A Thesis

entitled

Neuromuscular Measures in Female Patients with Knee Osteoarthritis: A Pilot Study

by

Devon M. Eley

Submitted to the Graduate Faculty as partial fulfillment of the requirements for the

Master of Science Degree in Exercise Science

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Luke Donovan, PhD, ATC, Committee Chair

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Abbey Thomas, PhD, ATC, Committee Member

_____

Michele Pye, PhD, ATC, Committee Member

_____

Dr. Patricia Komuniecki, Dean
College of Graduate Studies

The University of Toledo

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An Abstract of

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Context: Symptomatic knee osteoarthritis (OA) affects 12.1% of adults over the age of 60 in the United States, making OA the leading cause of disability for older adults in the U.S. OA is a degenerative disease characterized by joint space narrowing, development of osteophytes, and articular cartilage degeneration. Symptoms associated with knee OA include pain, loss of motion, and decreased functional ability. These factors lead to disability, decreased quality of life, and a higher risk of comorbidities including obesity and cardiovascular disease. OA has been shown to also affect voluntary quadriceps strength and activation, further impairing function and quality of life. These neuromuscular alterations affecting the injured joint are referred to as central activation deficits (CAD). This affects the ability to activate motor neurons around the joint for recruitment during normal muscular contractions. This results in decreased muscle contraction capabilities and becomes a problem when these deficits persist and limit the ability to regain optimal muscle function. However, it is not fully understood how these deficits contribute to and worsen knee OA. **Objective**: To understand how knee OA influences quadriceps strength and central activation. Additionally, we sought to determine if a group-based exercise intervention could augment CAD in women with

knee OA. **Design**: Pilot investigation with an embedded case series. **Setting**: Research laboratory. **Methods:** Baseline demographics were recorded on all participants. Baseline MVIC and CAR were measured using the burst superimposition technique. Baseline TMS measures (AMT, SICI, LICI, ICF) were calculated. Participants completed the 8-week therapeutic exercise intervention. Follow-up MVIC and CAR were recorded. **Participants**: Nine patients (age=57.11±5.28, height=1.71±0.06m, mass=90.52±22.58kg, BMI=30.81±6.69) completed baseline strength and CAD measures. Three patients (age=59.67±2.89, height=1.70±0.00m, mass=85.13±8.95kg, BMI=29.46±3.10) completed baseline strength and CAD testing followed by the 8-week therapeutic exercise intervention and follow-up testing. **Results**: At baseline, quadriceps strength was 1.70±0.74 Nm/kg and CAR was 0.97±0.03. TMS measures at baseline were: AMT=46.50±7.85%, SICI=0.52±0.27, ICF=2.17±0.97, and LICI=0.36±0.21.For the subset of women who completed the intervention, strength decreased from baseline to follow-up (2.22±0.83 Nm/kg and 1.67±0.67 Nm/kg, respectively), while CAR remained relatively unchanged 0.99±0.01 and 0.97±0.03.

Conclusions: Results show similarities among TMS between this and other studies done on this type of patient population. Quadriceps strength decreased after an 8-week therapeutic exercise intervention, which is counterintuitive. Additional studies are required to further understand the role of quadriceps central activation in the osteoarthritic process so that appropriate interventions can be developed and implemented.

Acknowledgements

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List of Abbreviations

%VA .....Percent Voluntary Activation

ACL .....Anterior Cruciate Ligament
AMI..... Arthrogenic Muscle Inhibition

BMI..... Body Mass Index

CAD..... Central Activation Deficit
CAF..... Central Activation Failure
CAR ..... Central Activation Ratio
CCT .....Central Conduction Time
CS .....Conditioning Stimulus
CSP .....Cortical Silent Period

$GABA_A$ .....Gamma-Aminobutyric Acid A
$GABA_B$ .....Gamma-Aminobutyric Acid B

ICF .....Intracortical Facilitation
ICI .....Intracortical Inhibition
ISI .....Interstimulus Interval
ITT .....Interpolated Twitch Technique

K/L .....Kellgren-Lawrence Grading Scale

LICI .....Long Interval Intracortical Inhibition

M1 .....Primary Motor Cortex
MEP .....Motor Evoked Potential
MFGA .....Maximum Force-Generating Ability
MT .....Motor Threshold
MVIC .....Maximal Voluntary Isometric Contraction

NMDA .....N-Methyl-$_D$-Aspartate
NPRS .....Numeric Pain Rating Scale

OA .....Osteoarthritis

PET .....Positron Emission Tomography

QAF .....Quadriceps Activation Failure

rTMS .....Repeated Transcranial Magnetic Stimulation

SIB .....Superimposed Burst
SICI .....Short Interval Intracortical Inhibition

T .....Tesla
TFOA .....Tibiofemoral Osteoarthritis
TMS .....Transcranial Magnetic Stimulation
TS .....Testing Stimulus
VAS .....Visual Analog Scale

Chapter One

Introduction

Osteoarthritis (OA) affects approximately 27 million adults ages 25 years and over in the United States[4] and costs over $60 billion annually to treat.[5,6] Further estimates suggest 12.1% of adults over the age of 60 have symptomatic knee OA[7] making osteoarthritis the leading cause of disability for older adults in the U.S.[7] Knee osteoarthritis is the most common form of OA.[7] In addition to osteoarthritis, these patients may also suffer from a number of comorbid health conditions, ranging from type II diabetes to hypertension and heart disease.[8]

A substantial proportion of the population over age 50[3,9] suffers from osteoarthritis due to the fact that there is an increased incidence of knee OA with aging. This may be associated with age-related increases in ligament stiffness, decreases in muscle strength and activation,[9] and subsequent alterations in joint kinematics. Osteoarthritis is more prevalent in women over 50, possibly because of hormonal changes that occur with menopause.[3,9] People with higher body mass index (BMI) are also at a greater risk of developing osteoarthritis due to greater joint loading.[10]

Osteoarthritis is a degenerative disease that is localized to the surrounding articular cartilage, subchondral bone, and marginal bone around diarthrodial joints.[11] It is characterized by the narrowing of the joint space between the tibia and femur, development of osteophytes, and articular cartilage degeneration.[6] Degeneration refers to a failure of the joint to perform necessary cellular maintenance due to excessive local stresses.[6] It has been shown that mechanical stress is directly proportional to the load

applied across the joint while it is inversely proportional to contact area,[6] therefore increased stresses can be caused by increased loads or decreased contact areas.

Previous researchers have shown that there is limited information on the underlying causes of knee OA and the reason why the disease progression is varied between patients.[9] Abnormal motion at the knee,[9] increased joint laxity,[9] varus alignment,[9] and a greater adduction moment all influence the load distribution between the medial and lateral plateaus.[6,9,10] These contribute to greater medial loads thus leading to decreased cartilage thickness.[6,9,10] This can be problematic in people who suffer from OA due to increased loading on the medial compartment of the knee during ambulation.[10] These factors, in combination with aging and hormonal changes, limit the ability of cartilage to adapt and repair to the damages associated with the progression of osteoarthritis.[9]

Symptoms associated with knee OA include pain,[4,6,11] decreased functional ability,[6] stiffness, crepitus, loss of motion, enlargement, synovitis, and angular deformities.[11] Osteoarthritis has shown to also affect voluntary quadriceps strength and activation. These factors lead to disability, decreased quality of life, and a higher risk of comorbidities.[8] It has been hypothesized that improving quadriceps strength will benefit locomotor biomechanics allowing for increased quadriceps related moments at the knee. However, researchers believe that neuromuscular function in OA patients is decreased as well.[8]

Current treatment strategies for OA include medications and injections to relieve pain and rehabilitation, including strengthening and increasing physical activity levels. If conservative treatments fail, patients ultimately undergo total joint arthroplasty.

Although the ability of rehabilitation to improve pain and physical function is not entirely understood, a recent systematic review reported moderate effects (d=0.32-0.52) of both walking and muscle strengthening exercises on improving pain and disability.[12] The literature reported a variety of exercise programs ranging from home-based exercise, group exercise, to individual training sessions. It has been shown that individual training sessions are the most effective in improving pain and physical function, however, group-based exercise programs seems promising.[13]

Group exercise has the potential to improve disease-related symptoms and a person's overall health status and quality of life. As described previously, OA is associated with multiple comorbid health conditions, which increase the financial burden on the healthcare system.[14] Group exercise also has the potential to reach a larger number of people in a shorter amount of time when compared to individual training programs. Research has shown that a combined program of aerobic walking and strengthening exercises helps to reduce pain and disability in an osteoarthritic population.[12] The successful development of a group-based therapeutic exercise program would be greatly beneficial to a larger population; however, a standardized approach has not yet been established.

Along with previously related symptoms, osteoarthritis is associated with neural alterations to the musculature surrounding the injured joint, often referred to as central activation deficits (CAD). Under the umbrella of CAD is arthrogenic muscle inhibition (AMI), which is an ongoing reflex inhibition of the healthy musculature that surrounds a damaged joint. This phenomenon affects the ability to activate motor neurons for recruitment during normal muscular contractions. Because neural drive is impaired to the

muscle, the motor neurons do not activate effectively, thus resulting in decreased muscle contraction capabilities. This becomes a problem when muscle activation deficits persist and limit the ability to regain optimal muscle function.[15] Thus, CAD contributes to quadriceps weakness by alterations in neural motor output when chronic joint injury or knee osteoarthritis is present. Diminished voluntary quadriceps activation is seen when compared to age-matched individuals without knee osteoarthritis. It is hypothesized that voluntary activation deficiencies must be addressed in order to regain the strength lost and to see functional therapeutic improvements.[8,15-17]

Scopaz et al.[17] reported that voluntary quadriceps activation prior to beginning rehabilitation did not predict potential strength gains over the 6-week exercise program. However, it is unknown if voluntary quadriceps activation improvements can improve strength.[17] Comparably, a study done by Pietrosimone et al.[8] reported that changes in voluntary neuromuscular activation could predict changes in quadriceps strength in knee OA patients.

