A Thesis

entitled

The Effects of Cryotherapy on Quadriceps Corticomotor Excitability in Patients with Anterior Knee Pain

by

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Submitted to the Graduate Faculty as partial fulfillment of the requirements for the Master of Science Degree in Exercise Science

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April 2015
An Abstract of

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Introduction: Central activation deficits (CAD) are a common occurrence following injury and could have long term implications such as developing early onset osteoarthritis. Individuals with anterior knee pain (AKP) have been seen to have higher magnitudes of CAD when compared to ACL deficient and ACL reconstructed populations. In addition, these deficits have been seen bilaterally suggesting that the activation deficit may be cortical in nature. The purpose of this study is to examine the effects of cryotherapy on quadriceps intracortical excitability in patients with and without anterior knee pain. Research Design: Case-control Methods: Thirteen participants (6 AKP: age 20.17±2.64 years; height 1.60±0.04 m; mass 63.67±5.86 kg and 7 Healthy: age 22.86±1.07 years; height 1.66±0.75 m; mass 71.10±15.95 kg) reported for two sessions, one week apart, during which they received either a cryotherapy intervention or no intervention. The order of condition was randomized and concealed from the tester. Measures of short and long interval intracortical inhibition (SICI and LICI), intracortical facilitation (ICF) and pain were recorded at baseline, and again at 10, 20, 35, and 50 minutes after intervention application (control or cryotherapy). SICI, LICI, and ICF were
assessed using transcranial magnetic stimulation, while pain was assessed using a 10cm visual analog scale. **Statistical Analysis:** Mixed models ANOVAs with repeated measures on time were used to analyze pain, SICI, ICF, and LICI. Paired T-tests were used to determine statistically significant events in the event of a significant interaction. The *a priori* alpha level was *P*<0.05. **Results:** There was significant group by time interaction within LICI in the cryotherapy condition (*P*=0.025). *Post hoc* t-tests revealed LICI was significantly lower at 35 minutes compared to baseline during the control session in the healthy participants (Baseline: 0.48±0.28; 35 minutes: 0.33±0.17; *P*=0.042). There was a significant group-main effect for ICF (*P*=0.050) during the cryotherapy condition, but not the control condition. *Post hoc* testing revealed that at the 10 minute time interval ICF was significantly higher in the healthy group as compared to the AKP group (AKP: 0.85±0.22; Healthy: 1.33±0.48; *P*=0.044). During the control session there was a significant increase in pain over time within the AKP group at each time interval [(Baseline: 1.23±2.08cm; 10 minutes: 1.96±2.13cm *P*=0.016; 20 minutes: 2.14±2.11cm; *P*=0.008; 35 minutes: 2.68±3.2cm; *P*=0.047; 50 minutes: 2.94±3.25cm; *P*=0.027)]. Additionally, pain was significantly higher in the AKP group at 10 and 20 minutes compared to the healthy group [(10 minutes: AKP: 1.96±2.13cm; Healthy: 0.00±0.00cm; *P*=0.047), (20 minutes: AKP: 2.14±2.11cm; Healthy: 0.00±0.00cm; *P*=0.032)]. **Conclusion:** It is difficult to address the changes revealed in ICF and LICI in healthy participants. To begin, LICI significantly decreased in the absence of intervention at 35 minutes. There is no reasonable explanation for this decrease aside of the variation in our collected data. During cryotherapy in the healthy group there was a significant increase in ICF at 10 minutes. This suggests that cryotherapy despite have little affect on our
inhibitory measures, may have been able to facilitate. However, neither of these findings continued to trend in their respective directions at subsequent time points. Interestingly, there was a significant increase in pain within the AKP group when no cryotherapy was administered. We did not see this trend during their cryotherapy session, potentially suggesting that cryotherapy has the ability to limit pain from increasing. Despite several interesting findings, due to our limited sample size further research is needed to truly understand the role of cryotherapy as both a pain moderator and disinhibitory modality in patients with AKP
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List of Abbreviations

AKP..........................anterior knee pain
AMI..........................arthrogenic muscle inhibition
AMT..........................active motor threshold
CAD..........................central activation deficit
EMG..........................electromyography
ICF..........................intracortical facilitation
LICI..........................long interval intracortical facilitation
MEP..........................motor evoked potential
SICI..........................short interval intracortical inhibition
TMS ..........................transcranial magnetic stimulation
Chapter 1

Introduction

1.1 Introduction

Muscle weakness is a common occurrence following joint injury. Specifically at the knee joint, it is ordinary to see weakness that results from an inability to fully activate the quadriceps muscle group. Because the quadriceps plays an important role in attenuating loads across the knee joint, weakness of this muscle group further predisposes the knee to injury. Quadriceps weakness results in loads being transmitted across the knee joint at higher rates and magnitudes. Thus, failure of the body’s natural shock absorbing mechanics results in greater loads on the articular cartilage. Research strongly suggests altered movement patterns caused by quadriceps weakness may, in part, explain the development of knee osteoarthritis (OA). OA can lead to decreased physical function, limiting one’s capability to work or even perform activities of daily living; thus, resulting in decreased quality of life and possible further health complications. There is no known cure for OA; therefore, research has focused primarily on combative measures addressing the inability to fully regain muscle strength.

The muscle weakness described above is attributable to a central activation deficit (CAD), which is defined as the inability to fully recruit the motoneuron pool. In a systematic review, it was found that populations experiencing anterior knee pain (AKP)
had greater CADs compared to both anterior cruciate ligament deficient and reconstructed populations. All three groups showed quadriceps weakness in the uninjured limb suggesting that CAD can occur in an asymptomatic knee, potentially indicating the involvement of corticospinal pathways.4,7-9 This suggests the need for clinicians to take a bilateral approach when treating a unilateral knee joint injury.

Two motor output pathways that may contribute to CAD are the spinal reflexive and corticospinal pathways. Reflexive pathways are a network of afferent receptors, interneurons, and motor neurons. Afferent information is sent from receptors to the spinal cord, which in turn sends an inhibitory or excitatory efferent signal to the target musculature. The corticospinal pathway consists of motor commands sent from the cortex to the medulla. From the medulla, motor commands split into two descending pathways within the spinal cord, of which 90% of the axons cross over to the contralateral side and form the lateral corticospinal tract.10 This tract is responsible for the control of distal musculature. The other 10% forms the anterior corticospinal tract, primarily responsible for the control of proximal muscles. Motor commands continue down both tracts within the spinal cord until they synapse on an alpha motoneuron.10

Cryotherapy, a modality commonly used to control swelling and pain, has demonstrated disinhibitory properties in both healthy and injured populations.1,4,5,8,11 Hopkins et al.4 conducted a knee effusion study observing the effects of cryotherapy on spinal reflex excitability. Cryotherapy not only disinhibited the quadriceps following the effusion, but facilitated spinal reflex excitability beyond pre-effused levels.4 It is hoped that by increasing or restoring quadriceps central activation, this will optimize the ability to regain quadriceps strength.4,5,9 Though cryotherapy has been reported to alter spinal
reflex excitability, it is also important to look at the effect it has on corticospinal pathways because CADs are likely a net result of influences from both corticospinal and spinal reflexive pathways. Understanding the efficacy of disinhibitory modalities could prove useful in changing rehabilitation paradigms and, in the long-term, potentially reduce the prevalence of post-traumatic OA and co-morbidities that have become burdensome on the healthcare system. Therefore, there is dire need to continue to investigate disinhibitory modalities and the role they may play in the rehabilitation process.

1.2 Statement of the Problem

Quadriceps central activation, and thus muscle strength, is impaired bilaterally in individuals with AKP. Quadriceps weakness alters lower extremity biomechanics and may lead to reduced physical function and OA. Cryotherapy may improve volitional muscle activation. However, the effect of cryotherapy on corticospinal and intracortical excitability is unknown. Better understanding of the role of cryotherapy on corticospinal and intracortical excitability is imperative to developing effective treatments for individuals with AKP.

1.3 Statement of Purpose

The purpose of this study is to determine the effects of cryotherapy on quadriceps corticospinal and intracortical excitability in people with and without AKP.

1.4 Specific Aims and Hypotheses

Specific Aim 1: To examine the effects of cryotherapy on quadriceps strength and excitability of the intracortical pathway of the vastus medialis between participants with AKP and healthy controls. Excitability will be measured by Short Intracortical Inhibition
(SICI), Long Intracortical Inhibition (LICI), and Intracortical Facilitation (ICF) paradigms.

**Hypothesis 1.1:** Corticospinal and intracortical excitability will be increased following a 20-minute cryotherapy application as evidenced by increased SICI and LICI measures and increased ICF values. Further, ICF will remain lower in participants with AKP compared to healthy controls in spite of cryotherapy application.

**Hypothesis 1.2:** We hypothesize that corticospinal and intracortical excitability will remain increased in the AKP group at the 35 minute and 50 minute time points after initiation of the cryotherapy application, as compared to the healthy control group

**Specific Aim 2:** To examine the effect of cryotherapy on perceived pain measured via visual analog scale.

**Hypothesis 2.1:** Following 20 minutes of cryotherapy application to the knee joint, there will be a decrease in pain as indicated by a smaller measurement on a 10 cm visual analog scale. We hypothesize that perceived pain will remain reduced at 35 and 50 minute time points.

### 1.5 Operational Definitions

- **AKP-** Anterior knee pain. Participants must present with AKP that: 1) has been diagnosed by a medical professional (physician, physician’s assistant, athletic trainer, etc.); 2) is diffuse and has lasted 8 weeks or more; or 3) pain that increases with activity
• AMI- Arthrogenic muscle inhibition. Ongoing inhibition of musculature surrounding a joint due to injury or distention of the joint; due to afferent activity disruption caused by injury

• AMT- Active motor threshold. Defined by the lowest intensity needed to elicit 4/8 positive MEPs

• CAD- Central activation deficit. Reduction in voluntary activation, representing a decrease in the number of motor units or a reduction in firing rate of motor units that are recruited

• EMG- Electromyography. Surface electrodes used to collect electrical output from the quadriceps

• ICF- Intracortical facilitation. A subthreshold stimulus followed by a suprathreshold stimulus separated by 15ms.

