonow, M., & Krogsgaard, M. (2001). Sensorimotor control of knee stability. A review. *Scandinavian Journal of Medicine & Science in Sports, 11*(2), 64-80. doi:10.1034/j.1600-0838.2001.011002064.x

Steinberg, N., Siev-Ner, I., Peleg, S., Dar, G., Masharawi, Y., Zeev, A., & Hershkovitz, I. (2012). Joint range of motion and patellofemoral pain in dancers. *International Journal of Sports Medicine, 33*(7), 561-566. doi:10.1055/s-0031-1301330

Suter, E., Herzog, W., & Bray, R. C. (1998). Quadriceps inhibition following arthroscopy in patients with anterior knee pain. *Clinical Biomechanics (Bristol, Avon), 13*(4-5), 314-319.

Suter, E., Herzog, W., De Souza, K., & Bray, R. (1998). Inhibition of the quadriceps muscles in patients with anterior knee pain. *Journal of Applied Biomechanics, 14*(4), 360-373.

Suter, E., McMorland, G., Herzog, W., & Bray, R. (1999). Decrease in quadriceps inhibition after sacroiliac joint manipulation in patients with anterior knee pain. *Journal of Manipulative and Physiological Therapeutics, 22*(3), 149-153.

Tassinari, C., Rubboli, G., Gardella, E., Cantalupo, G., Calandra-Buonaura, G., Vedovello, M., Meletti, S. (2005). Central pattern generators for a common semiology in fronto-limbic seizures and in parasomnias. A neuroethologic approach RID A-4231-2010. *Neurological Sciences, 26,* S225-S232. doi:10.1007/s10072-005-0492-8

Taylor, J. L., & Gandevia, S. C. (2004). Noninvasive stimulation of the human corticospinal tract. *Journal of Applied Physiology (Bethesda, Md.: 1985), 96*(4), 1496-1503. doi:10.1152/japplphysiol.01116.2003

Teismann, I. K., Suntrup, S., Warnecke, T., Steinstraeter, O., Fischer, M., Floeel, A., . . . Dziewas, R. (2011). Cortical swallowing processing in early subacute stroke. *Bmc Neurology, 11*, 34. doi:10.1186/1471-2377-11-34

Thomee, R., Augustsson, J., & Karlsson, J. (1999). Patellofemoral pain syndrome: A review of current issues. *Sports Medicine (Auckland, N.Z.), 28*(4), 245-262.

Thomee, R., Grimby, G., Svantesson, U., & Osterberg, U. (1996). Quadriceps muscle performance in sitting and standing in young women with patellofemoral pain syndrome and young healthy women. *Scandinavian Journal of Medicine & Science in Sports, 6*(4), 233-241.

Urbach, D., & Awiszus, F. (2002). Impaired ability of voluntary quadriceps activation bilaterally interferes with function testing after knee injuries. A twitch interpolation study. *International Journal of Sports Medicine, 23*(4) doi:10.1055/s-2002-29074

Verbunt, J., Seelen, H., Vlaeyen, J., Bousema, E., van der Heijden, G., Heuts, P., & Knottnerus, J. (2005). Pain-related factors contributing to muscle inhibition in patients with chronic low back pain - an experimental investigation based on superimposed electrical stimulation RID A-3829-2009. *Clinical Journal of Pain, 21*(3), 232-240. doi:10.1097/00002508-200505000-00006

Voigt, M., Jakobsen, J., & Sinkjaer, T. (1998). Non-noxious stimulation of the glenohumeral joint capsule elicits strong inhibition of active shoulder muscles in conscious human subjects. *Neuroscience Letters, 254*(2), 105-108.

Wang, Z. H., Zeng, X. Y., Han, S. P., Fan, G. X., & Wang, J. Y. (2012). Interleukin-10 of red nucleus plays anti-allodynia effect in neuropathic pain rats with spared nerve injury. *Neurochemical Research, 37*(8), 1811-1819. doi:10.1007/s11064-012-0795-0

Weir, J. P., Beck, T. W., Cramer, J. T., & Housh, T. J. (2006). Is fatigue all in your head? A critical review of the central governor model. *British Journal of Sports Medicine, 40*(7), 573-586. doi:10.1136/bjsm.2005.023028

Wikstrom, E. A., Naik, S., Lodha, N., & Cauraugh, J. H. (2010). Bilateral balance impairments after lateral ankle trauma: A systematic review and meta-analysis. *Gait & Posture, 31*(4), 407-414. doi:10.1016/j.gaitpost.2010.02.004

Woolf, C. J. (2011). Central sensitization: Implications for the diagnosis and treatment of pain. *Pain, 152*(3 Suppl), S2-15. doi:10.1016/j.pain.2010.09.030

Yang, J. F., Lam, T., Pang, M. Y., Lamont, E., Musselman, K., & Seinen, E. (2004). Infant stepping: A window to the behaviour of the human pattern generator for walking. *Canadian Journal of Physiology and Pharmacology, 82*(8-9), 662-674. doi:10.1139/y04-070

Yang, J. F., Stephens, M. J., & Vishram, R. (1998). Transient disturbances to one limb produce coordinated, bilateral responses during infant stepping. *Journal of Neurophysiology, 79*(5), 2329-2337.

Yang, T. T., Gallen, C., Schwartz, B., Bloom, F. E., Ramachandran, V. S., & Cobb, S. (1994). Sensory maps in the human brain. *Nature, 368*(6472), 592-593. doi:10.1038/368592b0

Yi, M., & Zhang, H. (2011). Nociceptive memory in the brain: Cortical mechanisms of chronic pain. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience, 31*(38), 13343-13345. doi:10.1523/JNEUROSCI.3279-11.2011

Yoshida, Y., Mizner, R. L., Ramsey, D. K., & Snyder-Mackler, L. (2008). Examining outcomes from total knee arthroplasty and the relationship between quadriceps strength and knee function over time. *Clinical Biomechanics, 23*(3) doi:10.1016/j.clinbiomech.2007.10.008

CHAPTER 2

BILATERAL QUADRICEPS INHIBITION IN UNILATERAL ANTERIOR KNEE PAIN IS NOT ATTRIBUTABLE TO GAMMA LOOP DYSFUNCTION

2.1 Introduction

Persistent quadriceps weakness is a common consequence of pain or injury at the knee (Hart, Pietrosimone, Hertel, & Ingersoll, 2010; Rice & McNair, 2010). When such muscle weakness is present with joint pathology, but in the absence of damage to the muscle or its innervating nerve, it is known as arthrogenic muscle inhibition (AMI) (Hopkins & Ingersoll, 2000). AMI has been shown to be present in a wide range of knee joint pathologies, such as osteoarthritis (Rice, McNair, & Lewis, 2011), anterior cruciate ligament (ACL) rupture (Konishi, Konishi, & Fukubayashi, 2003), post-ACL repair (Konishi, Aihara, Sakai, Ogawa, & Fukubayashi, 2007), and anterior knee pain (Drover, Forand, & Herzog, 2004; Suter, Herzog, De Souza, & Bray, 1998a; Suter, Herzog, & Bray, 1998b; Suter, McMorland, Herzog, & Bray, 1999; Thomee, Grimby, Svantesson, & Osterberg, 1996). AMI is also known to affect other joints of the body, being reported in both the hip (Freeman, Mascia, & McGill, 2012), ankle (Klykken, Pietrosimone, Kim, Ingersoll, & Hertel, 2011; McVey, Palmieri, Docherty, Zinder, & Ingersoll, 2005), and shoulder (Hsu, Boardman, Luo, & An, 2000; Voigt, Jakobsen, & Sinkjaer, 1998). While some studies have demonstrated that AMI improves over time (Rice & McNair, 2010), others suggest that it can remain even four years after injury (Becker, Berth, Nehring, Awiszus, 2004). Because of its pervasiveness, AMI is a concern in the rehabilitation of knee joint pathology. AMI is thought to be responsible for the fact that quadriceps strength can remain decreased despite resistance training (Hurley, Jones, Newham, 1994). Quadriceps weakness may impair dynamic knee stability (Keays, Bullock-Saxton, Newcombe, & Keays, 2003) and physical functioning (Yoshida, Mizner, Ramsey, &

Snyder-Mackler, 2008; Urbach & Awiszus, 2002), increase the risk of re-injury (Fyfe, Opar, Williams, & Shield, 2012), and contribute to the progression of osteoarthritis (Segal et al., 2009; Mikesky et al., 2006).

Interestingly, AMI is known to affect both limbs in the presence of unilateral pathology. In fact, the muscles contralateral to injury are often inhibited to a similar magnitude as the ipsilateral muscles (Hart et al. 2010; Rice & McNair, 2010). Such bilateral effects have been shown in patients with ACL deficiency, post ACL repair, and in individuals with anterior knee pain (AKP) (Konishi et al., 2003; Konishi et al., 2007; Suter et al., 1998a). The mechanisms underlying these bilateral effects have not been fully elucidated.