Knee osteoarthritis has been shown to alter central activation and voluntary quadriceps strength. Central activation ratio (CAR) is expressed as a percentage of voluntary force production compared to the total force produced during a superimposed electrical stimulus.[18] It provides a measure of voluntary motor neuron pool excitability and indicates that there are motor units that are not activated during a voluntary contraction.[19] During central activation testing, an electrical stimulus is delivered onto a muscle during a maximal volitional contraction. This causes an increased production in muscle toque by recruiting inhibited motor units and increasing motor unit firing frequency.[18] A CAR of 1.0, or 100%, indicates complete activation of the muscle.

Anything less than this value would suggest an insufficiency of the muscle to reach full activation.[18,20] Testing CAR using the burst superimposition method is uncomfortable for many participants,[18] though, and patient drop-out and compliance may be problematic.

Another method to assess CAD is through transcranial magnetic stimulation (TMS). TMS involves magnetic fields passing through the scalp and skull allowing for noninvasive brain stimulation. Large, brief currents travel through a wire coil placed on the scalp. As the electrical stimulus is delivered, an electrical current travels into the underlying brain. Relatively focal stimulation can be achieved by using the associated double-cone coil. The primary motor cortex is the location on the brain in which the largest motor evoked potential (MEP) is produced.[21] TMS can activate corticospinal neurons with monosynaptic connections to upper and lower limb spinal motorneurons which produces short latency MEPs in contralateral muscles.[22]

Because osteoarthritis symptoms go beyond localized pain, it is important to assess each variable to further understand the deficits attributed to OA. Central activation deficits result in decreased quadriceps strength, thus increasing knee adduction moments, medial joint loading, and pain. Understanding how neural output affects transient quadriceps function will help to develop new treatment methods in the hopes of slowing, or preventing, the osteoarthritis degeneration process.

Statement of the problem

Due to the fact that osteoarthritis affects approximately 27 million people over the age of 25 in the United States, and is extremely cost effective to treat, it is necessary to develop a conservative treatment in order to decrease the symptoms associated with OA

and ultimately improves quality of life. Without proper understanding and treatment, this disease will lead to long-term problems that will be life altering. This pilot study will help future researchers to better understand the neuromuscular impairments present in patients with knee OA, and will suggest an easy, effective, and low cost method of implementing a large-scale rehabilitation program.

Statement of the purpose

Specific Aim 1: The purpose of this pilot investigation was to understand how knee OA influences quadriceps activation.

Specific Aim 2: A secondary purpose of this study was to determine if a group-based exercise intervention could augment CAD and strength in women with knee OA.

Specific Aim 3: A tertiary purpose of this study was to determine baseline TMS measures in women with knee OA.

Research Hypotheses

Hypothesis 1: Baseline data collected from this pilot study will help researchers in the hopes of understanding knee OA further.

Hypothesis 2: A group-based exercise intervention will improve CAD in women with knee OA.

Hypothesis 3: Baseline TMS data collected from this study will help future researchers understand deficits associated with knee OA.

Limitations

As with any research investigation, this study presented with several limitations. Due to the assessors performing the exercise intervention with the treatment group, there was no blinding, resulting in a chance of possible bias. Due to multiple exclusionary criteria, up to ~30% of participants were not able to participant in TMS and CAR testing.[18] We were not able to match control subjects completely due to varying BMI, activity levels, severity of OA, and the duration for which the participants have suffered from OA. However, this data was be tracked to allow for retrospective analysis.

Also, we instructed participants to refrain from beginning new exercise programs; however, we ultimately could not control what they participated in outside of our study. We could not control for medication (NSAIDS or other prescription medication) that the participants took during our study; however, we asked the participants to log this information, as well as physical activity, during the weeks while taking part in our study. This allowed for tracking of this information, in which we could retrospectively assess. Additionally, we could not predict if or when testing equipment will malfunction, therefore possibly being unable to adequately test each subject. A final limitation is revealed in the exclusion criteria. We did not include people with a BMI $\geq$ 40 kg/m^2, however, because a high BMI is an associated risk factor for knee osteoarthritis, too many people may end up being excluded in which important data could be extracted.

Significance of the study

Because over 27 million adults over the age of 25 in the United States suffer from OA and it costs over $60 billion annually to treat, it is necessary to find a way to slow or

prevent the progression of OA. People who suffer from OA also suffer from a number of comorbid health conditions (type II diabetes, hypertension, heart disease). The current treatments for OA include medications and injections to relieve pain combined with exercise to promote increases in strength and physical activity. Because there is no cure for OA, patients who do not respond to conservative management ultimately undergo total joint arthroplasty. This pilot study furthered our knowledge regarding how knee OA influences quadriceps activation. Finally, this study was able to determine how effective a group-based exercise program is at improving quadriceps function. By performing and evaluating this research, patients who suffer from OA will possibly have an additional treatment to attempt before undergo total joint arthroplasty. Positive findings will lead to an improvement in the quality of life for those who suffer the burden of knee OA.

Chapter Two

Literature Review

The purpose of this literature review is to detail the: 1) prevalence of osteoarthritis, 2) anatomy of the tibiofemoral joint, 3) causes of tibiofemoral osteoarthritis, 4) pathomechanics of osteoarthritis, 5) central activation deficit, 6) current treatment strategies, 7) central activation deficit assessment, and 8) transcranial magnetic stimulation.

Prevalence of Osteoarthritis

Osteoarthritis (OA) affects approximately 27 million adults ages 25 years and over in the United States[4] and costs over $60 billion annually to treat.[5,6] Further estimates suggest 12.1% of adults over the age of 60 years have symptomatic knee OA[7] making osteoarthritis the leading cause and most common form[5,7] of disability for older adults in the United States.[7] Osteoarthritis is the most common form of arthritis[4] and is one of the most prevalent chronic diseases in the world.[11,12,14,16,23,24] Research has shown that OA is among the leading conditions that result in work limitations.[24] Knee osteoarthritis, also known as tibiofemoral osteoarthritis (TFOA), is the most common form of OA.[7] In addition to osteoarthritis, these patients may also suffer from a number of comorbid health conditions, ranging from type II diabetes to hypertension and heart disease.[8] Ultimately, chronic OA, especially when associated with the lower limbs, may result in reduced physical fitness and lead to an increased risk of developing cardiovascular comorbidities.[23] OA has a significant impact on patient quality of life and on healthcare costs.[9,14] OA is the most frequent need for total joint arthroplasty and is becoming

identified in adults at younger ages.[16] There is currently no cure or preventative measure for those who suffer from OA.[5]

Prevalence studies from 1991-1994 reported that 37% (13.3 million) of US adults ages 60 and older had radiographic evidence of osteoarthritis while 12% (4.3 million) had symptomatic radiographic OA.[7] Studies have also shown that increasing age, females, and non-Hispanic black race/ethnicity, obesity, and occupational overuse displayed the greatest prevalence of knee OA.[3,4,7] These numbers have increased dramatically over the years. In a 2003-2005 prevalence study by Helmick *et al*.,[24] the authors reported that over 21.6% of adults (46.4 million people) aged 18 years and older had self-reported doctor-diagnosed arthritis. Studies suggest that the prevalence of OA is expected to increase by 40% in the next 25 years, affecting over 67 million people.[14,24]

Tibiofemoral Joint Anatomy

For the purposes of this literature review, an understanding of the tibiofemoral joint must be discussed to comprehend tibiofemoral osteoarthritis.

The main joint in the knee is the tibiofemoral joint (TFJ). The femur (convex surface) and tibia[25] (concave surface) articulate to form a hinge joint allowing for flexion and extension within the sagittal plane around the frontal axis. Typical range of motion at this joint is 0-135°. Additionally, this joint allows for some medial and lateral rotation, but only when the joint is in a flexed position.

Articular cartilage is located on the articular surfaces of the femur and tibia. Articular cartilage is a highly specialized connective tissue on the ends of diarthrodial joints that provides a smooth surface for proper joint motion.[26] Because the blood

supply to the articular cartilage is poor, damage to this structure is irreversible and will lead to joint degeneration.

Multiple ligaments stabilize the TFJ. The anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL), and lateral collateral ligament (LCL) all help to maintain joint stability.[25] The ACL is located on the anterior aspect of the tibia and crosses superiorly and posteriorly attaching on the posterior aspect of the lateral femoral condyle. The two main bundles of the ACL include the anteromedial and posterolateral bundle; it functions to prevent anterior translation of the tibia on the femur. The PCL is located on the tibia and crosses superiorly and anteriorly to attach on the anterior aspect of the medial femoral condyle. This ligament functions to prevent posterior translation. The MCL is located on the medial aspect of the TFJ attaching from the adductor tubercle of the femur to the medial surface of the tibia. This ligament prevents valgus and external rotation forces. Finally, the LCL passes from the lateral femoral condyle to the head of the anterior fibula and prevents varus and internal rotation forces.

Many dynamic restraints act on the TFJ as well.[25] The extensor mechanism, located on the anterior surface of the tibiofemoral joint, is attributed to the quadriceps femoris muscles. This muscle group consists of the rectus femoris, vastus intermedius, vastus lateralis, and the vastus medialis oblique. Posteriorly, the hamstring groups works to flex the TFJ. This group consists of the biceps femoris, semitendinosus, and semimembranosus. The popliteus is also located on the posterior aspect of the TFJ and aids in initiating knee flexion. Medially, the pes anserine group (sartorius, gracilis, and semitendinosus muscles) crosses the posterior medial joint and attaches to the tibia via

the pes anserine tendon. The adductor magnus, located medially as well, attaches to the adductor tubercle and acts as a medial stabilizer of the TFJ. Finally, the lateral aspect of the knee consists of the iliotibial band, which attaches to Gerdy's tubercle, and provides lateral stability to the TFJ.