• LICI- Long interval intracortical inhibition. Two consecutive suprathreshold stimuli separated by 100ms

• MEP- Motor evoked potential. An electrical potential elicited within the motor cortex that is recorded peripherally and has an amplitude ≥100µV.

• SICI- Short interval intracortical inhibition A subthreshold stimulus followed by a suprathreshold stimulus separated by 3ms

• TMS- Transcranial magnetic stimulation. Testing method used to establish corticospinal and intracortical contributions to neuromuscular activity.
Chapter 2

Review of the Literature

Understanding the neuromuscular alterations surrounding the knee joint in people with AKP could aid in the development of treatment and rehabilitative procedures to improve both short and long-term patient outcomes. Disinhibitory modalities are a subset of clinical treatments that may help to improve neural deficits. The purpose of this literature review is to: 1) review knee joint anatomy as it relates to AKP; 2) examine mediators of central activation deficits; 3) discuss the reliability and paradigms of transcranial magnetic stimulation; 4) inspect the use of cryotherapy in relation to reducing central activation deficits.

2.1 Anterior Knee Pain

AKP is a common lower extremity pathology encountered in orthopedic practice.\textsuperscript{12-15} Within the active running population alone, it has been approximated that 2.5 million will be diagnosed with AKP annually.\textsuperscript{16} AKP becomes more concerning as it hold a recurrence rate of 70-90%.\textsuperscript{16} Despite the high rate of occurrence, the underlying factors that contribute to AKP are often under debate.\textsuperscript{12-15} The most commonly identified contributors to AKP is abnormal patellofemoral alignment and/or improper tracking of the patella throughout joint movement. Improper tracking and alignment creates abnormal joint stress and subsequent cartilage degradation.\textsuperscript{14} Individuals experiencing
AKP have greater patellofemoral joint stress during walking as compared to individuals who are asymptomatic. Prolonged and constant stress may expedite the degradation of joint tissue. The vastus medialis (VM), serves as an important medial dynamic stabilizer of the patellofemoral joint. Contact area and pressure within the patellofemoral joint are mediated by neuromuscular control between the VM and the vastus lateralis. Dysfunction of the VM may cause abnormal patellar alignment within the trochlear groove. Throughout a range of motion altered contact area and pressure result in maltracking of the patella. This is further complicated in knee flexion and/or weight bearing, when patellofemoral contact area is at its highest.

2.2 Central Activation Deficit

Central activation deficit (CAD) is characterized by diminished motor drive to muscles surrounding a joint, resulting in an inability to fully or optimally contract the muscle. Clinically, CAD presents as muscle weakness. When CAD originates in the joint, it is referred to as arthrogenic muscle inhibition, a pre-synaptic and post-synaptic ongoing spinal reflex inhibition. Arthrogenic muscle inhibition is a mechanism to protect an injured joint from further damage by “shutting down” the surrounding musculature. Reduced excitability mediated by corticospinal and intracortical pathways has been suggested as a contributing factor in CAD; however, which motor pathway may be more influential in CAD of the knee is not well understood. There are many potential causative factors for CAD; pain, intracapsular swelling, degenerative changes to articulating surfaces, inflammation, and general joint laxity; all have influence on mechanoreceptors within the joint. Whether in isolation or in harmony, it is suspected that altered afferent signals arising from these
symptoms are possible causes for the reflexive inhibition leading to CAD.\textsuperscript{2-4,9,18,19} Conversely, CAD has frequently been reported in the absence of pain and in the absence of significant joint effusion, suggesting that CAD may also occur in an asymptomatic knee.\textsuperscript{2,4,8,9} Expanding on this hypothesis, CADs have been reported in the contralateral limb, despite sustaining little to no damage.\textsuperscript{3,6,7,9} Contralateral limb involvement has been hypothesized as an attempt by the central nervous system to normalize activation levels between injured and uninjured sides.\textsuperscript{6} The bilateral presence of CAD supports theories that it may be cortically driven.

\textbf{2.2.1 Mechanoreceptors and Neurotransmitters}

It is widely accepted that mechanoreceptors play a role in CAD, however the exact mechanisms are not entirely clear.\textsuperscript{2,3,7-9,18,21} When mechanoreceptors react to unnatural stimuli such as pain, laxity, and pressure; they emit unusual afferent activity. This influx of afferent activity causes mechanoreceptors to send information to Ib inhibitory interneurons, which, in turn send an inhibitory signal to the alpha motorneuron, potentially presenting as a CAD.\textsuperscript{9,18,20} In the knee, there are four types of mechanoreceptors: 1) Ruffini endings, 2) Golgi-tendon like organs, 3) Pacinian Corpuscles, and 4) free nerve endings. The primary roles of Ruffini endings are to detect the proximity of a joint throughout its range of motion, and to detect intracapsular pressure changes. Ruffini endings adapt to stimuli slowly and if subjected to a persistent stimulus may have a lengthy discharge of afferent activity, prolonging the presence of CAD. A joint experiencing hypermobility or intrarticular effusion would cause abnormal afferent activity from Ruffini endings. Golgi-like receptors resemble golgi tendon organs. They are found primarily in the ligaments of the knee and adapt quickly to rapid changes.
in tendon length. A ligamentous structure under stress or damage would cause Golgi-like receptors to discharge irregular afferent information.\textsuperscript{9,18} Pacinian corpuscles work much like Ruffini endings by transmitting signals relative to joint proximity. However, Pacinian corpuscles are quick adapting and have a low firing threshold; they will discharge afferent information anytime a joint is moving.\textsuperscript{9,18} Lastly, free nerve endings serve as pain receptors. Free nerve endings are thought to play a role in CAD; however, their significance of this role in CAD is not fully known.\textsuperscript{9,18}

Neurotransmitters also have a role in CAD. When neurotransmitters bind to a specific receptor on the synaptic membrane it causes an inhibitory or facilitory potential. Inhibitory neurotransmitters cause ion channels to open that hyperpolarize the synaptic membrane, making it difficult for other neurotransmitter synapsing on the membrane to generate an action potential.\textsuperscript{18} The neurotransmitter that is most often associated with CAD is \textit{\textgamma}-aminobutyrate (GABA).\textsuperscript{3,18} Both GABA\textsubscript{A} and GABA\textsubscript{B} receptors can uptake the GABA neurotransmitter. GABA\textsubscript{A} receptors are primarily post synaptic\textsuperscript{23}, if bound to GABA\textsubscript{A} the permeability of chloride ions increases.\textsuperscript{18} GABA\textsubscript{B} receptors are located both pre and post synaptically.\textsuperscript{23} When bound to GABA\textsubscript{B} the conductance of potassium channels increase, whereas the conductance of calcium currents decrease. Because of the role of calcium in transporting substances across the synaptic membrane, the change in the amount of calcium present alters the release of neurotransmitters.\textsuperscript{18}

\textbf{2.2.2 Interneurons}

Interneurons comprise a massive network that constantly relay sensory and supraspinal information throughout the spinal cord. Interneurons receive information
from sensory afferent fibers, descending fibers, and other interneurons. The final destination of this information is at alpha and gamma motorneurons. With such a complex network, interneurons receive both inhibitory and excitatory signals; however, it is the net effect of these signals that is relayed to the motorneuron pool.

Ia interneurons are inhibitory in nature. Ia interneurons receive input from the corticospinal tract and have projections into antagonist MN pools. Ib interneurons receive information from Golgi tendon organs, afferent joint and cutaneous receptors, and some Ia interneuron fibers from corticospinal tracts. The net effect of information at these interneurons determines the signal that will be sent to the alpha motor neuron; either excitatory or inhibitory.

2.2.3 Pathological groups

Central activation deficits are seen following acute and chronic injuries. CADs have been documented months, and in some cases years, after the initial injury. This becomes a plaguing factor in rehabilitation, it is not uncommon that quadriceps strength deficits are never fully restored.

When comparing patient populations with anterior cruciate ligament deficiency (ACLd), patients who had an anterior cruciate ligament reconstruction (ACLr), and patients with AKP, Hart et al. found that the magnitude of CAD in patients with AKP was significantly higher, despite not having a traumatic ligamentous injury.

Weakness of the quadriceps decreases the ability for the knee joint to attenuate loads throughout movement, resulting in unnatural forces on articulating surfaces. These unnatural loads may serve as an early indicator or cause for OA in the knee. Youssef et al. used a rabbit model to show the relation between muscle weakness and joint
degeneration. Using a botulinum toxin type-A injection, muscle weakness was chemically induced in rabbits. A control of rabbits received sham injections. After the injections, animals were left alone for four weeks until outcome measures were recorded. It was found that experimental injection limbs had significantly lower quadriceps torque and mass deficits as compared to the controls. Finally, it was found that retro-patellar degenerative grades were much higher (more degeneration) on experimental rabbits as compared to the control. Although these results are specific to animal models, this data supports the claim that quadriceps muscle weakness serves as a risk factor for the onset and progression of degenerative changes to the patellofemoral joint.

2.3 Transcranial Magnetic Stimulation

Transcranial magnetic stimulation (TMS) is a non-invasive tool used to activate the motor cortex. With specific parameters, this widely used tool can assess corticospinal and intracortical excitatory and inhibitory circuits. By running an electrical current through a coil that is fitted within the outer cone, electrons are forced to move about the coil. The movement of electrons generates a magnetic field that is discharged from the coil into the motor cortex. As this magnetic field moves into the brain it generates electrical currents that stimulate neurons. TMS can be administered in several different ways. The shape of the coil, number of pulses administered, and timing of the pulses can all be used to elicit specific responses. If TMS is administered through a single cone the magnetic field is strongest around the rim of the cone. However, if a double-cone (butterfly) is used, the magnetic field is strongest where the cones intersect. Pulses can be single, paired, or in a train. A single TMS pulse lasts less than 1 millisecond and stimuli may be delivered up to a maximal intensity of 2 Tesla.
Stimuli are administered from TMS to elicit a motor evoked potential (MEP), an electrical potential sent from the motor cortex to a target muscle, measured via surface electromyography. TMS can be used to identify a person’s motor threshold. Motor Threshold refers to the lowest stimulus needed to excite a population of motor cortex neurons. Paired-pulses are administered with an interstimulus interval (ISI) between individual pulses, or simultaneously through separate coils. A train of TMS pulses delivered at rates from 1-25 Hz can last anywhere from milliseconds to seconds. For the purposes of this study a bulk of the information reviewed will focus on paired-pulse TMS parameters.