Some insight into the mechanisms of bilateral AMI may be gained by examining the literature on quadriceps tendon vibration. Prolonged vibration (i.e. 20 minutes at a frequency of ~50 Hz) to the infrapatellar tendon of healthy individuals on one limb causes a decrease in knee extensor force on the vibrated side (Shinohara, 2005; Rice et al., 2011; Konishi et al., 2003; Konishi et al., 2007). In one instance this effect of unilateral vibration has even been shown to result in decreased force production on the non-vibrated side (Jackson & Turner, 2003). While a definitive mechanism has not been established, the force decrements post-vibration are thought to occur due to alterations in a reflex known as the gamma (γ) loop (Shinohara, 2005; Jackson & Turner, 2003). The γ loop is a spinal reflex in which γ-motoneurons innervate muscle spindles, which in turn provide feedback about muscle length to the homonymous α-motoneuron pool through Ia afferent fibers (Manuel & Zytnicki, 2011). Prolonged vibration appears to attenuate afferent feedback of Ia fibers (Shinohara, 2005) by increasing their discharge thresholds

(Hayward, Nielsen, Heckman, & Hutton, 1986), increasing presynaptic inhibition (Hultborn, Meunier, Pierrot-Deseilligny, & Shindo, 1987), and depleting neurotransmitter stores at their synapses (Curtis & Eccles, 1960). Since the activation of high threshold α-motoneurons requires feedback regarding tension, an intact γ loop is necessary to achieve full muscle activation (Kouzaki, Shinohara, & Fukunaga, 2000; Bongiovanni, Hagbarth, & Stjernberg, 1990; Hagbarth, Kunesch, Nordin, Schmidt, & Wallin, 1986). Disruption of the loops function via prolonged vibration therefore decreases a muscle's force production ability, with typical deficits of 8-10% being reported in the literature (Rice et al., 2011; Konishi et al., 2003; Konishi et al., 2007).

However, when prolonged vibration is applied to the infrapatellar tendon of individuals with a knee joint pathology known to cause quadriceps inhibition, no additional inhibition or force deficits are observed. This has been shown in individuals with knee osteoarthritis (Rice et al., 2011), ACL rupture (Konishi et al., 2003), and post-ACL repair (Konishi et al., 2007). In each case, prolonged quadriceps tendon vibration led to knee extension force deficits in healthy controls, but not in individuals with pathology. Furthermore, Konishi et al. (2003; 2007) demonstrated that this lack of force deficit post-vibration occurs in both the pathologically affected and unaffected limbs. It has been proposed that the lack of effect indicates a pre-existing dysfunction of the γ loop. In other words, if γ loop function has been altered due to lack of sensory feedback from joint receptors located in a torn ACL for example, then the ability of muscles to produce maximal force would 1) already be impaired and 2) not be affected by prolonged vibration because the loop cannot habituate to sensory input that it is not sensing properly. Therefore, γ loop dysfunction has been proposed to be a mechanism that may explain the

existence of bilateral quadriceps AMI when unilateral knee pathology is present (Konishi et al., 2003; Konishi et al., 2007).

Despite the apparent link between joint damage, γ loop dysfunction and bilateral deficits suggested by Konishi (2003; 2007), other research suggests that joint damage is not necessary in order for bilateral deficits to occur. For instance, bilateral AMI has also been reported in individuals with AKP (Drover et al., 2004; Suter et al., 1998a; Suter et al. 1999; Thomee et al., 1996). Anterior knee pain syndrome is characterized by pain at or around the patellofemoral joint (Mann et al., 2007), and is commonly used interchangeably with patellofemoral pain syndrome (PFPS) (Thomee, Augustsson, & Karlsson, 1999). The pathogenesis of AKP is unclear, often presenting insidiously with no history of trauma or radiographic changes (Mann et al., 2007). It may be possible that the pathophysiology of AKP is similar to that of other chronic pain conditions, involving maladaptive changes in the nervous system, which is itself not well understood (Apkarian, Baliki, & Geha, 2009; Basbaum, Bautista, Scherrer, & Julius, 2009). Thus, it appears AKP presents a case of bilateral AMI that cannot be attributed to damage to knee joint receptors.

Because the pathophysiology of AKP does not appear to involve obvious structural damage to the knee joint or its surrounding tissues, this pathology provides an ideal population to study the hypothesis that bilateral deficits are due to γ loop dysfunction resulting from structural damage at the knee. The published literature has not yet investigated the presence of γ loop dysfunction in AKP patients. Thus, this present study will investigate the mechanisms of bilateral quadriceps inhibition with knee joint pathology by exploring the role of γ loop dysfunction in AKP. If γ loop dysfunction is

found in this population, then it remains a plausible mechanism of bilateral quadriceps inhibition, but cannot be attributed to damaged sensory receptors. If γ loop dysfunction is not found, then the bilateral deficit in unilateral AKP cannot be attributed to the dysfunction, and other mechanisms must be considered. The results of this research will add to the body of knowledge related to mechanisms underlying bilateral effects of injury.

2.1.1 Purpose

The purpose of this study was to assess whether individuals with AKP and bilateral muscle inhibition exhibit possible γ loop dysfunction as tested using prolonged quadriceps tendon vibration.

2.1.2 Research Question

What effect does prolonged infrapatellar tendon vibration of the painful and non-painful legs have on maximal quadriceps force production in those with unilateral AKP and bilateral quadriceps inhibition?

2.1.3 Hypothesis

Prolonged vibration of the infrapatellar tendon will not change maximal quadriceps force production levels in either the painful or non-painful legs of individuals with unilateral AKP. This will be contrary to changes that will be observed in control participants, where prolonged vibration of the quadriceps tendon will result in reduction in force production.

2.2 Methods

2.2.1 Participants

Participants with anterior knee pain as well as healthy controls were recruited from Memorial University in St. John's, Newfoundland, Canada. As AKP lacks reliable clinical tests (Nunes, Stapait, Kirsten, de Noronha, & Santos 2013; Cook, Mabry, Reiman, & Hegedus, 2012), AKP participants were included if they reported a two or greater month history of unilateral anterior, retropatellar, or peripatellar knee pain during or following activities such as running, squatting, kneeling, climbing stairs, or prolonged sitting. Age and gender matched control participants were recruited if they had no history of AKP. Participants in either group were excluded if they reported any history of knee trauma, radiographic findings indicating macroscopic knee joint pathology, or any musculoskeletal or neurological signs or symptoms that may have confounded results. Ethical approval was obtained from the Interdisciplinary Committee on Ethics in Human Research at Memorial University.

2.2.2.1 Pain Characteristics and Knee Function

Participants were asked to complete subjective measures of pain severity, knee function, and kinesiophobia. Pain severity was measured with the Numerical Pain Rating Scale (NPRS) ranging from 0 (no pain) to 10 (worst pain imaginable). The NPRS is a valid measure of pain intensity in a wide range of clinical populations, and is equally if not more valid than competing scales (Ferreira-Valente, Pais-Ribeiro, & Jensen, 2011). Knee function was measured using the Lysholm scale (Lysholm, 1982). Originally created for evaluating outcomes of knee ligament surgery, the Lysholm scale has since

been revised (Tegner, 1985) and is considered appropriate for evaluation of knee function in various knee pathologies (Collins, Misra, Felson, Crossley, & Roos, 2011), including AKP (Domenech, Sanchis-Alfonso, Lopez, & Espejo, 2012). The revised version was used, which includes eight items: 1) limp, 2) support, 3) locking, 4) instability, 5) pain, 6) swelling, 7) stair climbing, and 8) squatting, with the final sum score being rated from 0 (severe impairment) to 100 points (no impairment) (Tegner, 1985). Kinesiophobia refers to the maladaptive pain-related fear associated with avoidance behaviours and avoidance of movement and physical activity (Miller, Kori, & Todd, 1991). The Tampa Scale of Kinesiophobia (TSK) questionnaire assesses fear of injury due to movement via 17 items rated from 1 (strongly disagree) to 4 (strongly agree) with questions such as "pain lets me know when to stop exercising so that I don't injure myself". While the TSK has not been adequately validated (Lundberg, Grimby-Ekman, Verbunt, & Simmonds, 2011), it remains a frequently used measure in pain research.

2.2.2 Experimental Design

Participants attended the laboratory on three separate occasions. The first two sessions involved testing participants' knee extension maximum voluntary isometric contraction (MVIC) before and after prolonged vibration, with left and right limbs tested on separate days in random order. The third day involved testing participants level of quadriceps activation in each leg using a triggered interpolated twitch technique (ITT) described below. The initial session began with familiarizing participants with equipment and procedures, acquiring informed consent, and completing the questionnaires described above.