Another important aspect of the TFJ is the menisci. The menisci are fibrocartilage disks that act as a cushion within the TFJ. These structures are located between the femur and tibia in both the medial and lateral compartments of the knee joint.[27] To allow for proper articulation between the tibia and femur, the menisci are flat and concave, respectively. The medial meniscus is C-shaped and an attachment site for the MCL, while the lateral meniscus is O-shaped. The menisci deepen the articulation between the femur and tibia to increase joint load absorption and distribution and assist in joint lubrication by reducing friction during physical activity. A healthy meniscus can be made up of 70% water[27] and, if damaged, can contribute to the onset and progression of OA.

Causes of Osteoarthritis

A substantial proportion of the population over age 50[3,9] years suffers from osteoarthritis.[5] The disproportionate number of cases of OA in older adults may be caused by increased ligament stiffness and decreased muscle strength and activation,[9] which lead to abnormal joint kinematics. Factors that contribute to a diagnosis of osteoarthritis include age, genetic predisposition, obesity, female sex, decreased bone density, joint laxity, increased mechanical loading, repetitive loading (seen in sport and in occupations such as farming, construction, and mining[5]), and malalignment of the joint.[5]

Inflammation may also be a factor in the symptoms and diagnosis of OA; however, it can be argued that inflammation is a cause of the specific pathomechanics associated with this disease.[3] Increased life expectancy, decreased physical activity, and increased body weight all contribute to an increase in the prevalence of OA.[14] Osteoarthritis is more prevalent in women over 50, possibly because of hormonal changes that occur with menopause.[3,9] Women have a greater chance of developing knee osteoarthritis that requires surgical interventions[5,14] due to an increased impact when evaluating aspects relating to quality of life (pain, disability, and mood).[11,14]

People with higher body mass index (BMI) are also at a greater risk of developing osteoarthritis due to greater joint loading.[11] Rudolph *et al*.[28] looked at age related changes with osteoarthritis and found that the osteoarthritic population had a significantly increased BMI when compared to a control group ($P \leq 0.002$), which led to an increased genu varum angle ($P < 0.001$), increased medial laxity ($P = 0.001$), decreased quadriceps strength ($P < 0.001$), and decreased walking speeds ($P = 0.023$).[28] All of these factors, in combination, explain the process of tibiofemoral osteoarthritis and how further joint breakdown and degeneration occurs.

Another cause of tibiofemoral osteoarthritis can be explained by quadriceps musculature weakness.[16,28] Quadriceps strength is necessary not only for normal biomechanical movement patterns, but also for energy absorption and force dissipation around the knee joint.[8] When an individual displays decreased quadriceps strength, gait alterations will occur leading to increased symptoms and joint breakdown. Quadriceps weakness is thought to come from previous joint injury, previous joint surgery[15,29], arthritis, or generalized joint laxity[3,5,6,8,9,15,29] and may be a result of central activation

failure,[8] which will be explained later. Spinal reflex and corticospinal pathways become altered following joint injury or effusion. This alteration leads to an alteration in the neural excitability of the quadriceps musculature, which may explain the decline in voluntary quadriceps activation in those who suffer from TFOA. Quadriceps strength loss is a result of the decline in voluntary quadriceps activation.[8] Because quadriceps strength is also related to functional performance and an individual's force generating capacity, research has shown that by improving quadriceps strength and altering knee movement during walking, symptoms such as pain and function have improved, thus leading to a decrease in the OA disease progression.[16,28]

Pathomechanics

Osteoarthritis is a degenerative disease that is localized to the surrounding articular cartilage, subchondral bone, and marginal bone around diarthrodial joints.[11] It is characterized by the narrowing of the joint space between the tibia and femur, development of osteophytes, and articular cartilage degeneration.[4,6] Degeneration is thought to be a result of abnormal motion at the knee,[9] and refers to a failure of the joint to perform necessary cellular maintenance due to excessive local stresses.[6] It has been shown that mechanical stress is directly proportional to the load applied across the joint while it is inversely proportional to contact area,[6] therefore increased stresses can be caused by increased loads or decreased contact areas. Conversely, the absence of loads also leads to articular cartilage breakdown; because cartilage needs to be loaded in order for water and nutrients to flow through and maintain proper health. Without any

mechanical deformation caused from extrinsic loads, fluid and nutrients will not have a way to flow through the tissue, thus resulting in further cartilage breakdown.[30]

Previous researchers have shown that there is limited information on the underlying causes of knee OA[6,9,11] and the reason why the disease progression is varied between patients.[9] Abnormal motion at the knee,[9] increased joint laxity,[9] varus alignment,[9] and a greater adduction moment all influence the load distribution between the medial and lateral plateaus.[6,9,10] Felson[3] (Figure 1) and Andriacchi *et al.*[9] described a cause and progression of medial compartment TFOA to come from a varus alignment of the knee leading to increased loading on the medial side. Their results displayed a 3.5x greater chance of developing cartilage loss if an individual presents with increased medial loading.[3,9] It has been shown that an increased knee adduction moment during gait influences the distribution of bone density in the proximal tibia also resulting in an increased load on the medial tibial plateau.[6,9] These factors contribute to greater medial

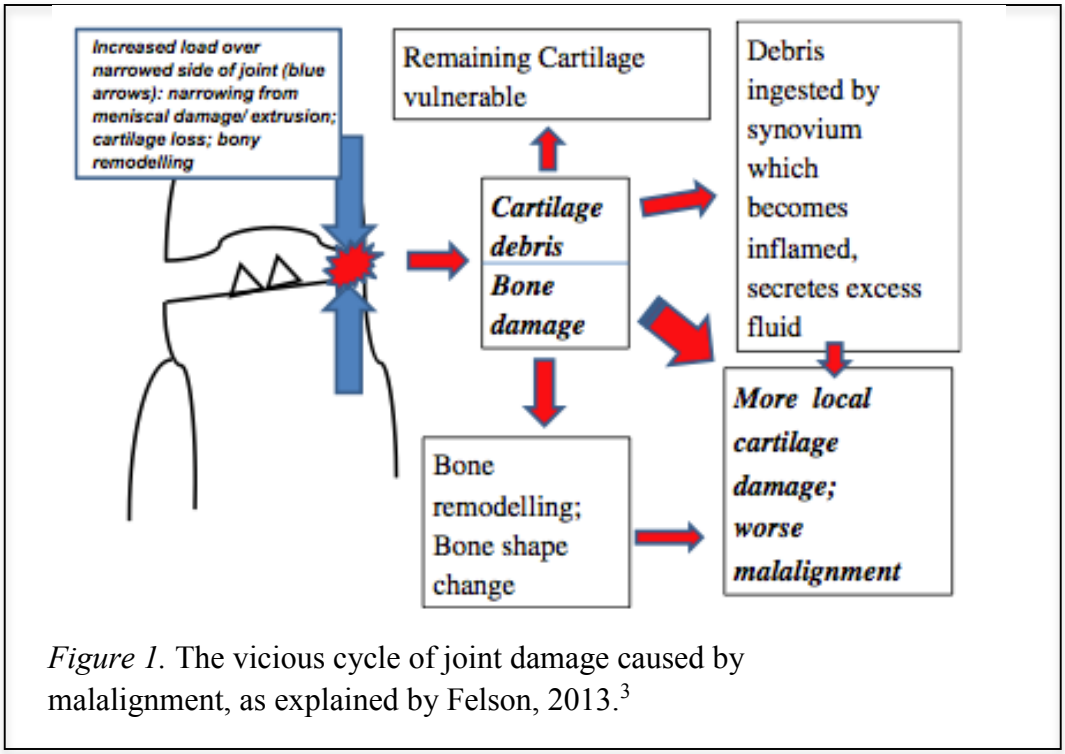

Figure 1. The vicious cycle of joint damage caused by malalignment, as explained by Felson, 2013.[3]

loads, thus leading to decreased cartilage thickness.[6,9,10] This can be problematic in people who suffer from OA due to increased loading on the medial compartment of the knee during ambulation,[10] as stated previously. Eighty-two percent of osteoarthritic knees are clinically mal-aligned, and 60% of TFOA is due to malalignment.[3] This predisposes clinically malaligned knees to increased focal loading and further joint damage.[3] These factors, in combination with aging and hormonal changes, limit the ability of cartilage to adapt to and repair the damages associated with the progression of osteoarthritis.[9] Martin[11] stated that once OA is present, all factors become consumed by the pathomechanics of the disease progression. Unfortunately, the repair process cannot keep up with cartilage breakdown.[11] However, the neuromuscular and musculoskeletal systems can be altered to affect the adaptive response to this disease[9] and will be described later.