Paired-pulse TMS is a well-documented technique in which a subthreshold or suprathreshold conditioning stimulus precedes a suprathreshold test stimulus. These parameters have been used to study intracortical inhibition and facilitation of both upper and lower extremities. Two types of inhibition that can be studied by TMS are short-interval intracortical inhibition (SICI) and long-interval intracortical inhibition (LICI). SICI responses are elicited with a condition stimulus set at 80\% of the motor threshold and a test stimulus set at 120\% of the motor threshold, they are separated by an ISI of 1-6 ms. It is suggested that SICI occurs within the cortex rather than subcortical structures, as positron emission tomography has shown a positive correlation between SICI and cerebral blood flow in the motor cortex. Evidence proposes that SICI may be mediated by pre synaptic GABAb receptors. When comparing a MEP elicited with SICI protocols it should appear reduced compared to an MEP elicited at 120\% of motor threshold. This resembles the activation of an inhibitory network. SICI is found to be reduced in many neurological and psychiatric disorders. Some of the disorders include
Parkinson’s, Alzheimer’s, Tourette’s, and schizophrenia. Reduced SICI may represent cortical plasticity following peripheral injuries.

When paired-pulses are separated by an ISI of 50-200ms, a LICI response is elicited. LICI consists of two suprathreshold stimuli set at 120% of the motor threshold. At an ISI greater than 50ms LICI occurs in the motor cortex and not subcortically. Following the test stimulus there is a suppression of muscle contraction known as the cortical silent period. LICI is thought to be controlled by GABAb receptors, identified by a decrease in neurotransmitters resulting from changes in the membrane caused by alteration to sodium levels. Like SICI, LICI should reveal a decreased MEP as compared to 120% motor threshold. Research has also shown LICI to be abnormal in some neurological disorders including stroke, Parkinson’s and dystonia. In Patients with cerebellar degeneration an increased silent period can be observed.

Facilitory circuits can be stimulated through TMS. Intracortical facilitation (ICF) has similar testing protocols to SICI. ICF uses a condition stimulus set at 80% of the motor threshold and a test stimulus set at 120% of the motor threshold, they are separated by an ISI of 8-30ms. Like SICI and LICI, ICF occurs in the motor cortex, however, it is thought that glutamate is a primary mediator of the facilitory response. This facilitory response will result in a larger MEP elicited as compared to 120% motor threshold.

2.3.1 TMS Safety and Reliability

TMS is a relatively safe testing mechanism and has not been shown to cause any long-term effects. TMS has been noted to cause headaches in susceptible people and, on rare occasion, cause a seizure. When TMS is administered it produces an
audible click and the stimulus may also cause muscles of the face to twitch and the eyes to blink, this can be discomforting to the subject.\textsuperscript{20} Screening is needed to identify conditions (Table 2.1) that may put the participant at high risk for adverse effects.

In regards to motor threshold, inter-investigator reliability, intra-investigator reliability, and test-retest reliability have all shown high intraclass correlation coefficient (ICC) scores (.94, .98 and .97 respectively), indicating a strong reliability.\textsuperscript{25} High ICC have been observed in measuring MEP at 2 and 4 weeks following baseline measurements. MEP at 100\% of AMT on the dominate vastus medialis had ICC of .93 at 2 weeks and .71 at 4 weeks.\textsuperscript{20} For the testing paradigms of this project SICI, LICI, and ICF have all shown high ICC for 5\% activation of MVIC (.93, .81, .83 respectively). When assessing intracortical excitability within a single testing session these paradigms may be reliable.\textsuperscript{29}

### 2.4 Treatment for Central Activation Deficit

Currently, a majority of rehabilitation protocols engage the patient in therapeutic exercises targeted at increasing strength and improving function, but without specifically addressing CAD.\textsuperscript{1,2} This may result in the patient performing tasks with sub-optimal motor recruitment which may lead to increased rate of fatigue, increased risk of subsequent injury and increased risk of chronic dysfunction.\textsuperscript{1} A more effective strategy may be to restore activation deficits before engaging the patient in therapeutic exercises, thus allowing the patient to optimally recruit the proper motoneurons for the desired task. Optimal recruitment may facilitate greater strength gains and improve functional movement patterns, as well as, improve distribution of forces across the joint.\textsuperscript{1} Modalities such as transcutaneous electric nerve stimulation (TENS), focal knee joint cooling,
manual therapy, and neuromuscular electrical stimulation all have previously demonstrated the potential to reduce CAD.\textsuperscript{1,4,5,7,8}

Of these modalities, TENS and cryotherapy are most widely acknowledged.\textsuperscript{4,5,7,8} TENS can be utilized for both sensory and motor stimulation. TENS is a modality often used to decrease pain. Sensory TENS provides the neural system with an influx of excitatory signals, these signals may override inhibitory signals being sent from the injured joint.\textsuperscript{1,8} TENS that is targeting motor stimulation can elicit a contraction of the targeted muscle. When used in combination with therapeutic exercises TENS has been shown to increase quadriceps strength and normalize gait patterns in patients with osteoarthritis.\textsuperscript{1}

Cryotherapy is also a commonly used modality for pain.\textsuperscript{4,8} Like TENS, cryotherapy has demonstrated the ability to increase quadriceps activation after application \textsuperscript{5,8,11} and even facilitate activation beyond baseline measurements in an artificial knee effusion study.\textsuperscript{4} Cryotherapy has been used with rehabilitative exercises to restore range of motion and return to normal activities at a quicker rate.\textsuperscript{8} Cryotherapy is thought to increase the activity of superficial mechanoreceptors and thermoreceptors in the skin, the afferent activity resulting from this is theorized to override inhibitory afferent signals being sent from an injured joint. Reduction or prevention of afferent inhibitory signals could potentially lead to a decrease in inhibition at the muscle.\textsuperscript{1}

One way to simulate muscle inhibition is to artificially induce joint swelling. Hopkins \textit{et al.}\textsuperscript{4} used this technique to assess the efficacy of disinhibitory modalities. Subjects were allocated into one of three groups, one received cryotherapy for 30 minutes, one received TENS for 30 minutes, and the third received no treatment to serve
as a control. Hoffmann reflex was used to measure motorneuron pool recruitment. Following a 30-minute treatment, both TENS and Cryotherapy groups showed the ability to disinhibit the knee joint. The cryotherapy group showed the ability to facilitate the MN beyond pre-effused levels.\(^4\)

In a similar study, Pietrosimone \textit{et al.}\(^8\) observed the effects of TENS and focal knee joint cooling on central activation ratio, a measurement of one’s ability to volitionally contract a muscle. The study consisted of three randomly allocated groups of individuals who were diagnosed with a history of tibiofemoral osteoarthritis. The cryotherapy group was subjected to 20 minutes of treatment, whereas the TENS group was subjected to 45 minutes of treatment, the control group was not exposed to an intervention. Before application of the intervention, baseline measurements were collected; outcomes were then obtained at 20, 30, and 45 minutes after initiation of the treatment. Upon completion it was found that the TENS group had a higher central activation ratio at 20, 30, and 45 minutes compared to the control group. At 20 and 45 minute the cryotherapy group was also higher than the control group. However, compared to the aforementioned study, there were no significant differences when comparing treatment groups. This information supports previous claims that both TENS and cryotherapy can individually reduce inhibition.\(^8\)

Previous theories \(^8,\text{\textit{11}}\) have suggested that the spinal reflex pathways mediate the impact these modalities have on increasing muscle activation. It is proposed that the influx of excitatory signals supersede afferent inhibitory signals, allowing for an increased activation of the motorneuron pool.\(^8,\text{\textit{11}}\) Other theories suggest that these modalities trigger mechanisms that descend from higher brain centers causing the
inhibition of Ib Interneurons and result in higher levels of activation.\textsuperscript{8} However, further research is needed to fully understand the exact mechanisms by which these modalities reduce inhibition. In order to compare the results of our proposed study to prior studies, our treatment protocol and time variables will reflect the previously mentioned studies.\textsuperscript{8,11} We will utilize a cryotherapy intervention; as ice is inexpensive, easy to use, easily accessible to clinicians, and has minimal adverse effects.\textsuperscript{1} In contrast to previous studies, we will focus on corticospinal excitability to assess the effects of cryotherapy on this pathway. If it is found that cryotherapy indeed has an effect on corticospinal pathways, it may spark further research on current and potential disinhibitory modalities. This could help clinicians address the need to disinhibit muscles before rehabilitation protocols, potentially leading to better outcomes post rehabilitation and an improved quality of life in the future.
Chapter 3

Methods

3.1 Study Design: Case-Control

Participants reported for two test sessions where they received the cryotherapy and control interventions. The order for the test session condition was randomized prior to participant enrollment and determined during the first session by opening a sealed, opaque envelope containing the assigned condition. Test sessions were conducted one-week apart during the same time of day. Outcome measures were recorded before the intervention (baseline) and at 10, 20, 35, and 50 minutes after the intervention is applied. The cryotherapy application was removed after 20 minutes. A curtain was erected over the subject’s legs to blind the investigator from the test condition.

3.2 Participants

People with AKP as well as healthy individuals were recruited for this study. After an AKP participant was enrolled, he/she was matched with a healthy control participant based on age, sex, body mass index and activity level measured by Tegner activity scale. Participants were recruited from local orthopedic and sports medicine clinics, the general
population at the University of Toledo, local running shops, local crossfit gyms, and a local running club.