2.2.2.1 Surface electromyography (EMG)

During the two vibration protocol days, surface EMG recording electrodes (Meditrace Pellet Ag/AgCl discs and 10mm in diameter, Covidien, Canada) were placed on the vastus lateralis and hamstrings according to Criswell & Cram (2010), with the ground electrode placed approximately over the lateral epicondyle of the femur. During the ITT testing day, only quadriceps EMG was measured. Prior to electrode placement, skin was shaved, abraded and cleaned with alcohol to ensure signal quality. EMG was sampled at 2000Hz using a Biopac (Biopac System Inc., DA 100: analog-digital converter MP150WSW; Holliston, Massachusetts) data acquisition system (impedance = 2MΩ, common mode rejection ratio >110 dB [50/60 Hz], noise >5 μV). A Blackman 61 dB bandpass filter set between 10 and 500 Hz was applied to the signal prior to digital conversion, and the signal was amplified with a gain of 1000. Data was recorded with the software program AcqKnowledge 4.1.1 (Biopac Systems Inc.) and stored on a personal computer for further analysis.

2.2.2.2 Effect of vibration on knee extension force

Each day began with participants performing a general warm up of cycling for 5 minutes at a cadence 50 rpm. Following the general warm up, participants were seated on a chair such that hips and knees were flexed at 90° without their feet touching the floor. A padded strap was placed around the shin of the leg being tested. This strap was attached to a cable connected to a load cell (Omega Engineering Inc., LCCA 250, Don Mills, Ontario, Canada) which measured the force produced when the subjects attempted to extend their knee with maximal voluntary force. To eliminate upper body involvement, a

belt was placed across the waist and participants were instructed to cross their arms over their chest during the protocol. A specific warm up for knee extensors was performed. This warm-up included 10 isometric contractions at an intensity of ~50% of perceived maximum with a work to rest ratio of 2/2 seconds. Participants were given one minute of rest before beginning MVIC testing. Prior to vibration, participants completed 4 MVIC's to ensure their highest force was achieved without excessive repetitions potentially causing fatigue. MVIC's were performed for 5 seconds with 2 minutes of rest between trials. Force was sampled using the same data acquisition device as EMG.

A percussion device (Foredom® Model 500 Massager) was used to deliver vibration to the limb being tested on a given day (Figure 2.1). The percussion device was attached to a vertical steel rod such that the height could be adjusted to each participant, while remaining secure for prolonged vibration. Following completion of the final MVIC trial participants were immediately prepared for the vibration protocol by applying the percussor to their infrapatellar tendon (See Fig 2.2).

Figure 2.1. Foredom percussion device used to deliver vibration to the infrapatellar tendon.

The appropriate vibration location was determined using anatomical landmarking by palpation of the area between the patella and the tibial tuberosity. Participants remained seated in the chair used for MVIC trials while percussion was applied for 20 minutes at a frequency of 50 Hz. This frequency has been reported by the literature as the most effective for inducing muscle inhibition (Konishi, 2007). Similarly based on previous literature (Konishi, 2007), the percussor was configured such that a force of roughly 30 Newtons (N) was applied to the tendon. This was controlled for by tightening the percussor head with straps using a handheld spring weighing scale. Participants were asked to sit in a relaxed manner and avoid movement of the vibrated leg during application. Visual inspection of percussor position was done through-out the trial to ensure no shift in site of delivery of vibration occurred. If any migration of the percussor did occur then necessary adjustments were made. If adjustments resulted in a cessation of vibration longer than 30 seconds, the participant was given a 5 minute break, and the 20 minute vibration was restarted from the beginning. Finally, an MVIC was performed as soon as possible within one minute of the end of vibration.

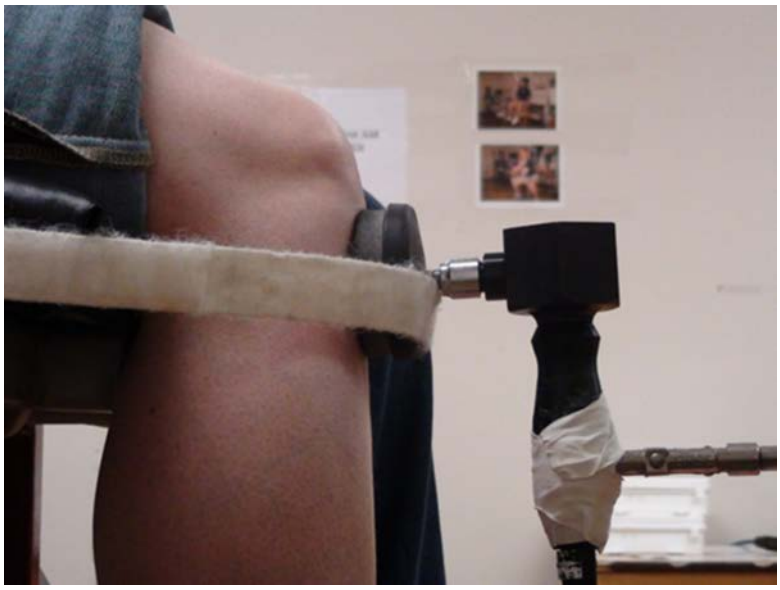

Figure 2.2. Experimental setup used during vibration of infrapatellar tendon.

2.2.2.3 Interpolated twitch technique (ITT)

AKP participants recruited for this study had mild symptoms (Table 2.1) and were otherwise young and healthy. Therefore ITT was used to quantify voluntary quadriceps activation to ensure AKP and control groups differed in this regard. Following completion of the two days of vibration testing participants returned for a third day of testing during which quadriceps voluntary activation (%VA) was measured. The %VA was quantified in both legs using an ITT protocol that was based on the work of Krishnan, Allen, & Williams (2009). Participants were set up in a similar fashion as for the MVIC testing previously described. Surface EMG was collected from vastus lateralis to determine when stimulation arrived to the muscle. Following EMG electrode placement, participants were prepped for ITT by having two stimulating electrodes attached the limb being tested. These 5x3 cm electrodes were placed across the thigh at

~3 cm above the knee cap and on the anterior thigh ~5 cm below the groin. The basic principal of ITT is based on the fact that if a muscle is truly maximally activated then additional electrical current delivered to the muscle will not result in any additional force production. In order to implement this protocol the level of electrical stimulation needed to sufficiently stimulate the muscle must be determined. This was done using a protocol described by Behm et al. (1996). Briefly, a series of small magnitude stimulations were delivered to limb while subjects were relaxed. Stimulations were delivered using a Digitimer stimulator (DS7AH, Digitimer Ltd., Welwyn Garden City, Hertfordshire, UK). Stimulations came in the form of doublets, delivered at a frequency of 100Hz. The magnitude of these stimulations was increased until the knee extensor force elicited by the stimulation plateaued. The stimulation level at which maximum twitch force was elicited was used for all superimposed stimulations delivered in the remainder of the session.

Once a suitable level of stimulation was determined, the ITT protocol was performed. While most ITT protocols deliver the stimulus to the contracting muscle either after a certain time has passed (Behm, Power, & Drinkwater, 2001) or once the MVIC force subjectively reaches a plateau, the protocol used in the present study used an approach first introduced by Krishanan et al. (2009) and subsequently tested by Hong (2014). This protocol differs from others in that it does not deliver the stimulus to the contracting muscle until the force level reaches at least 97% of the participants' previously determined MVIC force. To determine the MVIC, the subject performed a knee extension MVIC followed by one or two more until two MVICs were within 95% of each other. The highest of these MVIC's was used to determine the force required to

trigger the interpolated twitch. Participants then carried out an MVIC, during which the interpolated twitch was delivered to the quadriceps only if the participant reached the force required. Following the doublet delivery participants were asked to relax completely, and 3 seconds later another stimulus was applied to the muscle to determine the potentiated resting twitch. This protocol was then repeated for the opposite limb. The order in which each limb was tested was randomized for each participant. Stimulus delivery was controlled using custom designed software created in AcqKnowledge 4.1.1 (Biopac Systems Inc.), and data was collected using the same software.

2.2.3 Data Analysis

The effect of vibration on knee extension force was determined by comparing participants MVICs pre and post-vibration. As four pre-vibration MVICs were performed we had to decide which of these trials would be used to represent the pre-vibration MVIC. The trial used was determined by selecting the maximum or peak force of the four trials. This peak was compared to the peak force from the immediately post-vibration trial. Both trials used in the comparison were normalized to the first pre-vibration trial on each day of testing.