Martin[11] explained the process of OA beginning with fissuring, pitting, and erosions on the associated articular cartilage. As the cartilage breaks down, it begins to fray. A loss of articular cartilage[5] leads to further joint degeneration through ulceration and enzyme release breakdown. Again, cartilage is damaged and lost, thus leading to subchondral bone sclerosis and marginal osteophyte formation. Bone marrow degeneration follows and cysts begin to form on the exposed bone. The joint capsule then thickens leading to an inflammation of synovial tissue. As an individual continues to weight bear during ambulation, their cartilage destruction advances resulting in pain and disability.[11]

Andriacchi *et al.*[9] further describe osteoarthritis in two phases. The Initiation Phase is caused by kinematic changes from pre-established patterns that cause a shift in

the normal load bearing regions of the cartilage. This begins with healthy cartilage where some condition causes a shift in the load bearing contact area of the associated joint. The load bearing contact point displays decreased cartilage thickness due to cartilage adaptation in increased areas of stress and friction. As explained earlier, older cartilage cannot adapt to changes in load bearing as quickly as younger cartilage. Slower shifts in load bearing capabilities of the knee initiates degenerative changes. This leads to the second phase of OA, as described by Andriacchi *et al*.[9] The Progression Phase occurs with increased loading. Tissues exceed the threshold where it becomes vulnerable to increased compressive loads and, in turn, causes the disease to progress faster. Once cartilage is degraded, the joint will breakdown more rapidly.[9]

Finally, Felson[3] added to these definitions. Mechanical overload, in combination with obesity, leads to chronic excess overloading. In the presence of a knee injury, focal increased stresses occur. When repetitive use patterns are seen, like in the occupational setting, chronic excess loading is once again present.[3] A combination of one or all of these factors contributes to a diagnosis of osteoarthritis (Figure 2).

As stated before, previous joint injury and surgery contribute to the progression of TFOA. Felson[3] reported that 40-50% of knee OA may be explained by previous or concomitant meniscal tears. Because a meniscal tear changes joint kinematics, thus leading to altered gait and improper loading and contact patterns, the risk of cartilage loss adjacent to a meniscal tear is extremely high. Studies completed by Englund *et al.*[31] indicated that 30-60% of adults aged 50 years and older had incidental meniscal tears without recalling previous injury to the affected knee. Englund explained that the chance

of developing OA within 30 months increased by 10x compared to those without meniscal tears.[31,32]

It has been argued that an individual's genetics may predispose him/her to osteoarthritis. However, research has shown that the genetics of OA as a joint specific disease is only due to the possibility of inheriting a predetermined joint shape.[3] Altered joint shape would lead to unnatural loading and contact patterns, thus resulting in cartilage breakdown and the progression of OA, as described earlier.

Symptoms associated with knee OA include pain,[4-6,11,12,23] decreased functional ability,[6,12,23] stiffness, crepitus, loss of motion, enlargement, synovitis, and angular deformities.[5,11] Those who suffer from OA experience difficulty performing activities of daily living, like walking, standing up from a chair, stair climbing, and housekeeping.[23]

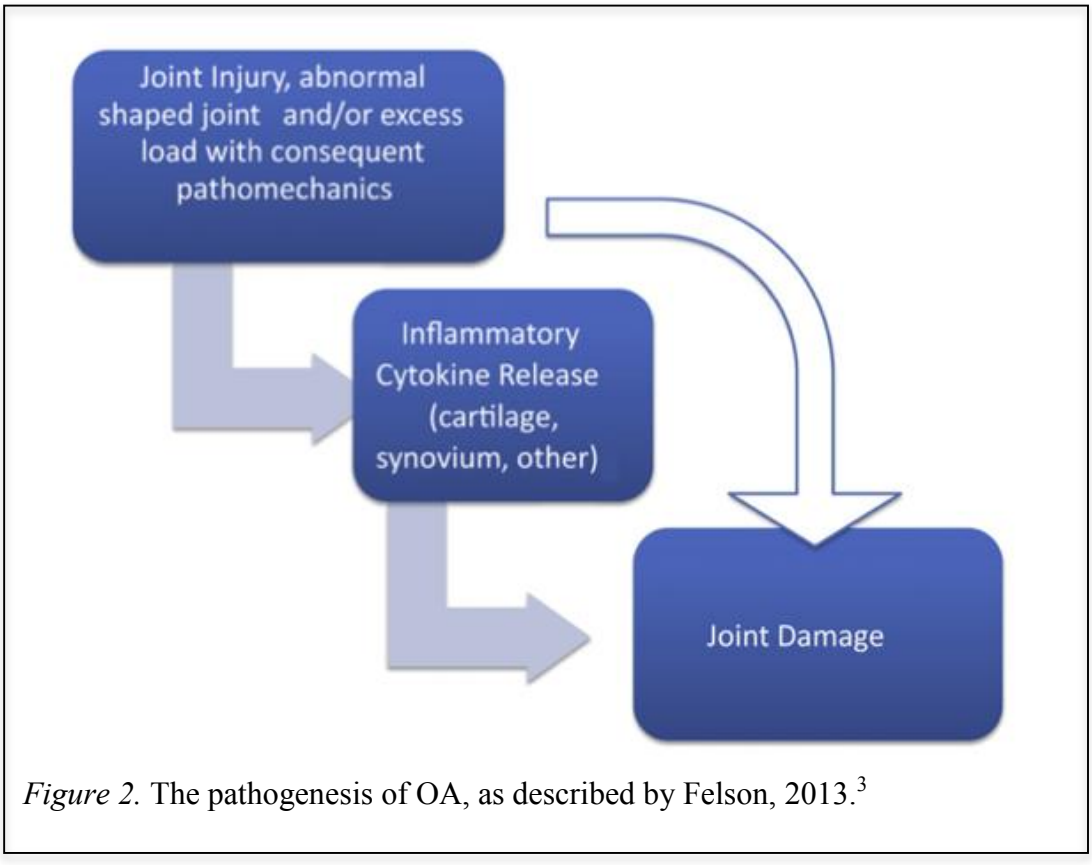

Figure 2. The pathogenesis of OA, as described by Felson, 2013.[3]

Osteoarthritis has shown to also affect voluntary quadriceps strength and activation. These factors lead to disability, decreased quality of life, and a higher risk of comorbidities.[8] Nonsurgical interventions need to be discovered that will help to improve the quality of life of patients who suffer from OA, in the hopes of avoiding total joint arthroplasty.[16] It has been hypothesized that improving quadriceps strength will benefit locomotor biomechanics allowing for increased quadriceps related moments at the knee. However, researchers believe that neuromuscular function in OA patients is decreased as well.[8]

Central Activation Deficit

Along with previously related symptoms, osteoarthritis alters neural drive to the musculature surrounding the affected joint. Central activation deficit (CAD) is a reduction in motor unit firing or failure to achieve maximal discharge rate from motor units that have been recruited[15] (Figure 3). Arthrogenic muscle inhibition (AMI), a type of CAD, is an ongoing reflex inhibition of the healthy musculature that surrounds a damaged or distended joint. This reflex affects the ability to activate motor neurons for recruitment during normal muscular contractions.[15] Joint effusions from acute[33,34] or chronic[35,36] mechanisms prevent full voluntary activation of the muscles surrounding the affected joint. CAD is commonly present following traumatic joint injuries like anterior cruciate ligament (ACL) injuries, but is also a factor following joint surgery, especially meniscectomy and total knee arthroplasty. It also presents with the onset of degenerative joint diseases, such as OA.[15,37]

CAD elicited by abnormal afferent information from the damaged joint results in a decrease in motor drive to the muscle, or muscle groups, that act across the affected joint. CAD contributes to the pathogenesis of degenerative joint diseases, especially OA, by decreasing muscle strength. Weakness and atrophy become apparent, due to the inhibition, which then prevents strength gains and exposes the joint to increased structural damage.[37] Because it alters neural drive to the muscle, the motor neurons do not activate effectively, thus resulting in decreased muscle contraction capabilities. Initially, the onset of CAD is a protective mechanism following joint injury. This becomes problematic, however, when muscle activation deficits persist and limit the ability to regain optimal muscle function.[15] As described earlier, the quadriceps function as a shock absorber for the knee joint, and when decreased muscle activity is present, the ability of the neuromuscular system to protect this joint is hindered, once again leading to further joint damage and early joint degeneration. It is hypothesized that voluntary activation deficiencies must be addressed in order to regain the strength lost and to see functional therapeutic improvements.[8,15-17]

Scopaz *et al*.[17] reported that voluntary quadriceps activation prior to beginning rehabilitation did not predict potential strength gains over the 6-week exercise program. However, it is unknown if voluntary quadriceps activation improvements can improve strength.[17] Comparably, a study done by Pietrosimone *et al*.[8] reported that changes in voluntary neuromuscular activation predicted 47% of the variance in changes in quadriceps strength in patients with knee OA ($P<0.001$). This study concluded that a small change in activation would equate to a much larger change in strength.[8]

In order to treat decreased quadriceps strength, activation much first be addressed. As previously described, joint diseases are often associated with muscle weakness following joint injury or effusion. Weakness can be attributed to alterations in neural motor output when joint injury or disease is present.[29,38] Decreased voluntary activation

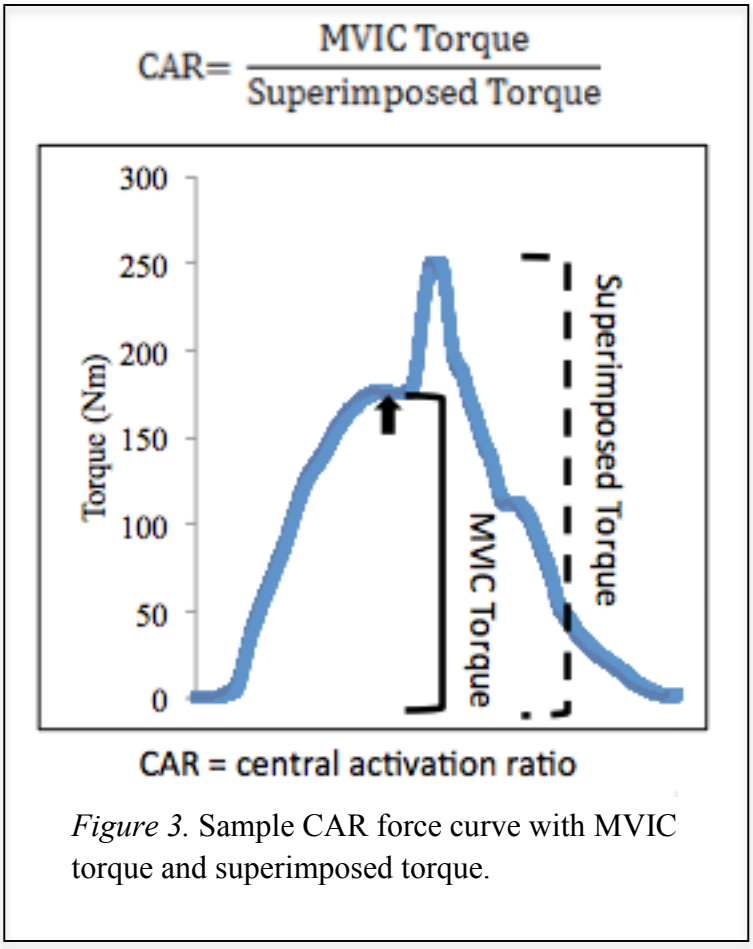

Figure 3. Sample CAR force curve with MVIC torque and superimposed torque.