Participants in the AKP group must have met one of the three inclusion criteria: 1) diagnosed with AKP by a physician, athletic trainer or physical therapist; 2) present with diffuse AKP for at least eight weeks; or 3) knee pain increases while performing at least one of the following activities: going up or down stairs, walking, running, squatting, or after sitting for a prolonged period of time. We measured outcomes on the symptomatic leg; in the event of bilateral symptoms we assessed the outcomes on the limb in which symptoms are worse.

Exclusion criteria included a previous history of lower extremity injury other than AKP, surgical procedures resulting in major structural changes to the knee joint, or currently receiving rehabilitation or had rehabilitation within the past year. Participants were excluded from the study if they: 1) had a history of concussion or head injury in the past 6 months; 2) history of stroke, cardiac condition, epilepsy, cranial neurosurgery, migraines, cancer in the brain or thigh musculature; 3) diagnosed psychiatric disorder; 4) had a cardiac pacemaker, implanted cardiac defibrillator or intracranial metallic clips; or 5) were currently pregnant/breastfeeding. Participants were instructed to refrain from consuming caffeine and acetaminophen for at least 12 hours prior to testing as these may influence TMS measures.

### 3.3 Sample Size Estimation

Based on a previous study on people with quadriceps dysfunction it is estimated that to achieve a power of 0.8 with an effect size of 0.5, that 22 total participants (11 per
group) will be needed. It is estimated that 30% of individuals will not have recordable TMS measures. Therefore, we aim to enroll at least 15 participants in each group (30 total). All participants will provide written, informed consent approved by the institutional review board at the University of Toledo prior to performing any of these proposed experiments. Testing will be conducted in the Musculoskeletal Health and Movement Sciences Laboratory at the University of Toledo.

3.4 Visual Analog Scale for Pain

Pain at the indicated time point was measured on a 10cm line labeled 0-10 with 10 being the worst pain imaginable and 0 indicating no pain. The participant drew a mark perpendicular to the line, indicating his/her current perceived pain level. Pain was assessed immediately prior to the application of the experimental condition as well as 10, 20, 35, and 50 minutes after its application.

3.5 Quadriceps Strength Assessment

Participants were positioned in a Biodex System 2 Pro dynamometer (Biodex Medical Systems, Shirley, NY) with the hips flexed to 85° and the knee flexed to 70° to allow placement of ice bags (Figure 3-1). The ankle was securely attached using an ankle cuff to allow for accurate torque readings. Participants were instructed to cross their arms over their chest during all trials to minimize upper extremity involvement. Following submaximal warm-up contractions at 25, 50, and 75%, participants were instructed to perform a series of quadriceps maximal volitional isometric contractions (MVICs). Visual feedback regarding real time torque output was provided using a custom written computer
program (Visual Basic, Redman, Washington). Participants performed MVICs until the peak torque generated during two trials is within 5% of each other. A maximum of five repetitions were performed with 60s rest between trials to minimize fatigue. The peak torque value over the maximal effort trials was normalized to participant body mass (Nm/kg) and used to quantify strength. Additionally, 5% of the non-normalized MVIC value was determined for use during TMS testing.

3.6 Transcranial Magnetic Stimulation Testing

Two 10mm, pre-gelled Ag-AgCl (EL503, BIOPAC Systems Inc) surface electromyography (EMG) electrodes were positioned 2cm apart over the vastus medialis. The hair over the collection sites was shaved and the skin over the recording electrode site debrided and cleaned with alcohol. Analog-to-digital signal conversion was processed with a 16-bit convertor (MP150, BIOPAC Systems Inc., Goleta CA, USA). Electromyography signals were sampled at 2000Hz with EMG amplification set at a gain of 1000Hz. Participants will wear a lycra swim cap with a coordinate grid mapped on it, which allows the investigator to optimally position the magnetic coil.

3.6.1 Optimal Stimulating Point Detection

Participants were instructed to perform an isometric knee extension contraction equivalent to 5% of their previously determined MVIC during delivery of all TMS stimuli. This was accomplished by the use of realtime visual feedback. To determine the optimal stimulating point, a double cone coil (Magstim Company, Wales, UK) was positioned over the vertex of the cranium and Magstim Rapid² (Magstim Company, Wales, UK) was used.
to produce a maximum magnetic stimulus of 1.4 Tesla. The coil was moved in a systematic manner starting from the coordinates (0,0) on the swim cap’s grid in the contralateral direction of the limb being tested. Two stimuli were delivered at each coordinate with the stimulator output at 55%. This continued until the coordinate where the greatest and most consistent MEP was identified. In the event that no MEPs were elicited, the stimulator output was increased in 5% increments until the optimal stimulating point was detected. All subsequent stimuli were delivered at this coordinate.

3.5.2 Motor Threshold Determination

Active motor threshold (AMT) was determined as the lowest stimulator output necessary to elicit at least 4/8 MEPs with an amplitude $\geq 100\mu V$.\textsuperscript{32} Sets of eight stimuli were delivered over the optimal stimulating point. Machine output was set initially at 55%. The stimulus intensity was increased or decreased for subsequent sets of stimuli based on the number of MEPs obtained during the previous set. For example, if eight MEPs were detected at 55%, machine output was decreased.

Once AMT was determined, one set of 8 stimuli at 120% were delivered. The MEP amplitudes from these stimuli were averaged and used to normalize paired pulse MEPs.

3.5.3 Paired Pulse Paradigms

Three paired pulse paradigms were conducted: short interval intracortical inhibition (SICI), long interval intracortical inhibition (LICI), and intracortical facilitation (ICF). Paired pulse testing involves the delivery of two stimuli, a conditioning followed by a test stimulus. For SICI and ICF the conditioning stimulus is a subthreshold stimulus,
while for LICI it is suprathreshold. In all three paradigms the conditioning stimulus is followed by a suprathreshold test stimulus. The stimuli were separated by various inter-stimulus intervals (ISIs; Table 3.1).

One set of 8 pairs of stimuli were delivered for each paradigm. The MEP amplitudes recorded during paired pulse testing were normalized to those recorded during single pulse testing at 120% AMT.

3.6 Intervention

Participants reported for two sessions separated by one week. Randomized test conditions of a cryotherapy intervention and a control intervention where the participant remained seated on the dynamometer were implemented. All previously described outcome measures were obtained prior to the test condition being applied and again 10, 20, 35, and 50 minutes following application of the test condition.

3.6.1 Cryotherapy Condition

For the cryotherapy intervention, participants received two, 1.5 L ice bags filled with crushed ice secured to the anterior and posterior aspects of the knee using an elastic bandage by an experienced clinician. The clinician was careful to avoid contact between the ice bag and the vastus medialis as much as possible for 20 minutes. Care was taken to place the ice over the joint and not the muscle so as not to interfere with EMG data collection. The investigator obtaining outcome measures was blinded to test condition, leaving the room during test condition application and using curtains to block the investigator’s view of the participant for the remainder of testing.
3.6.2 Control Condition

During the control intervention, participants were instructed to sit quietly on the dynamometer while curtains were positioned to block the view of the investigator and ensure blinding of the test condition.

3.7 Statistical Analysis

Baseline demographics (Age, Mass, Height, and Strength) were analyzed using independent t-tests. Separate mixed model analyses of variance (ANOVAs) with repeated measures on time were used to analyze pain, AMT, SICI, ICF, and LICI between and within condition (cryotherapy and control) and group (AKP and healthy) over time (baseline and 10, 20, 35, and 50 minutes). In the event of significant group by time interactions ($P<0.05$) for any dependent variable, post hoc t-tests were used to determine specific statistical differences. A priori alpha levels were set at $P<0.05$ for all inferential statistics. Cohen’s $d$ effect size and associated 95% CIs were calculated comparing cryotherapy and control sessions from both groups for each time point compared to baseline to provide an understanding of the magnitude of change in the MEP. Effect sizes were interpreted as $\geq 0.80$ was large, 0.50 to 0.79 as moderate, 0.49 to 0.20 as small and $<0.20$ as trivial. All statistics were evaluated using SPSS statistical software version 19.0 and Microsoft Excel.
Chapter 4

Results

4.1 Demographics

All baseline measurements were equal between groups with the exception of age. The mean age of the healthy population was older than that of the AKP group ($P=0.030$; Table 4.1).

4.2 Strength

Quadriceps strength did not differ between groups, within conditions, or over time (Table 4.2).

4.3 Transcranial Magnetic Stimulation Data

Cryotherapy Condition (Table 4.3, Figure 4-1)

There was not a significant group by time interaction for any TMS measures during the cryotherapy condition. Furthermore, there were no significant group main effects for SICI and LICI. However, there was a significant group-main effect for ICF ($P=0.050$). Post hoc testing revealed that during the cryotherapy condition AKP subjects had higher ICF values than that of the healthy group ($P=0.044$) at the 10 minute time interval. In addition, the effect sizes between baseline and each time point ranged from small to trivial with confidence intervals that crossed zero for both groups during both
conditions. However, there was one large effect size in the healthy group at 35 minutes ICF (0.83; -0.26; 1.92), but the confidence interval crossed zero.

Control Condition (Table 4.4, Figure 4-2)

There were no significant group by time interactions with the exception of LICI in the no cryotherapy/control condition ($P=0.025$). Post hoc t-tests revealed LICI was significantly lower at 35 minutes compared to baseline during the control session in the healthy participants ($P=0.042$). There were no significant time main effects for SICI or ICF. There were no significant time main effects for SICI or ICF. Furthermore, there were no significant group main effects. In addition, the effect sizes between baseline and each time point ranged from small to trivial with confidence intervals that crossed zero for both groups during both conditions with the exception of one large effect size in the healthy group at 50 minutes ICF (0.80; -0.29; 1.89), but the confidence interval crossed zero.

4.4 Pain

Cryotherapy Condition

During the cryotherapy condition, there was not a significant group by time interaction ($P=0.583$). In addition, there were no significant differences in pain between time intervals for either group when comparing cryotherapy and control conditions.