EMG was digitally filtered using an finite impulse response high pass filter with a frequency cut off fixed at 20Hz to remove any movement artifact (De Luca, Gilmore, Kuznetsov, & Roy, 2010). The filtered EMG signal was then full-wave rectified and integrated, using trapezoid integration, to determine integrated EMG (iEMG) over an interval of 3 seconds which included the peak force of the MVIC. This 3 second interval was typically determined by finding the instant that peak MVIC occurred and then

integrating the EMG for the seconds before and after that time point. If the peak force occurred either early or late in the contraction it resulted in the 3 second window including resting EMG. To prevent this the window was shifted either forward or backward so that it included the time period when force was peak but did not include EMG from before the muscle was active. All iEMG values were then normalized to iEMG from the first pre-vibration trial on each day of testing.

Quadriceps %VA was calculated for each leg using the following formula:

$$\%VA = \left[1 - \frac{a - b}{c}\right] \cdot 100$$

where a is the force evoked by the electrical stimulus during MVIC, b is the voluntary force at the time of stimulus delivery to the muscle (where time of delivery was determined via the spike in vastus lateralis EMG), and c is the force produced by electrical stimulus during rest (3 seconds after the contraction). Figure 2.3 presents a visualization of the data used for the calculation, taken from a representative ITT trial from an AKP participant.

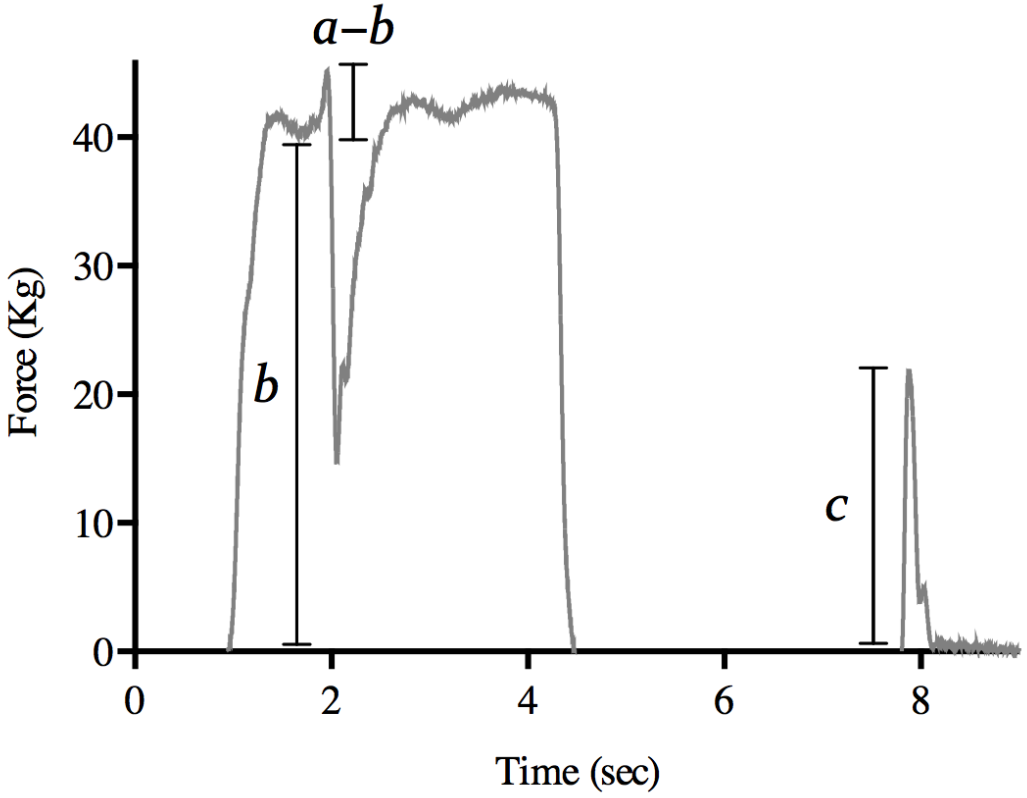

Figure 2.3 Illustration of components used to calculate percent voluntary activation (%VA) from a representative interpolated twitch technique (ITT) trial. Components: *a*, force (Kg) evoked with superimposed stimulus during MVIC; *b*, voluntary force at the time of stimulus delivery; *c*, force produced by electrical stimulus during rest (3 seconds after the contraction).

2.2.4 Statistical Analysis

As force and %VA data was collected for each limb in both AKP and control participants, each limb was assigned to one of four groups. The data from each limb of AKP participants were placed into either affected (the knee with pain) or unaffected groups. Control participant right and left limbs were assigned to two groups analogous to the AKP groups. All groups were matched for gender and limb dominance. Normality and homogeneity of variances tests were conducted on both dependent variables (%VA

and Force) using Kolmogorov-Smirnov and Levene's tests, respectively. If the assumption of homogeneity of variance was violated, the Welch's robust test was used. Independent samples two-tailed t-tests were performed on patient characteristic data to ensure groups were not comprised of different populations, except with respect to knee pain and function.

A one way analysis of variance (ANOVA) was performed on %VA data across four groups. Rather than reduce statistical power with numerous post-hoc comparisons, the following hypothesis driven planned contrasts were performed. To ensure quadriceps inhibition was bilateral in the AKP group, and that quadriceps activation was similar between control limbs, planned contrasts were performed between the limbs of each group. To confirm the presence of quadriceps inhibition in the AKP group compared to the control group as a whole, a planned contrast was then conducted between the AKP and control groups with both limbs combined. Cohen's *d* effect sizes (Cohen, 1988) were calculated for statistically significant contrasts.

Two way repeated measures ANOVAs were conducted on knee extension force, quadriceps iEMG, and hamstrings iEMG using the maximum pre-vibration and immediate post-vibration values across four groups (2 times x 4 groups). Tukey corrected post-hoc t-tests were performed if a statistically significant main effect was found. Cohen's *d* effect sizes were reported for any statistically significant results.

2.3 Results

Twenty two participants (n = 22) were recruited, twelve with AKP and ten controls. Patient characteristics are presented in Table 2.1. Statistically significant differences were found between groups with respect to age, pain severity, and knee function. Kinesiophobia did not reach statistical significance at $p = 0.06$, but did exhibit a large effect size (Cohen's $d = 0.79$).

Table 2.1 Participant characteristics. Presented as mean (standard deviation) or group total (% of group). NPRS, Lysholm, and TSK scales range from 0-10, 0-100, and 17-68, respectively. * indicates significant difference between AKP and control groups ($p < 0.05$).

Characteristic	AKP group (n = 12)	Control group (n = 10)
Age (years) *	23.4 (3.8)	20.2 (1.4)
Height (cm)	172.7 (7.2)	166.9 (9.4)
Mass (kg)	70.2 (7.2)	63.7 (10.5)
Female	10 (83.3%)	8 (80%)
Right side dominant	10 (83.3%)	10 (100%)
Right side painful	8 (66.7%)	-
Pain severity (NPRS) *	3.1 (1.4)	0 (0)
Knee function (Lyshom) *	73.3 (13.7)	98 (6.3)
Kinesiophobia (TSK)	38 (11.6)	29.6 (7.4)

Four out of twelve AKP participants and one out of ten healthy controls either did not consent to the ITT portion of the study or chose to discontinue with the ITT testing before it was completed. Assumptions of normality were not violated for either variable in any group. Assumptions of homogeneity of variance were not violated except when

comparing %VA between pain and control groups (Levene's test: $p < 0.05$). Thus, Welch's robust test statistic was used for the ANOVA of %VA.

Prior to the vibration intervention, there was a statistically significant difference in %VA between groups ($F_{(3,12.27)} = 4.10$, $p = .032$). Planned contrasts revealed no differences in %VA between right and left limbs of the AKP group or between control right and left limbs. Given the similarity between limbs in both groups %VA data from all AKP limbs and all control limbs were combined and an additional contrast was performed to determine if AKP %VA differed from control %VA. This comparison revealed that those in the AKP group had 9.2% lower %VA than controls ($t_{(13.36)} = 3.45$, $p = .004$, Cohen's $d = 1.13$). %VA for each group is reported in means and SD in Figure 2.4. Three out of the eight participants in the pain group who completed the ITT protocol did not exhibit quadriceps activation failure, defined as >95 %VA (Hart et al. 2010), while the remainder exhibited values < 90 %VA.