is caused by descending corticospinal alterations.[8] Without proper activation, the affected muscles will voluntarily decline and cause muscle dysfunction. Decreased muscle strength is a major predictor for disability. Aging is said to be related to impaired neuromuscular function, more specifically intracortical changes. This is an additional factor that leads to muscular weakness, and if present in the lower extremity, is associated with decreased gait speed, balance, sit-to-stand activities, stair climbing, and an increased

risk of falling.[39,40] However, research has shown improved pain and function in subjects with TFOA who remain physically active. Stevens-Lapsley *et al*.[39] compared active (at least 30 minutes per day, 3 times per week) younger and active older adults for impaired neuromuscular function and found no statistically significant differences between the groups ($P>0.05$).[39] By remaining physically active, neuromuscular function was not decreased; thus, quadriceps strength was maintained, leading to improved measures of function. It is important to understand the influences of changing quadriceps activation and the effect it has on quadriceps strength. Pietrosimone *et al*.[8] concluded that focusing on voluntary activation in patients with TFOA is appropriate for increasing quadriceps strength.[8] A reduction in pain and disability, as occurs with improvements in quadriceps strength, may possibly prevent the onset of further joint degeneration and disease.

Central activation deficit assessment

Knee osteoarthritis has been shown to alter central activation and voluntary quadriceps strength. Several methods exist by which to assess the alterations in neural drive to the muscle. Among these are burst superimposition, interpolated twitch technique, and transcranial magnetic stimulation (TMS) testing.

It is well know that patients with TFOA have greater quadriceps strength deficits when compared with age- and sex- matched controls. Quadriceps activation failure (QAF) is the inability to fully activate the quadriceps muscles and is determined by comparing the decreased voluntary maximum isometric quadriceps torque output with the torque output produced during the superimposition of an electric stimulus on an MVIC (Figure 3). It is estimated that knee OA patients experience 8-25% activation failure.[38,41]

It is thought that QAF is the result of altered sensory information from the joint mechanoreceptors,[42] which is why it is common following joint injury and is present in TFOA.[43] QAF affects physical function by decreasing the ability to absorb shock at the knee. Without proper shock attenuation, increased forces are place upon the knee, leading to early joint degeneration.[43]

Petterson *et al*.[38] identified determinants of quadriceps weakness in knee OA patients. Results showed a 20% decrease in quadriceps MVIC in the affected leg when compared to the unaffected limb ($P<0.001$). Quadriceps CAR of OA limb was also 8% lower than the contralateral limb ($P<0.001$). This study concluded that changes in activation values equate to much larger changes in strength.[38]

Additionally, Lewek *et al*.[41] looked at age related changes in subjects with OA and found a significant difference in quadriceps strength in OA subjects when compared to the control group ($P=0.010$) and concluded that OA subjects suffered from a 24% deficit in strength. Alternately, no significant differences were found in BMI and CAR between groups ($P=0.230$ and $P=0.233$, respectively). A 95% activation was considered to be full activation. However, 50% of the OA subjects were unable to full activate their quadriceps to the predetermined value, indicating that as a group, they were beginning to show a reduction in activation beyond the cause of aging.[41]

Another study looking at the relationship between quadriceps strength and physical function in knee OA patients concluded that age, BMI, numeric pain rating scale (NPRS) during burst superimposition, and number of years since their diagnosis of OA had no significant correlation. A small significant difference was found with age and QAF, explaining that women suffered more than men ($P<0.05$). Women also displayed

lower strength than men (P<0.01). They concluded that quadriceps strength and physical function is moderated by the degree of QAF. Increased QAF and decreased quadriceps strength resulted in an increased difficulty with physical function. However, increased QAF and increased quadriceps strength resulted in better physical function when compared to those without CAF.[42]

Finally, Scopaz *et al*.[17] compared pretreatment quadriceps activation and strength after therapeutic exercise in knee OA subjects. Results displayed a significant association between baseline quadriceps activation and strength (P<0.001). Although, increase baseline quadriceps activation correlated with increased strength, it did not predict quadriceps strength at the 2-month follow up (P=0.18).[17] This study did not report on adherence to the exercise program and as previously mentioned, in order to maintain the benefits of any exercise program, the individual must continue to exercise.

Burst superimposition testing

The first method, Superimposed Burst (SIB), involves superimposing a train of pulses on an MVIC. The maximum volitional force is compared to the total force produced by the electrical stimulus of the volitional contraction.[18,41] This method allows for the motor units throughout the muscle to be directly stimulated.[18,19] As described earlier, the CAR is used to determine activation. A CAR of 1.0, or 100%, indicates complete activation of the muscle. Anything less than this value would suggest an insufficiency of the muscle to reach full activation.[18,20] The SIB method is used to measure the maximum force-generating ability (MFGA). MFGA is the total force produced by the volitional contraction and the stimulation.[44] Burst superimposition testing allows for the measurement of a central activation ratio (CAR). CAR is a

measurement of voluntary motorneuron pool excitability that is used to estimate maximal volitional muscle activation.[18,19] Motor units that are not recruited during a maximum voluntary isometric contraction (MVIC) are stimulated via an exogenous electrical stimulator and muscle activation is expressed as a percentage of voluntary force production compared to the total force produced during the superimposed stimulus (Equation 1).[18,45] CAR is reported to be affected by alterations in both motor unit recruitment and firing frequency. This decreases the ability of the muscle to generate force. Optimal muscular activation could lead to alterations in neuromuscular control, like the ability to alter gait and physical activity kinematics, which, in turn, would prevent or slow the progression of joint degeneration.[15] It is important for the muscle to be fully activated in order for the electrical stimulus to generate additional force above that of the contraction. Because volitional muscle force increases as a result of increases in discharge rate and motor unit recruitment, fewer inactivated motor units are available to be stimulated.[41] Research has shown that proper practice, motivation, and feedback are vital to achieve maximal activation.[19,41,43]

Equation 1. CAR = MVIC / (MVIC + Burst Superimposition)

Interpolated Twitch Technique

Similar to the burst superimposition testing described above is the interpolated twitch technique (ITT). The ITT involves superimposing a single percutaneous electrical stimulus[45] over a motor nerve during various levels of muscle contractions as well as on the resting state.[41,44] This causes an increase in muscle torque production by recruiting inhibited motor units or by increasing motor unit firing frequency.[18]

The percent voluntary activation (%VA) can be calculated by taking the twitch force at rest by the difference of the superimposed twitch force from one (Equation 2). Although this method has been shown to elicit milder pain, it is reported that this is an inadequate way to estimate voluntary activation failure at high levels of force.[41]

Equation 2. %VA = 1 – Superimposed Twitch Force at MVC / Twitch Force at Rest

Discomfort with the SIB method is associated with the electrical stimulus and although it varies between subjects, studies show mild to moderate (3-4/10) pain on the visual analog scale (VAS). However, some patients may experience discomfort levels sufficient enough to cause withdrawal from clinical trials.[18,45] Also, this technique tends to overestimate an individual's activation of a muscle at submaximal volitional levels[41,44] by up to 10%.[45] Conversely, Pietrosimone *et al*.[19] reported this method to be more sensitive than the ITT technique when estimating the motor neuron pool excitability.[19] We will be using the SIB technique for the purposes of this study.