Control Condition

During the control condition, there was a significant group by time interaction ($P=0.001$), time-main effect ($P=0.001$), and group-main effect ($P=0.041$). Within the AKP group there was a significant increase in pain from baseline measures to the 20 minute time interval ($P=0.019$). Furthermore, at the 10 minutes ($P=0.016$), 20 minutes
(P=0.008), 35 minutes (P=0.047), and 50 minutes (P=0.027) time intervals, the AKP group saw significant increases in pain compared to their baseline measures during the control condition. Finally, when comparing baseline VAS pain scores to each time interval during the control condition, there was one moderate and one large effect size within the AKP group during (35 minutes: d=0.70; 50 minutes: d=0.82); however, both confidence intervals crossed zero. All other effects during each condition for both groups were considered trivial-small. (Table 4.5, Figure 4-3)
Chapter 5

Discussion

This study was conducted to investigate the effects of cryotherapy on quadriceps corticospinal and intracortical excitability in people with and without AKP. Overall, we observed minimal influence of the cryotherapy application on quadriceps corticospinal and intracortical excitability, with the exception of the ICF measures.

During the cryotherapy intervention, ICF was significantly higher in the healthy group compared to the AKP group at the 10 minute interval. The data suggest a minimal increase in ICF in the healthy group after initial cryotherapy application, indicating an increase in facilitation of the motor cortex. However, within the healthy group, this increase in ICF was not statistically significant. The increase in magnitude may elude to the notion that cryotherapy does not block inhibitory pathways but may allow for facilitation in healthy people. This notion may explain why a reduction in inhibition has been found in H-reflex and CAR studies following application of cryotherapy. It is important to note that the healthy group ICF values were lower than those previously collected in our laboratory. Previously, we examined agreement in TMS testing between investigators and sessions. We observed ICF values of 1.94 when using the same methods in a similar population of participants (unpublished data; Table 5.1). It is unclear why the ICF data are different between participant populations, it is possible that the
variability in the data is related to the small sample size. The data collected is hard to
determine.

There was a significant group by time interaction within the LICI outcomes. At 35
minutes we saw a significant decrease in LICI compared to baseline, suggesting an
increase in quadriceps intracortical inhibition. This finding occurred during the control
session; therefore, the change in LICI at the 35 minute time interval cannot be explained
by the intervention. This interaction is likely driven by the positive and negative
fluctuation of LICI within the healthy group. Furthermore, this finding is presumably a
result of variation within the testing. The amplitude of LICI MEPs seen in the population
we tested are congruent at baseline with that of previously recorded data (Table 5.1).

Contrary to our hypotheses, strength and pain did not change as a result of
cryotherapy application. Interestingly, however, during the control session the AKP
group reported significantly greater pain at each time interval compared to the healthy
group. Additionally, within the AKP there was a significant increase in pain between the
baseline and 20 minute time interval. It is a possibility that participants being seated with
their knee fixed at 70 degrees of flexion increased pain over time. Additionally,
participants performed several knee extension isometric contractions while they were
seated that may also have contributed to an increase in knee pain. The VAS scores in the
AKP group ranged from 1.96±2.13cm to 2.94±3.25cm over the control session. The
minimally clinically important difference for 10cm VAS evaluating worst pain in patients
with AKP is 2cm, which is close to the change in pain reported by our participants. The
amount of pain our participants reported can be classified as mild (0.5cm-4.4cm). It is
possible that had our participants been in more or less pain we would have seen a
different response to the cryotherapy intervention. Given the increase in pain observed during the control session and the possible reasons for this increase, it makes sense that cryotherapy application did not decrease pain. Any analgesic effects cryotherapy may have had on the knee could have been diminished by the testing position and repeated knee extension contractions that testing necessitated.

People with anterior knee pain have been found to have a higher magnitude of CAD as compared to ACLr and ACLd populations. Furthermore, these deficits happen bilaterally suggesting that CAD are not just reflexive in nature and may have contributions from higher brain centers. Fully understanding the etiology of CAD in the quadriceps could prove a useful tool in combating this impairment. This knowledge would change treatment strategies for patients following a variety of knee injuries, including those with knee OA, by enhancing rehabilitative techniques to adequately restore the quadriceps to full function. It has been suggested that reduced excitability of the corticospinal and intracortical pathways may be a contributing factor to CAD, though our data suggest otherwise. More research is needed to better understand these contributions.

Cryotherapy is an inexpensive, easily accessible, and easy to use modality. In addition, cryotherapy has been seen to have disinhibitory properties. Based on our results, a 20 minute application of cryotherapy to the knee joint did not significantly improve activation in either group. However, as discussed previously, ICF in the healthy group was higher than in the AKP group at 10 minutes of cryotherapy application. Though cryotherapy has an impact on spinal reflexive pathways, and, as such, influences muscle activation, there is no known influence of cryotherapy on corticospinal or
intracortical excitability. This may be related to the specific pathway that cryotherapy reduces pain, as well as, the pathways that induce inhibitory signals. Based on our data it would seem that these pathways have little overlap. While it is possible that cryotherapy promotes facilitation of the muscle, thereby “disinhibiting” it. Due to the small sample size and inherent variability in this measure we believe this outcome is likely the result of variability among participants.

There were several limitations associated with our study. Sample size estimations indicated that we would need 11 participants in each group (22 total) to achieve a power of 0.8. However, we were only able to recruit 13 total participants. Increasing our sample size to better parallel the sample size estimate may have changed the outcomes of our study. Further, three AKP participants had to be excluded from the results. One did not have recordable TMS data, one accidently received the same intervention, and the third failed to show up to the follow up session and could not be contacted to reschedule. It should also be noted that there were only two males who participated in this study, both as healthy participants, limiting the generalizability of our data. Currently these data are only applicable to females ages 18 to 23, with AKP, and no history of traumatic injury or surgery.

Conclusion

A Twenty minute application of cryotherapy did not influence intracortical excitability, muscle strength, or knee pain in participants with AKP. The results of this
study are promising, however, and suggest a possible influence of cryotherapy on intacortical facilitation of the quadriceps in healthy individuals. It is imperative to continue researching the effects of cryotherapy and other disinhibitory modalities for patients with AKP to improve rehabilitative outcomes and quality of life.
References


Figures and Tables

Table 2.1
Conditions that may increase the risk of adverse effects of TMS\textsuperscript{20}

<table>
<thead>
<tr>
<th>Condition</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy (effects on unborn child are unknown)</td>
<td>Personal or family history of seizures (including febrile seizures as an infant)</td>
</tr>
<tr>
<td>Metal implants in the head</td>
<td>Previous brain neurosurgery</td>
</tr>
<tr>
<td>Cardiac pacemakers</td>
<td>Unstable major medical conditions</td>
</tr>
<tr>
<td>Poorly-controlled migraine headaches</td>
<td>Medications that lower seizure threshold</td>
</tr>
<tr>
<td>History of majority head injury</td>
<td>Neurological disorders</td>
</tr>
<tr>
<td>History of stroke</td>
<td>Major psychiatric disorders</td>
</tr>
</tbody>
</table>

Figure 3-1
Participant Placement in Biodex: Participants will be seated with knees flexed to 70° of flexion and hips flexed to 85° flexion
Table 3.1
Paired Pulse Paradigms

<table>
<thead>
<tr>
<th>Paradigm</th>
<th>Conditioning Stimulus</th>
<th>Test Stimulus</th>
<th>ISI</th>
</tr>
</thead>
<tbody>
<tr>
<td>SICI</td>
<td>80% AMT</td>
<td>120% AMT</td>
<td>3ms</td>
</tr>
<tr>
<td>ICF</td>
<td>80% AMT</td>
<td>120% AMT</td>
<td>15ms</td>
</tr>
<tr>
<td>LICI</td>
<td>120% AMT</td>
<td>120% AMT</td>
<td>100ms</td>
</tr>
</tbody>
</table>

ISI= interstimulus interval; SICI= short interval intracortical inhibition; AMT: active motor threshold; ICF: intracortical facilitation; LICI: long interval intracortical inhibition

Table 4.1
Participant Baseline Demographics

<table>
<thead>
<tr>
<th>Participant Baseline Demographics (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Healthy (n=7)</td>
</tr>
<tr>
<td>----------------------------------------</td>
</tr>
<tr>
<td>Age (years)*</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Height (m)</td>
</tr>
<tr>
<td>Mass (kg)</td>
</tr>
<tr>
<td>BMI</td>
</tr>
<tr>
<td>Strength(N/kg)</td>
</tr>
<tr>
<td>Pain (cm on VAS)</td>
</tr>
</tbody>
</table>

*Healthy significantly older at baseline
### Table 4.2
Quadriiceps Maximal Voluntary Isometric Strength

<table>
<thead>
<tr>
<th></th>
<th>Healthy Group N=7</th>
<th>Anterior Knee Pain Group N=6</th>
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<tr>
<td></td>
<td>Baseline 35 minutes</td>
<td>Baseline 35 minutes</td>
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<tr>
<td>Mean±SD</td>
<td>Mean±SD Effect Size (LL, UL)</td>
<td>Mean±SD Effect Size (LL, UL)</td>
</tr>
<tr>
<td>No Cryotherapy</td>
<td>2.36±0.51</td>
<td>2.43±0.54 0.14 (-0.91,1.19)</td>
</tr>
<tr>
<td>Condition</td>
<td></td>
<td>2.58±0.58 -0.017 (-1.31,0.96)</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>2.40±0.51</td>
<td>2.34±0.46 -0.12 (-1.17,0.93)</td>
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<tr>
<td>Condition</td>
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<td>2.44±0.68 -0.04 (-1.18,1.09)</td>
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</table>
Table 4.3
Effects of Cryotherapy on Paired Pulse Measures Over Time in Both Healthy and Anterior Knee Pain Groups
Cohen’s d Effect Sizes with 95% Confidence Intervals