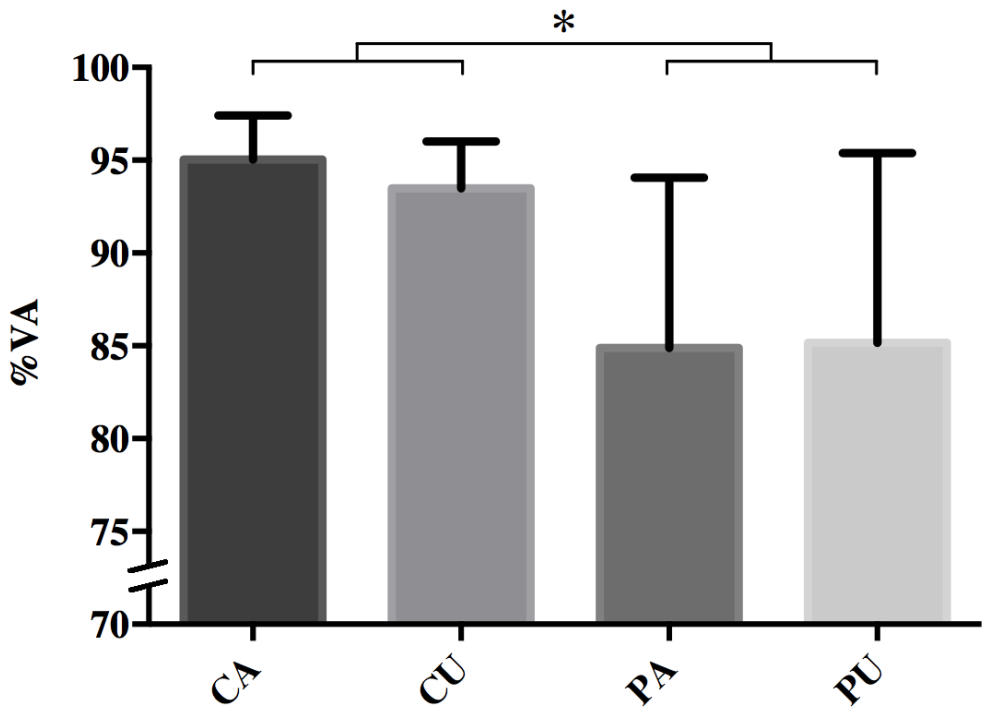

Figure 2.4 Quadriceps percentage voluntary activation (%VA) for each group. Groups defined as CA, control affected ('affected' referring to control group being matched to 'pain affected' group for proportion of dominant limbs); CU, control unaffected; PA, pain affected; PU, pain unaffected. * indicates that %VA was significantly lower (p = .004) in AKP groups compared to control groups. No statistically significant differences were found between limbs in either group (CA vs. CU, or PA vs. PU).

Following vibration, all participants demonstrated a statistically significant reduction in knee extension force ($F_{(1,40)}$ = 44.46, p < .001), resulting in an average 8.5% reduction in force (Cohen's d = 0.78). No statistically significant group effects were detected ($F_{(3,40)}$ = .034, p = .991), indicating that force reduction was consistently observed in both limbs across both AKP and control participants. Mean force (Newtons) pre and post vibration for each group is reported in Figure 2.5. No statistically significant

changes were detected in either quadriceps or hamstrings iEMG post-vibration. Quadriceps and hamstrings iEMG are depicted in Figures 2.6 and 2.7, respectively.

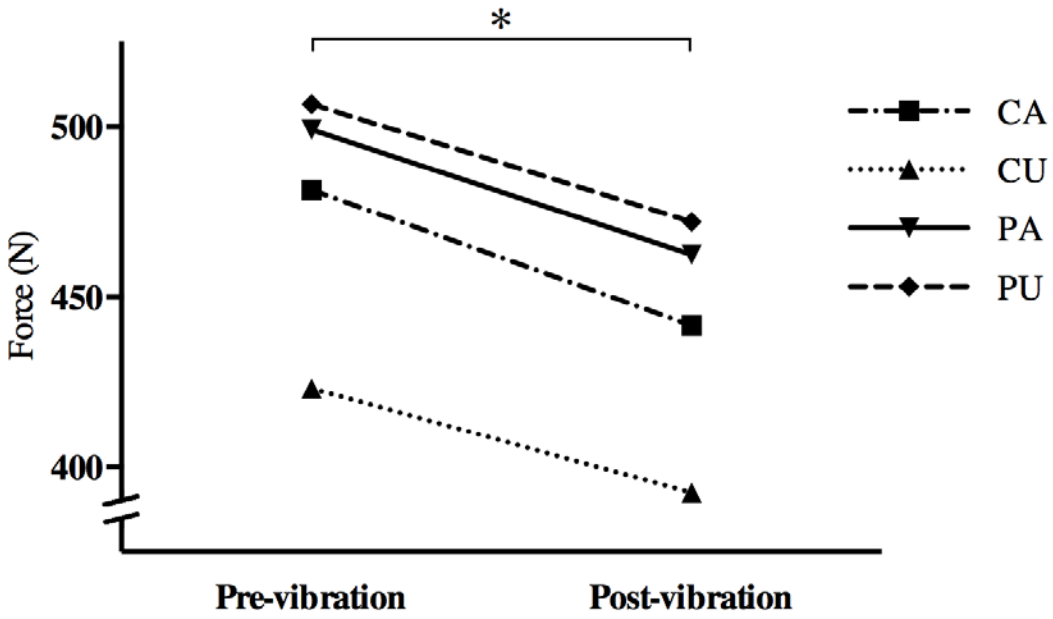

Figure 2.5 Effect of prolonged vibration on knee extension force for each group. Data presented as mean force (N) pre-vibration and post-vibration. * indicates statistically significant reduction in knee extension force post-vibration. No statistically significant differences were found between groups.

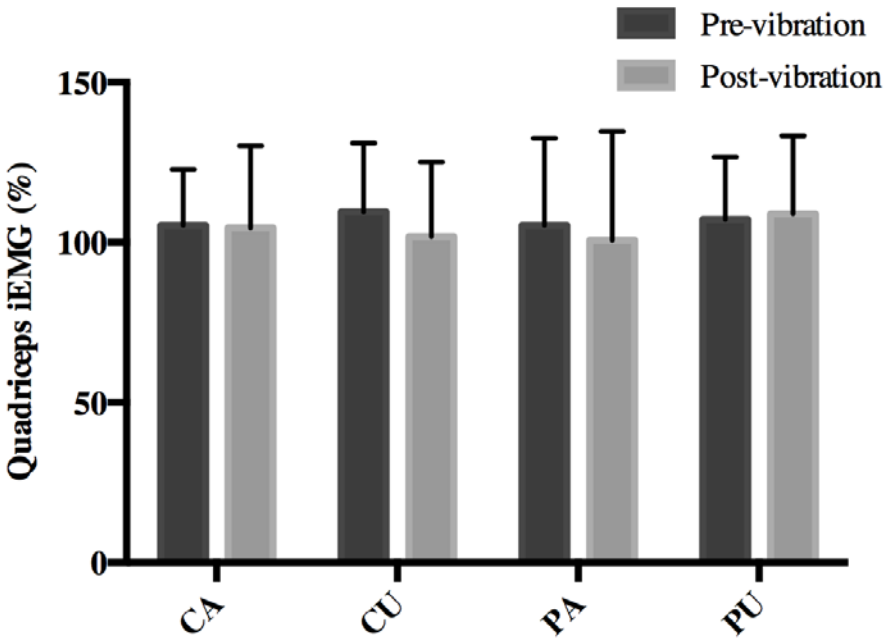

Figure 2.6 Quadriceps iEMG pre-vibration and post-vibration for each group. Mean and SD presented as percentage (%) of first pre-vibration knee extension MVIC trial.

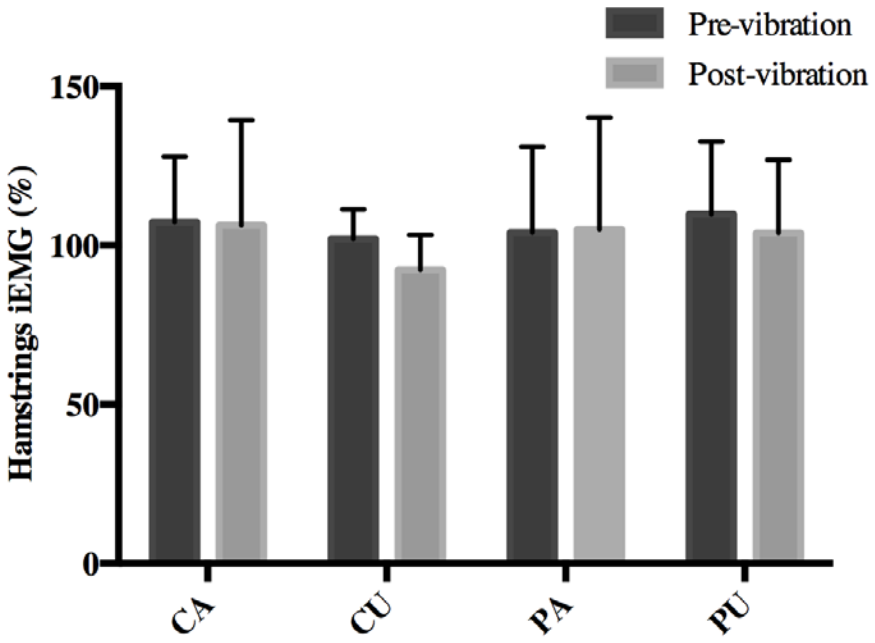

Figure 2.7 Hamstrings iEMG pre-vibration and post-vibration for each group. Mean and SD presented as percentage (%) of first pre-vibration knee extension MVIC trial.