Transcranial magnetic stimulation

Another method to assess central activation deficits is through transcranial magnetic stimulation (TMS). TMS is a safe and useful tool that measures aspects of human neurophysiology, more specifically corticospinal function,[46,47] including inhibitory and excitatory circuits in the human motor cortex.[48] TMS involves magnetic fields passing through the scalp and skull allowing for noninvasive brain stimulation. Large, brief currents travel through a wire coil placed on the scalp. As the electrical stimulus is delivered, an electrical current travels into the underlying brain. Relatively focal stimulation can be achieved by using the associated double-cone coil. The primary motor cortex (M1) is the location on the brain in which the largest motor evoked potential

(MEP) is produced.[21] TMS can activate corticospinal neurons with monosynaptic connections to upper and lower limb spinal motorneurons, which produces short latency MEPs in contralateral muscles.[22,46]

Rothwell[49] describe the process of TMS as follows. A magnetic stimulator consisting of a coil of wire connects to a large electrical capacitor; the capacitor is discharged through the coil and, through it, a very large current flows. A magnetic field perpendicularly oriented to the coil is produced. The current can reach values anywhere from 1.5-3 Tesla (T).[47] Because the magnetic field rapidly changes, it induces electrical eddy currents in any conductive structures nearby, including the brain. Neural tissue is then stimulated. This stimulation is

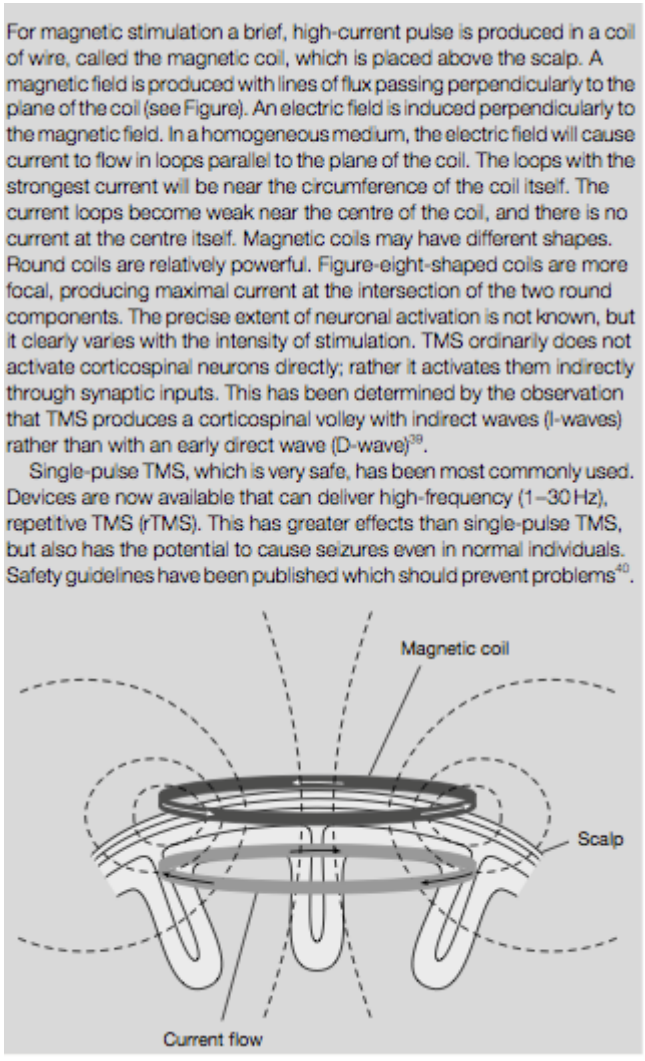

Figure 4. Physics and mechanisms of action of TMS, as explained by Hallett, 2000.[1]

attenuated, or decreased, at deep sites like the basal ganglia and thalamus located deep within the brain. Since the resistance of white matter is greater than that of the grey matter, currents that are induced in the subcortical tissues are most likely too small when compared to currents induced in surface layers of the cerebral cortex. Models of the current induced in a flat volume conductor show that components of the induced electric field perpendicular to the surface are exactly cancelled by an electrostatic charge that is induced on the surface, thus explaining why the electric field is parallel to the surface at all points. Figure of 8 coils are used to provide increased focal stimulation because the induced electrical field under the junction region is twice as large as that under the two wings. As the spatial derivative of the electric field parallel to the axon exceeds a certain value within a certain length of time, activation occurs, therefore an axon running parallel to the electric field will not be stimulated. This is due to the potential at all points along its length will be equal. Electromyography (EMG) responses in contralateral, particularly distal muscles, are evoked through magnetic stimulation of the motor cortex.[49]

In simpler terms, TMS uses the principle of inductance to deliver electrical energy across the scalp and to the brain. A stimulating coil of wire is placed on the head. A powerful and rapidly changing electrical current passes through the coil and produces a magnetic field that passes into the brain. The current changes within a few hundred milliseconds allowing the current to excite neurons located within the motor cortex.[1,21,47] The elicited current excites descending corticospinal tracts that will project on motor neurons within the targeted muscle,[15] thus producing excitatory responses in muscles[50] (Figure 4). This response provides information about any physiological changes that may

have occurred from joint injury or disease that consequently altered neuromuscular function.[39]

Two types of TMS testing include single-pulsed and paired-pulse testing. Single pulse TMS assesses corticospinal excitability by examining the motor threshold necessary to produce motor evoked potentials and silent periods;[39,40,51,52] central conduction time; and also maps muscle representations in the motor cortex.[2,21] Central conduction time (CCT) is the difference of the peripheral conduction time, which is obtained by spinal magnetic stimulation or by F-wave measurement, from the motor evoked potential (MEP) latency in the target muscle. CCT is delayed in diseases like multiple sclerosis, stroke, and sclerosis.[21] Motor threshold (MT) is the lowest TMS intensity capable of eliciting a small MEP (usually 50 μV at rest and 100 □V during active contraction). MT provides information about muscle representation of the central core neurons. MT likely represents neuronal membrane excitability.[21] MEPs are directly proportional to corticospinal projections while MT is indirectly proportional to corticospinal projections.[21,22] For example, muscles with weak corticospinal projections, such as the biceps or lower limb muscles, have steeper MT and lower MEP recruitment.[21,22] MEP amplitude is used to determine corticospinal excitability.[21] TMS testing can also report on stimulus/response curves, or recruitment curves. This refers to increases in MEP amplitude as TMS intensity increases. Recruitment curves can assess intrinsic neurons, which are less excitable and further away from the center of activation. Chen[21] reported that recruitment curves are related to the strength of corticospinal projections and are usually larger in muscles with a lower MT.[2,21] Cortical Silent Period (CSP) duration is the next variable associated with TMS testing. This signifies the

duration of the interruption of voluntary motor activity after TMS[21,53] and reflects the integrity and excitability of cortical inhibitory mechanisms. CSP onset is the point at which the post-stimulus EMG is significantly different from the pre-stimulus EMG. CSP offset is the initial point when the t-test fails to detect a significant difference.[53] The initial part of the CSP is due to spinal mechanisms while the final part is due to cortical mechanisms.[1] Finally, mapping of muscle representation, or brain mapping, is used to determine the primary motor cortex. Multiple scalp positions are stimulated using a figure-of-8 coil. The primary motor cortex, or M1, is affected by the location and excitability of the motor representation.[21]

Paired-pulse testing is the second type of TMS and is useful when assessing cortical excitability.[39,40] Short Interval Intracortical Inhibition (SICI) and Intracortical Facilitation (ICF) are the most commonly used paired-pulse tests. Both involve a subthreshold conditioning stimulus (CS) followed by a suprathreshold testing stimulus (TS).[22,40,48,52] The test response is inhibited at interstimulus intervals (ISIs) of 1-5ms and facilitated at ISIs of 8-30ms.[22,40,48,52] (Figure 5). Inhibition and facilitation take place in the motor cortex rather than in the subcortical structures.[21,22,40,46,54] SICI and ICF reflect the excitability of distinct inhibitory and excitatory interneuronal circuits within the motor cortex.[55] Furthermore, SICI can be attributed to the direct activation of fast corticospinal neuronal axons which monosynaptically connect to motorneurons.[46] SICI is mediated by gamma-aminobutyric acid A ($GABA_A$) receptors,[40,48,52] while ICF is mediated by excitatory glutamatergic interneurons and N-methyl-$_D$-aspartate (NMDA) receptors.[40] SICI is reduced in multiple neurologic and psychiatric disorders like Parkinson's disease, dystonia, Alzheimer's disease, Tourette's syndrome, and

schizophrenia. It is also reduced with peripheral injury and during voluntary muscle contraction due to the release of cortical representation from inhibition and its focus on producing the desired movement. ICF is decreased in cerebellar degeneration patients.[2]

Long Interval Intracortical Inhibition (LICI) is similar to SICI and ICF except that the CS and TS are both suprathreshold. Also, longer ISIs are used (50-200ms).[22,48,51,52] (Figure 5). LICI is mediated within the M1[40,51] by gamma-aminobutyric acid B ($GABA_B$) receptors.[40,48,52] LICI is associated with reduced motor cortex excitability[21,22,46,54] and is related to the suppression of voluntary muscle contraction following a suprathreshold TS, also known as the SP. LICI is abnormal in neurological disorders such as stroke, Parkinson's disease, and dystonia. Unlike SICI, LICI is not significantly affected by voluntary muscle activation.[2] Although TMS testing does not produce an uncomfortable sensation to the participant as seen in the burst

	SICI	LICI	ICF
Method			
Conditioning stimulus/S1 for SICF	Subthreshold TMS	Suprathreshold TMS	Subthreshold TMS
Test stimulus/S2 for SICF	Suprathreshold TMS	Suprathreshold TMS	Suprathreshold TMS
Interstimulus interval (ms)	1–6	50–200	8–30
Proposed neurotransmitter/receptor	$GABA_A$, ?DA	$GABA_B$	Glu
Findings			
Parkinson's disease	↓	↑	↔
Dystonia	↓	↓or↑	↔
Alzheimer's disease	↓	?	↔
Schizophrenia	↓	↔	↔
Cerebellar degeneration	↔	↑	↓

Figure 5. TMS Parameters, as explained by Chen, 2004.[2]

superimposition technique, previous studies assessing quadriceps activation with TMS have not provided a comprehensive analysis on how this cortically driven method compares with CAR methods.[18]

Changes in TMS variables depend on the associated disease. Chen *et al.*[21] reported significantly lower MT in the quadriceps femoris in lower limb amputees compared to unaffected limbs. Motorneuron pool recruitment by TMS at maximal stimulator output was greater on the amputated side than on the intact side. A reduction in SICI was seen on the amputated side, which suggests that reduced GABAergic inhibition may be a mechanism involved in motor reorganization.[21]