<table>
<thead>
<tr>
<th>TMS Measure</th>
<th>Healthy Group N=7</th>
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<th>Anterior Knee Pain Group N=6</th>
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<th>Mixed-Model ANOVA</th>
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<tr>
<td></td>
<td>Cryotherapy Condition Over Time</td>
<td></td>
<td>Cryotherapy Condition Over Time</td>
<td></td>
<td>Time-Main Effect</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>10 minutes</td>
<td>20 minutes</td>
<td>35 minutes</td>
<td>50 minutes</td>
</tr>
<tr>
<td>SICI</td>
<td>Mean±SD Effect Size (LL, UL)</td>
<td>Mean±SD Effect Size (LL, UL)</td>
<td>Mean±SD Effect Size (LL, UL)</td>
<td>Mean±SD Effect Size (LL, UL)</td>
<td>Mean±SD Effect Size (LL, UL)</td>
</tr>
<tr>
<td>0.51±0.43</td>
<td>0.65±0.23</td>
<td>0.63±0.26</td>
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<tr>
<td></td>
<td>(.33,1.38)</td>
<td>(-.73,1.38)</td>
<td>(-1.06,1.04)</td>
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<td>(-1.36,0.91)</td>
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<tr>
<td>ICF</td>
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<td>1.41±0.74</td>
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<tr>
<td></td>
<td>(.72,1.39)</td>
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<td>(.51,1.57)</td>
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<td>(.79,1.00)</td>
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<tr>
<td>LICI</td>
<td>0.51±0.31</td>
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<td>0.60±0.60</td>
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<td>(.21,1.84)</td>
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<td>(-1.46,0.65)</td>
<td>(.01,1.12)</td>
<td>(-1.27,0.99)</td>
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</table>

Effect sizes were calculated comparing baseline measurements to each time point
SICI= Short Intracortical Inhibition, LICI= Long Intracortical Inhibition, ICF= Intracortical Facilitation

#ICF significantly higher in Healthy at 10 minutes
§ ICF significantly higher in Healthy

**Figure 4-1**
Effects of Cryotherapy on ICF between Groups Over Time
Table 4.4
Effects of No Cryotherapy on Paired Pulse Measures Over Time in Both Healthy and Anterior Knee Pain Groups
Cohen’s d Effect Sizes with 95% Confidence Intervals

<table>
<thead>
<tr>
<th>TMS Measure</th>
<th>Healthy Group N=7</th>
<th>Anterior Knee Pain Group N=6</th>
<th>Mixed-Model ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
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<td>No Cryotherapy Condition Over Time</td>
<td>No Cryotherapy Condition Over Time</td>
<td>Time-Main Effect</td>
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<td>20 minutes</td>
</tr>
<tr>
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<td>Mean±SD</td>
<td>Mean±SD</td>
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<td>(-1.30,0.80)</td>
<td>(-0.69,1.43)</td>
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<tr>
<td>ICF</td>
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<td>LICI</td>
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<td>(-1.50,0.62)</td>
<td>(-1.12,0.98)</td>
<td>(-1.59,0.54)</td>
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</table>

Effect sizes were calculated comparing baseline measurements to each time point
SICI = Short Intracortical Inhibition, LICI = Long Intracortical Inhibition, ICF = Intracortical Facilitation
*Significant group by time interaction
βLICI significantly lower than baseline during control

**Figure 4-2**  
The Effects of Cryotherapy on LICI in Healthy Individuals Over Time
## Table 4.5
Pain Over Time for Cryotherapy and Control Interventions

<table>
<thead>
<tr>
<th>VAS in cm</th>
<th>Healthy Group N=7</th>
<th>Anterior Knee Pain Group N=5</th>
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<tr>
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<td>Mean±SD</td>
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<td>(LL, UL)</td>
<td>(LL, UL)</td>
<td>P-value</td>
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<td></td>
<td>(LL, UL)</td>
<td>(LL, UL)</td>
<td>P-value</td>
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<tr>
<td></td>
<td>Mean±SD Effect Size</td>
<td>Mean±SD Effect Size</td>
<td>P-value</td>
</tr>
<tr>
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<td>0±0</td>
<td>.393</td>
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<tr>
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<td>0±0</td>
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<td>.144</td>
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<td></td>
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<td>.02±0.24</td>
<td>.583</td>
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<tr>
<td></td>
<td>1.44±2.31</td>
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<td>.001</td>
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<tr>
<td>10 minutes</td>
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</table>

†Pain significantly increased compared to baseline at each time point in the AKP control session
§Pain was significantly higher in the AKP in the control session than in the healthy
†Pain was significantly higher than baseline and healthy
**Figure 4-3**
The Effects of the Control Intervention on Pain between Groups Over Time

# AKP in significantly more pain compared to healthy group
*AKP had significantly higher pain compared to baseline
Table 5.1
Unpublished TMS

<table>
<thead>
<tr>
<th></th>
<th>AMT</th>
<th>SICI</th>
<th>ICF</th>
<th>LICI</th>
</tr>
</thead>
<tbody>
<tr>
<td>OA</td>
<td>46.50±7.85</td>
<td>0.52±0.27</td>
<td>2.17±0.97</td>
<td>0.36±0.21</td>
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<tr>
<td>I1 S1</td>
<td>43.00±8.82</td>
<td>0.80±0.55</td>
<td>1.96±1.40</td>
<td>0.55±0.52</td>
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<td>I1 S2</td>
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<td>0.77±0.43</td>
<td>1.49±0.46</td>
<td>0.82±0.82</td>
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<td>I2 S1</td>
<td>43.00±8.82</td>
<td>0.85±0.69</td>
<td>1.92±1.11</td>
<td>0.55±0.52</td>
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<tr>
<td>I2 S2</td>
<td>41.38±7.97</td>
<td>0.79±0.41</td>
<td>1.66±0.44</td>
<td>0.79±0.63</td>
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</table>
Appendix A

Consent Forms
ADULT RESEARCH SUBJECT INFORMATION AND CONSENT FORM

The Effects of Cryotherapy on Quadriceps Corticomotor Excitability in Patients with Patellofemoral Pain

Principal Investigator: Michael Tevald PT, PhD

Other Staff: Michelle McLeod MA, ATC (Study Coordinator)
Robert Kunisch ATC (Co-Investigator)
Dr. David Sohn MD/JD (Co-Investigator)
Luke Donovan, PhD, ATC (Co-Investigator)

Contact Phone number(s): (419) 530-6673

What you should know about this research study:

- We give you this consent/authorization form so that you may read about the purpose, risks, and benefits of this research study. All information in this form will be communicated to you verbally by the research staff as well.
- Routine clinical care is based upon the best-known treatment and is provided with the main goal of helping the individual patient. The main goal of research studies is to gain knowledge that may help future patients.
- We cannot promise that this research will benefit you. Just like routine care, this research can have side effects that can be serious or minor.
- You have the right to refuse to take part in this research, or agree to take part now and change your mind later.
- If you decide to take part in this research or not, or if you decide to take part now but change your mind later, your decision will not affect your routine care.
- Please review this form carefully. Ask any questions before you make a decision about whether or not you want to take part in this research. If you decide to take part in this research, you may ask any additional questions at any time.
- Your participation in this research is voluntary.

PURPOSE (WHY THIS RESEARCH IS BEING DONE)
You are being asked to take part in a research study looking at nerve and muscle function of the leg. The purpose of the study is to determine if ice applied to your knee can change the way your nerves function to control muscles in your leg.
You were selected as someone who may want to take part in this study because you have patellofemoral (knee joint) pain, or you are a generally healthy individual. Up to 50 participants may be enrolled in this study at the University of Toledo.

**DESCRIPTION OF THE RESEARCH PROCEDURES AND DURATION OF YOUR INVOLVEMENT**

If you decide to take part in this study, you will be asked to report to the Musculoskeletal Health and Movement Science (MHMS) Laboratory in the Health and Human Services building (Room 1409). You will be asked to fill out an Exclusion Criteria Screening Sheet regarding your history of knee pain and rehabilitation of your lower extremity; joint hypermobility or connective tissue disorders; concussion or head injuries; stroke; heart condition; cranial neurosurgery; epilepsy; migraines; cancer in the brain or thigh musculature; diagnosed psychiatric disorder; cardiac pacemaker; implanted cardiac defibrillator; cochlear implants; and/or intracranial metallic clips.

After completing the Exclusion Criteria Screening Sheet, we will then test the neural function of your thigh musculature using **corticomotor testing**. There will be two test sessions 7-10 days apart lasting approximately 2 hours each. In one session ice will be applied to your knee for 20 minutes (see “Cryotherapy Intervention”). During the other session you will receive no cryotherapy intervention. The order of testing (cryotherapy vs. control) will be randomized. Corticomotor testing will be conducted prior to the application of the cryotherapy or control intervention, and will be repeated at 10, 20, 35 and 50 minutes after initial application. Below is a table illustrating the timeline for each session. The procedures are explained in depth below.

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Procedures</th>
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<tbody>
<tr>
<td>Arrival</td>
<td>Screening and consent (session 1 only)</td>
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<tr>
<td><strong>Baseline</strong></td>
<td>Preparation</td>
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<td></td>
<td>Muscle Strength Testing</td>
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<td></td>
<td>Brain Mapping</td>
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<td></td>
<td>Motor Threshold Determination</td>
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<tr>
<td></td>
<td>Single Pulse Testing</td>
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<td>Paired Pulse Testing</td>
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<td></td>
<td>Pain Assessment</td>
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<tr>
<td><strong>Intervention</strong></td>
<td>Cryotherapy vs. Control</td>
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<tr>
<td>10 Minutes Post Application of</td>
<td>Motor Threshold Determination</td>
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<tr>
<td>Intervention</td>
<td>Single Pulse Testing</td>
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<td>Pain Assessment</td>
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<td>20 Minutes Post Application of</td>
<td>Muscle Strength Testing</td>
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<td>Intervention</td>
<td>Motor Threshold Determination</td>
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<td>Pain Assessment</td>
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<td>Pain Assessment</td>
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</table>
Outcome Measures

Corticomotor Testing
This testing uses a tool called Transcranial Magnetic Stimulation to provide us with important information regarding how your brain communicates with the muscles in your thigh. We will place a special coil on your head to deliver very brief magnetic pulses through your skull to the area of the brain that controls your thigh muscles. The stimulation is not painful, but you may experience mild discomfort, and you will feel a brief contraction of the muscles in your thigh. The testing consists of several parts, which are described below. Total testing time will be approximately 2 hours.