2.4 Discussion

The purpose of this study was to examine γ loop function in a group of individuals with unilateral AKP and bilateral quadriceps inhibition. Prolonged quadriceps tendon vibration was used to assess γ loop dysfunction in an effort to determine whether γ loop dysfunction was a possible mechanism underlying the bilateral muscle inhibition experienced by this clinical population. Results indicated no evidence of dysfunction, suggesting that the bilateral inhibition present in the AKP group was unlikely to be related to alteration in γ loop dysfunction. This finding differs from previous literature, which has suggested γ loop dysfunction as a possible mechanism of bilateral quadriceps inhibition in unilateral knee pathology, potentially due to damaged sensory receptors (Konishi et al. 2007). These findings add new details to current understanding of both the nature of the bilateral deficit present in AKP and to the growing body of literature related to bilateral deficits associated with unilateral injury or pathology.

The results of this study differ from previous investigations of γ loop dysfunction in other knee pathologies. Konishi et al. (2003) found that prolonged vibration to the patellar tendon resulted in a decrease in knee extension force in controls, but not in individuals with previous ACL rupture, suggesting γ loop dysfunction in the latter group. Konishi et al. (2007) later found similar results for patients post ACL repair, and Rice et al. (2011) found the same in patients with knee OA. Furthermore, Konishi et al. (2003; 2007) found γ loop dysfunction to exist bilaterally, affecting the healthy limb as well. The authors of previous studies suggest γ loop dysfunction is due to damage to sensory receptors in the knee. However, the present study on individuals with AKP did not

indicate γ loop dysfunction. Following prolonged tendon vibration both the AKP and control groups experienced significant reductions in knee extension MVIC force. The average force reductions of ~8.5% observed in the present study were in line with previous literature utilizing similar vibration protocols (Rice et al., 2011; Konishi et al., 2003; Konishi et al., 2007). Based on these consistent reductions in maximum force production, the prolonged vibration appeared to affect γ loop function as expected, indicating no deficits in γ loop function in either group. These findings suggest that γ loop dysfunction does not appear to be related to the bilateral quadriceps activation deficits observed in the AKP group.

These results seem plausible given that AKP can occur in the absence of joint damage, which appears to be necessary for γ loop dysfunction. All previous reports of γ loop dysfunction, identified using the prolonged vibration method, have been reported in pathology where joint damage is present (Rice et al., 2011; Konishi et al., 2003; Konishi et al., 2007). AKP differs from many types of knee pathology in that it is known to cause bilateral quadriceps inhibition (Drover et al., 2004; Suter et al., 1998a; Suter et al. 1999; Thomee et al., 1996) but is not clearly associated with joint damage (Mann et al., 2007). The AKP group of the present study were included only if the onset of pain was insidious, excluding the presence of traumatic injury or radiographic findings. This AKP group was similar to others reported in the literature in that they exhibited bilateral quadriceps inhibition compared to healthy controls. Thus, results from the present study further support the hypothesis that γ loop dysfunction results from damaged sensory receptors in the joint. This suggests a different mechanism is responsible for bilateral quadriceps

inhibition in AKP compared with knee pathologies characterized by traumatic injury or degeneration.

If γ loop dysfunction does not explain the bilateral deficit in this population then other mechanisms must be responsible. One possibility that may explain the bilateral AMI observed in the AKP group is that it was supraspinally mediated. The perception of pain without obvious tissue damage is known to inhibit muscle activation (Dube & Mercier, 2011), even in muscles at a distance from the painful area (Verbunt et al., 2005). In the case of AKP, Park & Hopkins (2013) found that experimentally induced pain led to quadriceps inhibition through both involuntary (H:M ratio, Hoffman reflex normalized to motor response) and voluntary (quadriceps central activation ratio) pathways, with greater inhibition observed in measures of the latter. The authors suggested these results to indicate that inhibition is at least partly due to supraspinal mechanisms. Indeed, the processing and perception of pain is dominated by supraspinal processes (Apkarian et al., 2009; Moseley, 2007). The presence of pain itself may have been a sufficient cause of bilateral inhibition in the AKP participants of the present study, independent of tissue damage and γ loop dysfunction. The details are not yet clear, and require further investigation.

No significant differences were detected in quadriceps or hamstrings iEMG post vibration. This was surprising given the significant reduction in force production observed in both the groups. Previous research (Rice et al., 2011, Konishi et al., 2007) reported significant reductions in both vastus medialis and vastus lateralis EMG following prolonged vibration along with decreased knee extensor force. Our results may be due to the fact that force and EMG does not always exhibit a linear relationship

(Lawrence & De Luca, 1983), which is particularly the case at higher forces (Kamen & Gabriel, 2009), such as during the MVIC's performed during the present study. Furthermore, iEMG data exhibited considerable variation which may have led to significance tests yielding a type II error given the small sample size. Since there was no statistically significant change in iEMG post vibration in either quadriceps or hamstrings, the changes in force post-vibration cannot be attributed to changes in co-contraction.

While the focus of this research was to investigate the existence of bilateral AMI in AKP, the work was also done in an effort to add clarity to current understanding of the role that damaged sensory receptors and γ loop dysfunction play in bilateral deficits. These results appear to have provided additional evidence to support the role of sensory receptor damage in γ loop dysfunction, but it remains unclear if γ loop dysfunction causes bilateral quadriceps inhibition in unilateral knee pathology. While the existence of bilateral γ loop dysfunction in several clinical populations that have unilateral pathology (Rice et al., 2011; Konishi et al., 2003; Konishi et al., 2007) would suggest alterations in the γ loop may be linked to bilateral deficits, this of course does not establish causation. Further research is needed to better understand this potential link. If we start with the assumption that there is some causal link between γ loop dysfunction and bilateral deficits then the question that remains is how would γ loop dysfunction cause these bilateral effects. One possible mechanism is that the afferent receptors in the affected limb may send inhibitory signals or decreased feedback to the contralateral side via interneurons in the spinal cord. Alternatively, inhibitory signals or decreased feedback from the affected joint may be transmitted supraspinally resulting in descending inhibition bilaterally. No evidence exists to confirm these speculations. In both cases, decreased afferent discharge

from the affected limb is a common origin. Damage to sensory receptors is not the only possible mechanism affecting afferent discharge, with others including swelling, inflammation, and altered joint mechanics (Reeves & Maffulli, 2008; Dunham, Kelly, & Donaldson, 2008; Gomez-Barrena, Nunez, Ballesteros, Martinez-Moreno, & Munuera, 1999). In these cases, afferent feedback may be increased, rather than decreased as seen with joint damage (Rice et al., 2010). AKP itself seems to alter afferent activity, as Jensen et al. (2008) found that patients with AKP exhibited signs of abnormal sensory functioning in the painful area despite a lack of damage to the receptors themselves. In their study, different measures of sensory function showed an increase while others a decrease, and there was considerable heterogeneity between subjects. This unpredictable alteration in afferent activity seen in AKP may explain why affected individuals in the present study did not demonstrate γ loop dysfunction, which appears to require consistently decreased afferent feedback due to damaged sensory receptors.

Limitations of this study include issues with measuring %VA with ITT. Not all participants tolerated the twitch and opted out due to discomfort. This led to statistical analysis on %VA involving less participants. This was unlikely to be problematic, however, since the effect size for the planned contrast between AKP and control groups was large (cohen's $d = 1.13$) and statistical significance was found with conventionally acceptable power achieved ($1 - \beta = 0.82$). Another limitation includes the age of the AKP group being three years older than the control group. However, such a small age difference is unlikely to affect the experimental results. Another limitation with this analysis is that not all participants with AKP had reduced %VA. This led to significantly higher variance in the AKP group as shown in Figure 2, resulting in the need to use

Welsh's robust tests of significance. Furthermore, with substantially more participants, subgrouping could have been performed between individuals with AKP who had quadriceps inhibition compared to those who did not. It is possible that a strictly defined subgroup of AKP participants with quadriceps inhibition may have shown signs of γ loop dysfunction. Another limitation includes the fact that it was assumed that the only pathology present in the AKP group was the existence of unilateral knee pain. It is possible that members of this group had pathology affecting the other limb or that they had pre-existing sensory deficits that may have contributed to their bilateral muscle activation deficits. This doesn't seem likely as the participants did not report pain in the unaffected knee, nor were any other sensory, neurological or musculoskeletal deficits reported. Finally, AKP participants in the present study had relatively mild levels of pain averaging 3.1 on the NPRS. Although this is a typical level of pain for this condition, greater effects may have been observed in individuals with more severe pain.