A systematic review completed by Chen[2] resulted in the following. A positron emission tomography (PET) study showed a positive correlation between the amount of SICI and cerebral blood flow in the motor cortex. This suggests that SICI is involved with synaptic activation. Additionally, Chen revealed that LICI and SICI are mediated by different inhibitory circuits. SICI causes MEP inhibition through $GABA_A$ receptors while LICI causes MEP inhibition through postsynaptic $GABA_B$ receptors. The effects from inhibition influence neurons into generating descending I-waves leading to MEPs. LICI mediates through common inhibitory neurons, which inhibit SICI through $GABA_B$ receptors. Finally, Chen[2] reported a limitation to TMS testing in this review stating that it is not possible to study excitatory and inhibitory systems in complete isolation because the final cortical output is the result of an interaction between multiple systems. Therefore, it is possible that the changes seen in inhibition could be due to the changes seen in facilitation.[2]

McGinley *et al*.[40] compared young and old adults to determine age related changes associated with TMS testing at rest and during a sub-maximal wrist flexion contraction. Results showed increased SICI and LICI in older subjects when compared to younger subjects (P=0.04) and decreased ICF (P=0.02) under resting conditions. However, these differences disappeared during voluntary contraction. Additionally, the older subjects exhibited a longer silent period during contraction (P<0.01). Although this study did not report or account for physical activity level, these findings suggest an increased GABA mediated intracortical inhibition (ICI) with age.[40]

Although TMS testing paradigms are considered safe, there are always risks associated with testing. Ni *et al*.[52] explained that intracortical inhibitory and excitatory circuits in the human primary motor cortex modulate the excitability of corticospinal neurons.[52] Furthermore, the M1 is thought to be among the most epileptogenic of brain areas.[47] Because TMS is performed repeatedly over the M1, there is a risk of the induction of seizures. However, single-pulse TMS, that will be used in this research study, with stimuli delivered no more than once every few seconds, carries no significant risks. The risks become apparent when performing rTMS, or repeated Transcranial Magnetic Stimulation, which has led to seizure induction in patients and normal subjects.[21] rTMS allows for the facilitation or inhibition of cortical processes, but has been known to induce seizures[47] and, therefore, will not be used in this study.

Current Treatment Strategies

Current treatment strategies for OA include medications and injections to relieve pain and rehabilitation, including strengthening and increasing physical activity levels. If

conservative treatments fail, patients ultimately undergo total joint arthroplasty. Although the ability of rehabilitation to improve pain and physical function is not entirely understood, a recent systematic review reported moderate effects (d=0.32-0.52) of both walking and muscle strengthening exercises on improving pain and disability.[12] The literature reported a variety of exercise programs ranging from home-based exercise, group exercise, to individual training sessions. It has been shown that individual training sessions are the most effective in improving pain and physical function, however, group-based exercise programs seems promising.[13]

Therapeutic Exercise

As stated previously, the implementation of therapeutic exercise, involving aerobic walking and quadriceps strengthening,[12] has improved pain and function in a tibiofemoral osteoarthritic population. Therapeutic exercise has also been shown to improve quadriceps activation, which leads to increases in quadriceps strength.[8] Since decreased quadriceps strength leads to numerous consequences all enhancing the progression of OA, it is imperative that a therapeutic exercise strategy is established in order to benefit the most amounts of people.

Group exercise has the potential to improve disease-related symptoms and a person's overall health status and quality of life. As described previously, OA is associated with multiple comorbid health conditions, which increase the financial burden on the healthcare system.[14] Group exercise also has the potential to reach a larger number of people in a shorter amount of time when compared to individual training programs. Additionally, group based exercise is extremely cost-effective and is a way that older people can more readily access the program when introduced to community

centers or gymnasiums, for example. Fransen *et al*.[23] described group exercise as a way for people who are experiencing the same type of symptoms to gain social contact, thus allowing for greater compliance and adherence to the program.[13,23] Ultimately, it is very important to adhere to an exercise program in order to maintain the benefits that result from participation.[12,13]

Recent systematic reviews published by Fransen *et al*.[13,23] showed positive results for pain and physical function after completing therapeutic exercise. The 2002 study examined patients with knee OA that reported on self-reported pain and physical function following land-based physical therapy. Immediate moderate benefits (d=0.46) were found when looking at a reduction of pain while immediate small effects (d=0.33) were found when subjects reported their physical function.[23] The 2003 study concluded similar results with moderate effects for pain (d=0.40) and small effects for physical function (d=0.37). However, the latter treatment effects would be considered small due to Fransen comparing the results to treatment effects of drug therapy, such as analgesics or nonsteroidal anti-inflammatory drugs (NSAIDS), taken for knee pain.[13]

Additionally, Roddy *et al*.[12] completed a systematic review that compared the efficacy of aerobic walking and quadriceps strengthening in patients with TFOA. Pooled effect sizes for pain were 0.52 during aerobic walking and 0.39 during quadriceps strengthening, while for self-reported disability were 0.46 during aerobic walking and 0.32 during quadriceps strengthening. Although both methods reduced pain and disability, they did not account for the type, length, and duration of each exercise program included in the review. This study also concluded that many randomized controlled trials utilize hospital based therapy, which is not readily available to the

general public.[12] The successful development of a group-based therapeutic exercise program would be greatly beneficial to larger population; however, a standardized approach has not yet been established.

Conclusion

Osteoarthritis is a burden not only on the suffering individual, but also on the healthcare system. Currently, there is no cure for OA and patients ultimately undergo total joint arthroplasty. Because osteoarthritis symptoms go beyond localized pain, it is important to assess each variable to further understand the deficits attributed to OA. Central activation deficits result in decreased quadriceps strength, thus increasing knee adduction moments, medial joint loading, and pain. Understanding how neural output affects transient quadriceps function will help to develop new treatment methods in the hopes of slowing, or preventing, the osteoarthritis degeneration process. Research has shown that therapeutic exercise promotes not only a healthy lifestyle, but may also result in quality of life improvements for those who suffer from TFOA. Therapeutic exercise will help to improve neuromuscular function and improve quadriceps strength. This, in turn, will delay or prevent the onset of OA. By addressing the neuromuscular deficits through exercise, CADs will be improved leading to proper activation and firing patterns. This will help to restore proper functioning at and around the knee needed for correct gait, equal loading patterns, and pain-free activities of daily living. Group based therapeutic exercise presents with the opportunity to reach a greater number of people at a decreased cost. However, it is important to remember that adherence and compliance to any exercise program is necessary in order to experience the potential benefits. This

study will allow us to determine if voluntary quadriceps strength and neuromuscular control can be altered after the participation in an 8-week therapeutic exercise intervention.

The results expected from this study include: increased quadriceps MVIC, increased SICI and LICI, decreased ICF, decreased MT, and decreased CAR. If these results are positive, the therapeutic intervention program implemented in this study should be further utilized and could be implemented into community centers and gymnasiums. These results would help to encourage individuals suffering from TFOA to become active and participate in an exercise program. However, if these results do not prove to be true, a different intervention approach will need to be taken in order to address the problems associated with TFOA.

Chapter Three

Methodology

Research design

Study design: pilot investigation with an embedded case series.

Experimental Design

All participants had symptomatic knee osteoarthritis (OA) and had their neuromuscular measures recorded. Neuromuscular measures of interest include: quadriceps strength (maximal voluntary isometric contraction [MVIC]); quadriceps activation, elicited using the burst superimposition technique (SIB) and calculated using the central activation ratio (CAR); and quadriceps excitability, assessed via outcome measures retrieved through transcranial magnetic stimulation (TMS): motor threshold (MT); short and long interval intracortical inhibition (SICI and LICI, respectively); and intracortical facilitation (ICF). All participants read and signed an Institutional Review Board (IRB) approved informed consent form prior to participating (IRB #108105).

Participants

A total of 13 people enrolled and were screened in this study; however 4 participants dropped out prior to data collection because of time constraints. Nine participants completed baseline strength and CAR testing, while 3 of those went on to complete the full 8-week therapeutic exercise regime and follow-up testing. Six of the initial 13 participants qualified for TMS testing. Those participants underwent baseline TMS testing *(Figure 6, Figure 7).*

Each participant met the following inclusion criteria *(Table 1)*. If they met any of the exclusion criteria, they were disqualified from the study.

Table 1: *TMS Inclusion and Exclusion Criteria*	
INCLUSION CRITERIA:	
Age range between 50-65 years	
Have symptomatic knee OA as defined by the American College of Rheumatology *(Table 2)*[56,57]	
EXCLUSION CRITERIA:	
History of cardiovascular disease or any other medical condition that precludes safe participation in exercise	History of neurologic disorders, fibromyalgia, peripheral neuropathy, or rheumatoid arthritis
Impaired balance	Illicit drug use, alcohol abuse, or anyone currently withdrawing from any substance
Mental implants in the head, neck, or shoulders (excluding dental work)	Personal or familial history of seizures or epilepsy
Implanted foreign objects including ocular foreign objects, cochlear implants, brain stimulator, aneurysm clip, mediation pumps, intra-cardiac lines, or cardiac pacemakers	Currently taking medications that lower seizure threshold (e.g., tricyclic antidepressants, neuroleptic agents, Baclofen, Tramadol, etc.)
History of serious head injury, increased intracranial pressure, and/or loss of consciousness following head trauma	History of back/lower extremity surgery or back/lower extremity orthopedic injury in the past six months
Pregnant females	Body mass index (BMI) $\geq$40 kg/m^2
Current smokers	Inability to consistently comprehend and repeat back directions regarding details of the study

Table 2: *American College of Rheumatology Clinical Criteria for Knee Osteoarthritis (Altman et al,[57] Altman et al[56])*
PRESENTS WITH:
Knee pain
AND AT LEAST 3 OF 6:
Age > 50
Stiffness < 30 minutes
Crepitus
Bony tenderness
Bony enlargement
No palpable warmth

Testing sessions took place at the Musculoskeletal Health and Movement Sciences (MHMS) laboratory on the University of Toledo campus. The intervention sessions were performed at Friendship Baptist Church (FBC) of Toledo, OH and in the MHMS Laboratory.