Preparation
You will lie back in the chair of a dynamometer, which we will use to measure the strength of your thigh muscles. You will lie with your hands across your chest. Stickers (electrodes) will be placed on the skin overlaying the muscles of your legs to allow us to record the electrical activity of your muscles. We will position a special magnetic coil over the area of the scalp that corresponds with the target muscle and adjust the position of the coil until it is in the right spot. You will wear a swim cap on your head to allow us to make markings as necessary to ensure the coil remains in the same place. You will also be provided ear plugs to protect your ears from the noise associated with the delivery of the magnetic stimulus.

Each testing session will include the following measures of transcranial magnetic stimulation (TMS):
1) Muscle strength testing
2) Brain mapping
3) Motor threshold determination
4) Single pulse testing
5) Paired pulse testing

Muscle Strength Testing
This test helps the researchers determine how strong your thigh muscles are. This will be used to determine how hard you need to contract your thigh muscle during the magnetic stimulation testing. For this test, you will be asked to contract your thigh muscle as hard as you can and hold it for 5 seconds. You will be asked to perform this test no more than 5 times. You will be provided a warm up period and ample rest time between efforts. This test will take approximately 10 minutes.

Brain Mapping
This process helps the researchers find the best spot to place the coil on your head, called the optimal stimulating point. For this test, you will sit quietly in a chair while we move the magnetic coil around a small area of your scalp to stimulate different areas of your brain in order to find the area that best corresponds to your thigh muscle. This process will take approximately 10 minutes.

Motor Threshold Determination
This process helps the researchers determine at what machine intensity to perform the testing. For this test, you will sit quietly in a chair while the researcher places the coil over your optimal stimulating point. Sets of 8 magnetic stimuli will be delivered to your brain. The intensity of the stimulus will be varied up and down with each set until the researchers find the lowest intensity possible that makes your muscle contract 4 out of 8 times during a set. You may be asked to lightly (20%) contract your thigh muscle during this test. This process will take approximately 60 minutes.
Single Pulse Testing
The data collected during this test are used to normalize the rest of the data collected. Your thigh muscle contractions during this test help the researchers to interpret the data collected during your thigh muscle contractions in the other tests. The researcher will place the coil over your optimal stimulating point. Sets of 8 stimuli will be delivered. The intensity of the stimulus will be set to approximately 120% of your motor threshold, which was determined above. You may be asked to lightly (20%) contract your thigh muscle during this test. This process will take approximately 20 minutes.

Paired Pulse Testing
The data collected during this test tells the researchers about how your brain is controlling your thigh muscles. The researcher will place the coil over the optimal stimulating point. Sets of 8 pairs of stimuli will be delivered. The intensity of the stimuli will be based on your motor threshold and the time between the pairs of stimuli will vary between 1 and 100 milliseconds. You may be asked to lightly (20%) contract your thigh muscle during this test. This process will take approximately 30 minutes.

Pain Assessment
Throughout the testing procedure we will provide a sheet for you to mark the amount of pain or discomfort you are experiencing. The pain scale will be a 10 cm line. The far right of the line represents the most pain imaginable and the left side represents no pain at all. You will be asked to make a mark on that line during the testing procedures.

Cryotherapy Intervention
For the cryotherapy (ice) intervention, you will have two, 1.5 liter icebags secured to the front and back of your knee for 20 minutes. You will remain positioned in a dynamometer for the intervention process.

Control Session
For the control session, you will be asked to sit quietly for 20 minutes in the same position as discussed for the cryotherapy intervention.

RISKS AND DISCOMFORTS YOU MAY EXPERIENCE IF YOU TAKE PART IN THIS RESEARCH

**Likely Risks**
- Mild discomfort for a very brief period during the magnetic stimulation.
- Mild discomfort from the ice during the intervention.

**Less Likely Risks**
- Mild, transient skin irritation from the sticky electrodes.
- Minor discomfort (tinnitus or aural fullness) from noise associated with the magnetic stimulation pulse. To minimize this risk, you will wear ear plugs to wear during testing. Hearing loss has also been reported, but only in patients given repetitive magnetic stimulation to treat disorders such as depression. You will not be receiving repetitive magnetic stimulation.

**Very Unlikely Risks**
- Mild, transient headache following magnetic stimulation
- In people with a history of seizures there is a rare possibility of causing a seizure with the magnetic stimulation. You must tell us prior to testing if you have ever had a seizure so we can exclude you from the study.
disclose information that was obtained prior to the cancellation as necessary to maintain the integrity of the research study.

Except as noted in the above paragraph, your permission for us to use and disclose your protected health information will stop at the end of the research study. A more complete statement of University of Toledo's Privacy Practices is set forth in its Joint Notice of Privacy Practices. If you have not already received this Notice, a member of the research team will provide this to you. If you have any further questions concerning privacy, you may contact the University of Toledo's Privacy Officer at 419-383-6933.

IN THE EVENT OF A RESEARCH-RELATED INJURY
In the event of injury resulting from your taking part in this study, treatment can be obtained at a health care facility of your choice. You should understand that the costs of such treatment will be your responsibility. Financial compensation is not available through The University of Toledo or The University of Toledo Medical Center.

By signing this form you are not giving up any of your legal rights as a research subject. In the event of an injury, please contact Robert Kunisch, ATC (419) 577-7401 this line will be available for calls 24 hours a day.

VOLUNTARY PARTICIPATION
Taking part in this study is voluntary. You may refuse to participate or discontinue participation at any time without penalty or a loss of benefits to which you are otherwise entitled. If you decide not to participate or to discontinue participation, your decision will not affect your future relations with the University of Toledo or The University of Toledo Medical Center.

NEW FINDINGS
You will be notified of new information that might change your decision to be in this study if any becomes available.

ADDITIONAL ELEMENTS
There is no other additional information for this study.

Continued on Next Page
OFFER TO ANSWER QUESTIONS
Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think it over. If you have questions regarding the research at any time before, during or after the study, you may contact Dr. Michael Tevald, PT, Ph.D. at (419) 530-6673.

If you have questions beyond those answered by the research team or your rights as a research subject or research-related injuries, please feel free to contact the Chairperson of the University of Toledo Biomedical Institutional Review Board at 419-383-6796.

SIGNATURE SECTION (Please read carefully)

YOU ARE MAKING A DECISION WHETHER OR NOT TO PARTICIPATE IN THIS RESEARCH STUDY. YOUR SIGNATURE INDICATES THAT YOU HAVE READ THE INFORMATION PROVIDED ABOVE, YOU HAVE HAD ALL YOUR QUESTIONS ANSWERED, AND YOU HAVE DECIDED TO TAKE PART IN THIS RESEARCH.

BY SIGNING THIS DOCUMENT YOU AUTHORIZE US TO USE OR DISCLOSE YOUR PROTECTED HEALTH INFORMATION AS DESCRIBED IN THIS FORM.

The date you sign this document to enroll in this study, that is, today's date, MUST fall between the dates indicated on the approval stamp affixed to the bottom of each page. These dates indicate that this form is valid when you enroll in the study but do not reflect how long you may participate in the study. Each page of this Consent/Authorization Form is stamped to indicate the form’s validity as approved by the UT Biomedical Institutional Review Board (IRB).

Name of Subject (please print) __________________________ Signature of Subject or Person Authorized to Consent __________________________ Date __________________________ a.m. __________________________ p.m. __________________________

Relationship to the Subject (Healthcare Power of Attorney authority or Legal Guardian) __________________________

Name of Person Obtaining Consent (please print) __________________________ Signature of Person Obtaining Consent __________________________ Date __________________________

Name of Witness to Consent Process (when required by ICH Guidelines) (please print) __________________________ Signature of Witness to Consent Process (when required by ICH Guidelines) __________________________ Date __________________________

YOU WILL BE GIVEN A SIGNED COPY OF THIS FORM TO KEEP.
The Effects of Cryotherapy on Quadriceps Corticorotor Excitability in Patients with Patellofemoral Pain

Information Sheet

This study involves the use of a device known as transcranial magnetic stimulation (TMS). Three types of TMS testing can be performed: single pulse, paired pulse, and repetitive TMS. During single pulse testing, only one stimulus is delivered to you, the participant, at a time. During paired pulse testing, two stimuli are delivered at a time. During repetitive TMS testing, multiple stimuli are delivered at a time.

All types of TMS testing have been shown to be safe for use with human participants. While this study DOES NOT use repetitive TMS, the investigators would like to make you aware of some added risk associated with repetitive TMS testing. These include hearing loss and increased risk of seizures. Hearing loss has only been demonstrated as a result of testing performed on animals and has never been shown in humans. Seizures as a result of repetitive TMS testing have only been caused in people who have a personal history of seizure disorder.

Regardless, it is important that you make the investigators aware if you are taking any of the following medications that may lower your seizure threshold (make you more at risk for having a seizure as a result of repetitive TMS testing). These medications include:

- Amitriptyline
- Amoxicillin
- Anticholinergics
- Antihistamines
- Arabinoside
- Arquiprazole
- BCNU
- Bupropion
- Cefuroximine
- Chloramphenicol
- Chloroquine
- Chloropromazine
- Citalopram
- Clozapine
- Cyclophosphamide
- Cytosine
- Doxepine
- Duloxetine
- Fluoxetine
- Fluphenazine
- Fluvoxamine
- Foscarnet
- Ganciclovir
- Haloperidol
- Imipenem
- Imipramine
- Isoniazid
- Levofoxacin
- Lithium
- Maprotiline
- Mefloquine
- Methotrexate
- Metronidazole
- Mianserin
- Mirtazapine
- Norpramiline
- Olanzapine
- Paroxetine
- Penicillin
- Pimozide
- Quetiapine
- Reboxetine
- Risperidone
- Ritonavir
- Sertraline
- Sympathomimetics
- Venlafaxine
- Vincristine
- Ziprasidone

- Alcohol
- Amphetamines
- Angel's dust
- Cocaine
- Ecstasy
- Gamma-hydroxybutyrate (GHB)
- Ketamine
- MDMA
- PCP
- Phencyclidine
- Theophylline

Assigned Version Date 08/25/2014
Additionally, withdrawal from any of the following drugs can significantly lower your seizure threshold. It is important to let the investigators know if you are withdrawing from any of the following substances:

Alcohol
Barbiturates
Benzodiazepines
Chloral hydrate
Meprobamate
Appendix B

Data Collection Forms
TEGNER ACTIVITY LEVEL SCALE

Please indicate in the spaces below the HIGHEST level of activity that you participated in BEFORE YOUR INJURY and the highest level you are able to participate in CURRENTLY.