2.5 Conclusion

Unilateral AKP is associated with bilateral quadriceps inhibition when compared to healthy controls. Following prolonged tendon vibration, both groups experienced significant reductions in knee extension MVIC bilaterally, indicating an intact γ loop. Therefore, bilateral quadriceps inhibition in unilateral AKP cannot be attributed to γ loop dysfunction. It remains possible that γ loop dysfunction is responsible for bilateral quadriceps inhibition in unilateral knee pathologies that involve potential disruption of sensory structures in the knee, however as discussed above further research is needed. In cases of unilateral AKP with no history of traumatic injury or radiographic changes, pain perception itself may be sufficient in causing bilateral quadriceps inhibition. Once again further research should explore the possibility of other mechanisms, potentially centrally mediated.

2.6 References

Apkarian, A. V., Baliki, M. N., & Geha, P. Y. (2009). Towards a theory of chronic pain. *Progress in Neurobiology, 87*(2), 81-97. doi:10.1016/j.pneurobio.2008.09.018

Basbaum, A. I., Bautista, D. M., Scherrer, G., & Julius, D. (2009). Cellular and molecular mechanisms of pain. *Cell, 139*(2), 267-284. doi:10.1016/j.cell.2009.09.028

Becker, R., Berth, A., Nehring, M., & Awiszus, F. (2004). Neuromuscular quadriceps dysfunction prior to osteoarthritis of the knee. *Journal of Orthopaedic Research, 22*(4) doi:10.1016/j.orthres.2003.11.004

Behm, D., Power, K., & Drinkwater, E. (2001). Comparison of interpolation and central activation ratios as measures of muscle inactivation. *Muscle & Nerve, 24*(7), 925-934.

Behm, D. G., St-Pierre, D. M., & Perez, D. (1996). Muscle inactivation: Assessment of interpolated twitch technique. *Journal of Applied Physiology (Bethesda, Md.: 1985), 81*(5), 2267-2273.

Bongiovanni, L., Hagbarth, K., & Stjernberg, L. (1990). Prolonged muscle vibration reducing motor output in maximal voluntary contractions in man. *Journal of Physiology-London, 423*, 15-26.

Cohen, J. (Ed.). (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Collins, N. J., Misra, D., Felson, D. T., Crossley, K. M., & Roos, E. M. (2011). Measures of knee function: International knee documentation committee (IKDC) subjective knee evaluation form, knee injury and osteoarthritis outcome score (KOOS), knee injury and osteoarthritis outcome score physical function short form (KOOS-PS), knee outcome survey activities of daily living scale (KOS-ADL), lysholm knee scoring scale, Oxford knee score (OKS), Western Ontario and McMaster universities osteoarthritis index (WOMAC), activity rating scale (ARS), and tegner activity score (TAS). *Arthritis Care & Research, 63 Suppl 11*, S208-28. doi:10.1002/acr.20632

Cook, C., Mabry, L., Reiman, M. P., & Hegedus, E. J. (2012). Best tests/clinical findings for screening and diagnosis of patellofemoral pain syndrome: A systematic review. *Physiotherapy, 98*(2), 93-100. doi:10.1016/j.physio.2011.09.001

Criswell, E., & Cram, J. R. (2010). *Cram's introduction to surface electromyography* (2nd ed.) Jones & Bartlett Publishers.

Curtis, D. R., & Eccles, J. C. (1960). Synaptic action during and after repetitive stimulation. *Journal of Physiology-London, 150*(2), 374-398.

De Luca, C. J., Gilmore, L. D., Kuznetsov, M., & Roy, S. H. (2010). Filtering the surface EMG signal: Movement artifact and baseline noise contamination. *Journal of Biomechanics, 43*(8), 1573-1579. doi:10.1016/j.jbiomech.2010.01.027

Domenech, J., Sanchis-Alfonso, V., Lopez, L., & Espejo, B. (2012). Influence of kinesiophobia and catastrophizing on pain and disability in anterior knee pain patients. *Knee Surgery, Sports Traumatology, Arthroscopy : Official Journal of the ESSKA,* doi:10.1007/s00167-012-2238-5

Drover, J. M., Forand, D. R., & Herzog, W. (2004). Influence of active release technique on quadriceps inhibition and strength: A pilot study. *Journal of Manipulative and Physiological Therapeutics, 27*(6), 408-413. doi:10.1016/j.jmpt.2004.05.006

Dube, J. A., & Mercier, C. (2011). Effect of pain and pain expectation on primary motor cortex excitability. *Clinical Neurophysiology, 122*(11), 2318-2323. doi:10.1016/j.clinph.2011.03.026

Dunham, J. P., Kelly, S., & Donaldson, L. F. (2008). Inflammation reduces mechanical thresholds in a population of transient receptor potential channel A1-expressing nociceptors in the rat. *European Journal of Neuroscience, 27*(12), 3151-3160. doi:10.1111/j.1460-9568.2008.06256.x

Ferreira-Valente, M. A., Pais-Ribeiro, J. L., & Jensen, M. P. (2011). Validity of four pain intensity rating scales. *Pain, 152*(10), 2399-2404. doi:10.1016/j.pain.2011.07.005

Freeman, S., Mascia, A., & McGill, S. (2012). Arthrogenic neuromusculature inhibition: A foundational investigation of existence in the hip joint. *Clinical Biomechanics (Bristol, Avon),* doi:10.1016/j.clinbiomech.2012.11.014

Fyfe, J. J., Opar, D. A., Williams, M. D., & Shield, A. J. (2013). The role of neuromuscular inhibition in hamstring strain injury recurrence. *Journal of Electromyography and Kinesiology, 23*(3), 523-530. doi:10.1016/j.jelekin.2012.12.006

Gomez-Barrena, E., Nunez, A., Ballesteros, R., Martinez-Moreno, E., & Munuera, L. (1999). Anterior cruciate ligament reconstruction affects proprioception in the cat's knee. *Acta Orthopaedica Scandinavica, 70*(2), 185-193. doi:10.3109/17453679909011260

Hagbarth, K. E., Kunesch, E. J., Nordin, M., Schmidt, R., & Wallin, E. U. (1986). Gamma loop contributing to maximal voluntary contractions in man. *The Journal of Physiology, 380*, 575-591.

Hart, J. M., Pietrosimone, B., Hertel, J., & Ingersoll, C. D. (2010). Quadriceps activation following knee injuries: A systematic review. *Journal of Athletic Training, 45*(1), 87-97.

Hayward, L. F., Nielsen, R. P., Heckman, C. J., & Hutton, R. S. (1986). Tendon vibration-induced inhibition of human and cat triceps surae group I reflexes: Evidence of selective ib afferent fibre activation. *Experimental Neurology, 94*(2), 333-347. doi:10.1016/0014-4886(86)90107-X

Hong, X. (2014). *Comparisons between automatic force based triggering and manually triggered methods of quantifying quadriceps voluntary activation assessment.* (Unpublished Masters Thesis). School of Human Kinetics and Recreation, Memorial University, St. John's, Newfoundland, Canada.

Hopkins, J., & Ingersoll, C. (2000). Arthrogenic muscle inhibition: A limiting factor in joint rehabilitation. *Journal of Sport Rehabilitation, 9*(2), 135-159.

Hsu, H. C., Boardman, N. D.,3rd, Luo, Z. P., & An, K. N. (2000). Tendon-defect and muscle-unloaded models for relating a rotator cuff tear to glenohumeral stability. *Journal of Orthopaedic Research : Official Publication of the Orthopaedic Research Society, 18*(6), 952-958. doi:10.1002/jor.1100180615

Hultborn, H., Meunier, S., Pierrot-Deseilligny, E., & Shindo, M. (1987). Changes in presynaptic inhibition of ia fibers at the onset of voluntary contraction in man. *Journal of Physiology-London, 389*, 757-772.