BEFORE INJURY:  Level_________  CURRENT:  Level_________

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<thead>
<tr>
<th>Level</th>
<th>Activity</th>
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<tr>
<td>Level 10</td>
<td>Competitive sports- soccer, football, rugby (national elite)</td>
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<tr>
<td>Level 9</td>
<td>Competitive sports- soccer, football, rugby (lower divisions), ice hockey,</td>
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<tr>
<td></td>
<td>wrestling, gymnastics, basketball</td>
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<tr>
<td>Level 8</td>
<td>Competitive sports- racquetball or bandy, squash or badminton, track and</td>
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<tr>
<td></td>
<td>field athletics (jumping, etc.), down-hill skiing</td>
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<tr>
<td>Level 7</td>
<td>Competitive sports- tennis, running, motorcars speedway, handball</td>
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<tr>
<td></td>
<td>Recreational sports- soccer, football, rugby, bandy, ice hockey, basketball,</td>
</tr>
<tr>
<td></td>
<td>squash, racquetball, running</td>
</tr>
<tr>
<td>Level 6</td>
<td>Recreational sports- tennis and badminton, handball, racquetball, down-hill</td>
</tr>
<tr>
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<td>skiing, jogging at least 5 times per week</td>
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<tr>
<td>Level 5</td>
<td>Work- heavy labor (construction, etc.)</td>
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<tr>
<td></td>
<td>Competitive sports- cycling, cross-country skiing,</td>
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<td></td>
<td>Recreational sports- jogging on uneven ground at least twice weekly</td>
</tr>
<tr>
<td>Level 4</td>
<td>Work- moderately heavy labor (e.g. truck driving, etc.)</td>
</tr>
<tr>
<td>Level 3</td>
<td>Work- light labor (nursing, etc.)</td>
</tr>
<tr>
<td>Level 2</td>
<td>Work- light labor</td>
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<tr>
<td>Level 1</td>
<td>Walking on uneven ground possible, but impossible to back pack or hike</td>
</tr>
<tr>
<td>Level 0</td>
<td>Work- sedentary (secretarial, etc.)</td>
</tr>
<tr>
<td></td>
<td>Sick leave or disability pension because of knee problems</td>
</tr>
</tbody>
</table>


SURGICAL HISTORY

Have you had any additional surgeries to your knee other than those performed by Dr. Stone?

Yes / No

If Yes:

What procedure(s) were performed?

____________________________________________________________________________________

When was the surgery performed?

____________________________________________________________________________________

Who performed the surgery?

____________________________________________________________________________________

Assigned Version Date: 10/01/2014
APPENDIX

ANTERIOR KNEE PAIN (Sheet code: __________________)

Name: ___________________________ Date: __________________

Age: ________

Knee: L/R

Duration of symptoms: ______ years ______ months

For each question, circle the latest choice (letter), which corresponds to your knee symptoms.

1. Limp
   (a) None (5)
   (b) Slight or periodical (3)
   (c) Constant (0)

2. Support
   (a) Full support without pain (5)
   (b) Partial (3)
   (c) Weight bearing impossible (0)

3. Walking
   (a) Unlimited (5)
   (b) More than 2 km (2)
   (c) 1-2 km (2)
   (d) Unable (0)

4. Stairs
   (a) No difficulty (10)
   (b) Slight pain when descending (8)
   (c) Pain both when descending and ascending (5)
   (d) Unable (0)

5. Squatting
   (a) No difficulty (5)
   (b) Repeated squatting painful (4)
   (c) Painful each time (3)
   (d) Possible with partial weight bearing (2)
   (e) Unable (0)

6. Running
   (a) No difficulty (10)
   (b) Pain after more than 2 km (8)
   (c) Slight pain from start (6)
   (d) Severe pain (5)
   (e) Unable (0)

7. Jumping
   (a) No difficulty (10)
   (b) Slight difficulty (7)
   (c) Constant pain (2)
   (d) Unable (0)

8. Prolonged sitting with the knees flexed
   (a) No difficulty (10)
   (b) Pain after exercise (8)
   (c) Constant pain (5)
   (d) Pain forces to extend knees temporarily (4)
   (e) Unable (0)

9. Pain
   (a) None (10)
   (b) Slight and occasional (8)
   (c) Interferes with sleep (6)
   (d) Occasionally severe (3)
   (e) Constant and severe (0)

10. Swelling
    (a) None (10)
    (b) After severe exertion (8)
    (c) After daily activities (6)
    (d) Every evening (4)
    (e) Constant (0)

11. Abnormal painful kneecap (patellar) movements (subluxations)
    (a) None (10)
    (b) Occasionally in sports activities (6)
    (c) Occasionally in daily activities (4)
    (d) At least one documented dislocation (2)
    (e) More than two dislocations (0)

12. Atrophy of thigh
    (a) None (5)
    (b) Slight (3)
    (c) Severe (0)

13. Flexion deficiency
    (a) None (5)
    (b) Slight (3)
    (c) Severe (0)


Signed Version Date: 08/20/2012

Approved by UNIVERSITY OF TOLEDO IRB
Musculoskeletal Health and Movement Sciences Laboratory
Transcranial Magnetic Stimulation (TMS) Screening Questionnaire

1. Height: _______ Weight: _______ BMI: _______ (calculated by investigators)
2. Do you currently have pain in either knee? Yes No
   a. If yes, please rate your pain from 0 to 10 (0= no pain, 10= worst pain imaginable)
   b. Left: _______/10 Right: _______/10
3. Do you currently have any pain or medical conditions that limit your function? Yes No
   a. If yes, please describe ______________________________________________________

4. Do you smoke? Yes No
5. Do you have any of the following conditions:
   a. Fibromyalgia Yes No
   b. Diabetes Yes No
   c. Peripheral neuropathy (numbness, tingling, loss of sensation in hands or feet) Yes No
   d. Heart disease Yes No
   e. Migraine headaches Yes No
6. Do you have any metal implants anywhere in your head, neck, or shoulders (excluding dental work)? Yes No
7. Do you or any immediate family members have a history of seizures or epilepsy? Yes No
8. Has your physician ever diagnosed you with a neurologic disorder such as Parkinson’s disease, Multiple Sclerosis, or stroke? Yes No
9. Do you have any of the following in your body:
   a. Foreign objects in your eyes Yes No
   b. Cochlear (ear) implants Yes No
   c. Implanted brain stimulator Yes No
   d. Aneurysm clip Yes No
   e. Implanted medication pump Yes No
   f. Cardiac pacemaker Yes No
   g. Intra-cardiac lines Yes No
10. Is there a chance you could be pregnant? Yes No
PATELLOFEMORAL PAIN EVALUATION FORM

HISTORY

Mechanism of Injury: Overuse  Traumatic  Other______________
Where is the pain?______________________________
How long have you had pain?__________________________
When do you have pain?______________________________
Describe the pain:______________________________
Do you run? Yes  No  If so, how many miles per week?___________ miles
Do have pain while running? Yes  No  If so, how far into the run?___________ min
What was your running mileage prior to injury?___________ miles
Do you have a history of lower extremity surgery or injury?

Do you have pain anywhere else? Any other joints?

OBSERVATION

+  -  Edema  +  -  Ecchymosis
+  -  Quadriceps atrophy  +  -  Scars
Gait (excess pronation, etc):______________________________
Squat (excess IR, etc):______________________________

PALPATION

Peri-Patella + -
Retro-Patella/Facets + -
Patellar facets + -
Plica + -
Joint line + -
Patellar/Quad tendon + -
Distal IT band + -
Gerdy’s Tubercle + -
ROM/STRENGTH

Knee extension
  Seated
  Prone
Hip flexion
Hip extension
Hip adduction
Hip IR

SPECIAL TESTS

Patellar tilt test  + -
Patellar compression test (scour)  + -
Clarke’s Sign  + -
Valgus/MCL  + -
Varus/LCL  + -
Lochmans/Anterior drawer  + -
McMurrays  + -
Patellar glides (r/o instability)  

OTHER NOTES

________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

APPROVED BY
UNIVERSITY OF TOLEDO IRB

Assigned Version Date: 08/20/2012
Central Activation Ratio Data Collection Form

Subject # _______________  Date _______________  Leg Tested First ______

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<tr>
<th>Practice MVIC</th>
<th>Right Leg</th>
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*UT IRB #108082
Pt. Thomas, AC
Version Date: 10/24/12*
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+ = MEP; - = too low to be MEP; ↑=value higher than average; ↓= value lower than average
Subject: ________
Date: ________

Control Condition

Mark the spot that best represents your injured knee pain at rest

Absolutely
No Pain

Worst Pain
Imaginable

Assigned Version Date: 08/20/2012
Mark the spot that best represents your injured knee pain after 10 minutes.

Absolutely

No Pain

Worst Pain

Imaginable
Mark the spot that best represents your injured knee pain after 20 minutes.

Absolutely
No Pain


Worst Pain
Imaginable
Mark the spot that best represents your injured knee pain after 35 minutes.

Absolutely
No Pain

Worst Pain
Imaginable
Mark the spot that best represents your injured knee pain after 50 minutes

<table>
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<tr>
<th>Absolutely No Pain</th>
<th>Worst Pain Imaginable</th>
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Assigned Version Date: 08/20/2012