Hurley, M. V., Jones, D. W., & Newham, D. J. (1994). Arthrogenic quadriceps inhibition and rehabilitation of patients with extensive traumatic knee injuries (vol 86, pg 309, 1994). *Clinical Science, 86*(6)

Jackson, S. W., & Turner, D. L. (2003). Prolonged muscle vibration reduces maximal voluntary knee extension performance in both the ipsilateral and the contralateral limb in man. *European Journal of Applied Physiology, 88*(4-5), 380-386. doi:10.1007/s00421-002-0701-6

Kamen, G., & Gabriel, D. (2009). *Essentials of electromyography* Human Kinetics.

Keays, S. L., Bullock-Saxton, J. E., Newcombe, P., & Keays, A. C. (2003). The relationship between knee strength and functional stability before and after anterior cruciate ligament reconstruction. *Journal of Orthopaedic Research, 21*(2), PII S0736-0266(02)00160-2. doi:10.1016/S0736-0266(02)00160-2

Klykken, L. W., Pietrosimone, B. G., Kim, K. M., Ingersoll, C. D., & Hertel, J. (2011). Motor-neuron pool excitability of the lower leg muscles after acute lateral ankle sprain. *Journal of Athletic Training, 46*(3), 263-269.

Konishi, Y., Aihara, Y., Sakai, M., Ogawa, G., & Fukubayashi, T. (2007). Gamma loop dysfunction in the quadriceps femoris of patients who underwent anterior cruciate ligament reconstruction remains bilaterally. *Scandinavian Journal of Medicine & Science in Sports, 17*(4), 393-399. doi:10.1111/j.1600-0838.2006.00573.x

Konishi, Y., Konishi, H., & Fukubayashi, T. (2003). Gamma loop dysfunction in quadriceps on the contralateral side in patients with ruptured ACL. *Medicine and Science in Sports and Exercise, 35*(6), 897-900. doi:10.1249/01.MSS.0000069754.07541.D2

Kouzaki, M., Shinohara, M., & Fukunaga, T. (2000). Decrease in maximal voluntary contraction by tonic vibration applied to a single synergist muscle in humans RID C-6635-2009. *Journal of Applied Physiology, 89*(4), 1420-1424.

Krishnan, C., Allen, E. J., & Williams, G. N. (2009). Torque-based triggering improves stimulus timing precision in activation tests. *Muscle & Nerve, 40*(1), 130-133. doi:10.1002/mus.21279

Lawrence, J. H., & De Luca, C. J. (1983). Myoelectric signal versus force relationship in different human muscles. *Journal of Applied Physiology: Respiratory, Environmental and Exercise Physiology, 54*(6), 1653-1659.

Lundberg, M., Grimby-Ekman, A., Verbunt, J., & Simmonds, M. J. (2011). Pain-related fear: A critical review of the related measures. *Pain Research and Treatment, 2011*, 494196. doi:10.1155/2011/494196

Lysholm, J. (1982). Evaluation of knee ligament surgery results with special emphasis on use of a scoring scale. *The American Journal of Sports Medicine, 10*(3), 150; 150-154; 154.

Mann, G., Constantini, N., Hetsroni, I., Meidan, O., Dolev, E., Morgenstern, D., . . . Nyska, M. (2007). Anterior knee-pain syndrome. *Adolescent Medicine: State of the Art Reviews, 18*(1)

Manuel, M., & Zytnicki, D. (2011). Alpha, beta and gamma motoneurons: Functional diversity in the motor system's final pathway. *Journal of Integrative Neuroscience, 10*(3), 243-276.

McVey, E. D., Palmieri, R. M., Docherty, C. L., Zinder, S. M., & Ingersoll, C. D. (2005). Arthrogenic muscle inhibition in the leg muscles of subjects exhibiting functional ankle instability. *Foot & Ankle International / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society, 26*(12), 1055-1061.

Mikesky, A. E., Mazzuca, S. A., Brandt, K. D., Perkins, S. M., Damush, T., & Lane, K. A. (2006). Effects of strength training on the incidence and progression of knee osteoarthritis. *Arthritis & Rheumatism-Arthritis Care & Research, 55*(5) doi:10.1002/art.22245

Miller, R., Kori, S., & Todd, D. (1991). *The tampa scale.* Unpublished manuscript.

Moseley, G. L. (2007). Reconceptualising pain according to modern pain science. *Physical Therapy Reviews, 12*(3), 169-178. doi:10.1179/108331907X223010

Nunes, G. S., Stapait, E. L., Kirsten, M. H., de Noronha, M., & Santos, G. M. (2013). Clinical test for diagnosis of patellofemoral pain syndrome: Systematic review with meta-analysis. *Physical Therapy in Sport : Official Journal of the Association of Chartered Physiotherapists in Sports Medicine, 14*(1), 54-59. doi:10.1016/j.ptsp.2012.11.003

Park, J., & Hopkins, J. T. (2013). Induced anterior knee pain immediately reduces involuntary and voluntary quadriceps activation. *Clinical Journal of Sport Medicine, 23*(1), 19-24. doi:10.1097/JSM.0b013e3182717b7b

Reeves, N. D., & Maffulli, N. (2008). A case highlighting the influence of knee joint effusion on muscle inhibition and size. *Nature Clinical Practice Rheumatology, 4*(3), 153-158. doi:10.1038/ncprheum0709

Rice, D. A., McNair, P. J., & Lewis, G. N. (2011). Mechanisms of quadriceps muscle weakness in knee joint osteoarthritis: The effects of prolonged vibration on torque and muscle activation in osteoarthritic and healthy control subjects. *Arthritis Research & Therapy, 13*(5), R151. doi:10.1186/ar3467

Rice, D. A., & McNair, P. J. (2010). Quadriceps arthrogenic muscle inhibition: Neural mechanisms and treatment perspectives. *Seminars in Arthritis and Rheumatism, 40*(3), 250-266. doi:10.1016/j.semarthrit.2009.10.001

Segal, N. A., Torner, J. C., Felson, D., Niu, J., Sharma, L., Lewis, C. E., & Nevitt, M. (2009). Effect of thigh strength on incident radiographic and symptomatic knee osteoarthritis in a longitudinal cohort. *Arthritis & Rheumatism-Arthritis Care & Research, 61*(9) doi:10.1002/art.24541

Shinohara, M. (2005). Effects of prolonged vibration on motor unit activity and motor performance. *Medicine and Science in Sports and Exercise, 37*(12), 2120-2125.

Suter, E., Herzog, W., & Bray, R. C. (1998). Quadriceps inhibition following arthroscopy in patients with anterior knee pain. *Clinical Biomechanics (Bristol, Avon), 13*(4-5), 314-319.

Suter, E., Herzog, W., De Souza, K., & Bray, R. (1998). Inhibition of the quadriceps muscles in patients with anterior knee pain. *Journal of Applied Biomechanics, 14*(4), 360-373.

Suter, E., McMorland, G., Herzog, W., & Bray, R. (1999). Decrease in quadriceps inhibition after sacroiliac joint manipulation in patients with anterior knee pain. *Journal of Manipulative and Physiological Therapeutics, 22*(3), 149-153.

Tegner, Y. (1985). Rating systems in the evaluation of knee ligament injuries. *Clinical Orthopaedics and Related Research*, (198), 43; 43-49; 49.

Thomee, R., Augustsson, J., & Karlsson, J. (1999). Patellofemoral pain syndrome: A review of current issues. *Sports Medicine (Auckland, N.Z.), 28*(4), 245-262.

Thomee, R., Grimby, G., Svantesson, U., & Osterberg, U. (1996). Quadriceps muscle performance in sitting and standing in young women with patellofemoral pain syndrome and young healthy women. *Scandinavian Journal of Medicine & Science in Sports, 6*(4), 233-241.

Urbach, D., & Awiszus, F. (2002). Impaired ability of voluntary quadriceps activation bilaterally interferes with function testing after knee injuries. A twitch interpolation study. *International Journal of Sports Medicine, 23*(4) doi:10.1055/s-2002-29074

Verbunt, J., Seelen, H., Vlaeyen, J., Bousema, E., van der Heijden, G., Heuts, P., & Knottnerus, J. (2005). Pain-related factors contributing to muscle inhibition in patients with chronic low back pain - an experimental investigation based on superimposed electrical stimulation RID A-3829-2009. *Clinical Journal of Pain, 21*(3), 232-240. doi:10.1097/00002508-200505000-00006

Voigt, M., Jakobsen, J., & Sinkjaer, T. (1998). Non-noxious stimulation of the glenohumeral joint capsule elicits strong inhibition of active shoulder muscles in conscious human subjects. *Neuroscience Letters, 254*(2), 105-108.

Yoshida, Y., Mizner, R. L., Ramsey, D. K., & Snyder-Mackler, L. (2008). Examining outcomes from total knee arthroplasty and the relationship between quadriceps strength and knee function over time. *Clinical Biomechanics, 23*(3) doi:10.1016/j.clinbiomech.2007.10.008