Randomization

All participants' neuromuscular measures were tested on the leg affected by knee OA. In the case of bilateral knee OA, the limb with the greatest symptoms at baseline was tested. The order of variable testing during TMS assessments (SICI, LICI, CSP, and ICF) was randomized.

Order of assessment

Upon arrival to the MHMS laboratory, participants were provided with a standardized explanation of the study and completed the informed consent and baseline

demographic questionnaires. Voluntary quadriceps strength and neuromuscular measures followed.

Instrumentation

Voluntary quadriceps strength and central activation deficit

Voluntary quadriceps strength and CAD were measured using the Biodex Isokinetic Dynamometer (Biodex System 3 Biodex Medical Systems Inc., Shirley, NY, USA). Two 7x13cm Dura Stick II® (Chattanooga Group, Hixson, TN) self-adhesive electrodes were used to deliver the stimulus to the quadriceps muscles. Participants were able to visualize their torque output in real-time by means of a custom-written Visual Basic program. Data was captured using a BIOPAC MP150 unit (BIOPAC Systems Inc., Goleta, CA, USA) and associated AcqKnowledge software (BIOPAC Version 4.2.0, BIOPAC Systems, Inc.). The SIB utilized an exogenous square wave electrical stimulator and stimulation isolation unit (S88 and SIU8T, GRASS Technologies, West Warwick, RI, USA).

Corticospinal and intracortical excitability

Corticospinal and intracortical excitability of the quadriceps was measured via TMS, performed using the Magstim Rapid^2 (Magstim Company, Wales, UK) and associated double-cone coil (Magstim Company, Wales, UK). The maximal output of the stimulator was 2.0 Tesla. The magnetic stimulation did not exceed 1.2T due to the manufacturer advising not to exceed this output with our coil as we run the risk of melting the coil with repeated stimulation over 1.2T. TMS testing elicits a motor evoked potential (MEP) that was recorded in the vastus lateralis (VL) muscle. Two disposable,

10 mm pre-gelled, self-adhesive, Ag/AgCl surface electromyography electrodes (BIOPAC Systems, Inc.) were positioned 1.75 mm apart over the VL muscle belly. AcqKnowledge BIOPAC Software was used to visualize and record data.

Procedures

A single investigator collected all outcome measures. Measurements were recorded unilaterally on the limb that gives the subject the greatest disability.

Participants were seated in an upright position on the Biodex dynamometer with the hips and knees flexed to 85° and 90°, respectively. Straps were placed over their lap and bilaterally across the chest to restrict accessory movement during tests. The tibia, just proximal to the ankle joint, was secured to a pad on the arm of the dynamometer.

Quadriceps strength assessment

Prior to TMS testing, participants performed a series of maximal voluntary isometric contractions (MVICs) in the above-described position to determine voluntary quadriceps strength. Quadriceps strength measures were also utilized to determine muscle contraction levels required for active TMS testing. Participants were asked to cross their arms over their chest during each contraction to minimize upper extremity involvement, and also to maintain a flat position against the bottom and rear of the seat. Participants performed one warm-up contraction each at 25, 50, and 75% of their maximal ability. They then performed a series of quadriceps MVICs until the peak torques generated during two trials are within 5% of each other. Participants were provided with verbal and visual encouragement to elicit maximal effort. A maximum of 5 repetitions were performed and the peak value across all maximal effort trials was

normalized to participant body mass (kg) and used to quantify their isometric quadriceps strength (Nm/kg). A 60-second rest period between each trial was provided to minimize fatigue.

Burst superimposition testing

Corticospinal activation was assessed using the burst superimposition technique.[58] The participant remained positioned in the Biodex as previously described. Two 7x13cm self-adhesive stimulating electrodes were positioned on the proximal vastus lateralis (VL; with the medial border of the electrode aligned with the anterior superior iliac spine at the height of the greater femoral trochanter) and the distal vastus medialis (VM; with the lateral border of the electrode bisecting the patella 1.5 inches superior to the superior patella pole). Participants completed a warm-up at 25, 50, and 75% of their maximal effort while receiving submaximal stimulations at 25, 50, and 75% of the maximal 125 volts (100 pps train, 0.6 ms pulse duration, 100 ms train duration, and a 0.01ms pulse delay). Participants were asked to perform an MVIC with verbal and visual encouragement and once a plateau in torque output was reached, a supra-maximal electrical stimulus was delivered through the two electrodes placed superficially on the skin overlying the quadriceps. This added stimulus forcefully contracted any motor units within the muscle that were not activated voluntarily. Two trials were recorded with 60-seconds of rest between each trial. Activation was computed using the central activation ratio (CAR), which was the ratio of the participant's peak torque to the peak torque achieved during superimposition of the electrical stimulus.

Transcranial magnetic stimulation testing

Two 10-mm, pre-gelled Ag/AgCl surface electromyography (EMG) electrodes were positioned two centimeters apart over the belly of the VL, 10cm proximal to the lateral aspect of the superior patellar pole. Prior to electrode placement, the skin was shaved, debrided, and cleaned with isopropyl alcohol. Participants were given a Lycra swim cap to wear during testing. A pre-drawn grid on the swim cap allowed the investigator to position the TMS coil and ensure precise placement of the TMS coil across testing paradigms.[15] The grid was drawn as follows: perpendicular lines were drawn vertically on the swim cap and connected from the center of the occiput and nose, and from each external auditory meatus.[15] The investigators started at the coordinate (0, 0), moving systematically through the appropriate coordinates (those on the side of the head contralateral to the limb being tested). Two stimuli were delivered at each coordinate. The stimulator output was set at 55%. Machine output was increased if necessary and testing repeated until the optimal stimulating point was found. The optimal stimulating point was the coordinate yielding the largest, most consistent motor evoked potentials (MEPs) at 55% of the stimulator output. All subsequent stimuli were delivered over this location. Disposable earplugs were provided to participants once the swim cap was in place to minimize discomfort associated with the audible noise of TMS testing.[15]

Motor threshold testing

Participants remained in the same position seated on the dynamometer. Motor threshold was defined as the lowest stimulator output that elicits at least 4/8 positive MEPs.[59] A positive MEP had a peak-to-peak amplitude ≥100μV for active tests.[60] The double-cone coil was positioned over the motor cortex and the participant was asked to

contract her quadriceps to 5% of the previously determined MVIC during strength testing. Visual feedback was given to ensure proper activation. The participant received eight single stimuli at each stimulus intensity output. The stimulus intensity was initially set at 55% of machine output. The intensity was increased or decreased incrementally as necessary until threshold was determined. For example, if greater than 50% of the MEPs are positive during a given set, the stimulator intensity for the next set of stimuli would be reduced. Once active motor threshold (AMT) was determined, the machine output at which it was elicited was recorded. AMT was used to determine the stimulator output needed for subsequent testing.

Paired pulse testing

Three paired pulse paradigms were performed in a randomized order. Short interval intracortical inhibition (SICI) testing consisted of delivering a pair of TMS pulses separated by 1-5ms. The first pulse delivered was a subthreshold, conditioning stimulus (80% of AMT) while the second was a suprathreshold, test stimulus (120% of AMT). An interstimulus interval (ISI) of 3ms was used. Intracortical facilitation (ICF) utilized the same conditioning and test stimuli as SICI, though the interstimulus interval was set at 15ms. [21,54,55,61] Long interval intracortical inhibition **(**LICI) was performed similarly to SICI and ICF, though the interstimulus interval was set at 100ms. Both the conditioning and test stimuli for LICI were set at 120% of AMT. [21,54,55,61] Eight MEPs were recorded for each paradigm and normalized to the raw MEPs of 120% AMT determined during single-pulsed procedures.[21,54,55,61]

Statistical analysis

Means and standard deviations for all measures were calculated. Cohen's d effect sizes and 90% confidence intervals for pre to post strength measures and CAR were also calculated using Microsoft Excel 14.4.7. All data were represented graphically.

Chapter Four

Results

Thirteen patients enrolled in this study. Of those 13, nine were able to complete baseline strength and CAR measures and went on to begin the therapeutic exercise program. Since TMS testing has multiple exclusion criteria, we were only able to collect baseline TMS neuromuscular measures on six participants. Three patients completed the entire eight-week therapeutic exercise program, which allowed us to collect their follow-up strength and CAR measures *(Figure 8, Figure 9).*

Strength and Central Activation Ratio

Demographics for these nine subjects are displayed in Table 3. Normalized isometric strength resulted in an average of 1.70±0.74 Nm/kg *(Table 3)* for the nine participants who completed baseline testing.

As stated earlier, three participants (Age=59.67±2.89 years, Height=1.70 meters, Mass=85.13±8.95 kilograms, BMI=29.46±3.10 kg/m$^{2)}$ completed follow-up testing. Baseline normalized isometric strength was 2.22±0.83 Nm/kg. Baseline CAR was 0.99±0.01. Follow-up normalized isometric strength was 1.67±0.67 Nm/kg. Follow-up CAR was 0.97±0.03 *(Figure 9, Figure 12, Table 4).* Calculated effect sizes for strength and CAR were (*d* = -0.67 and *d* = -2*, respectively).*

TMS Testing

Six participants (Age: 56.17±5.12 y/o, Height: 1.68±0.08m, Mass: 75.75±6.39kg, BMI: 26.83±2.83 kg/m^2) completed baseline TMS testing. Average TMS variable testing

values are: AMT 46.50±7.85; SICI 0.52±0.27; ICF 2.17±0.97; and LICI 0.36±0.21 *(Table 5).*

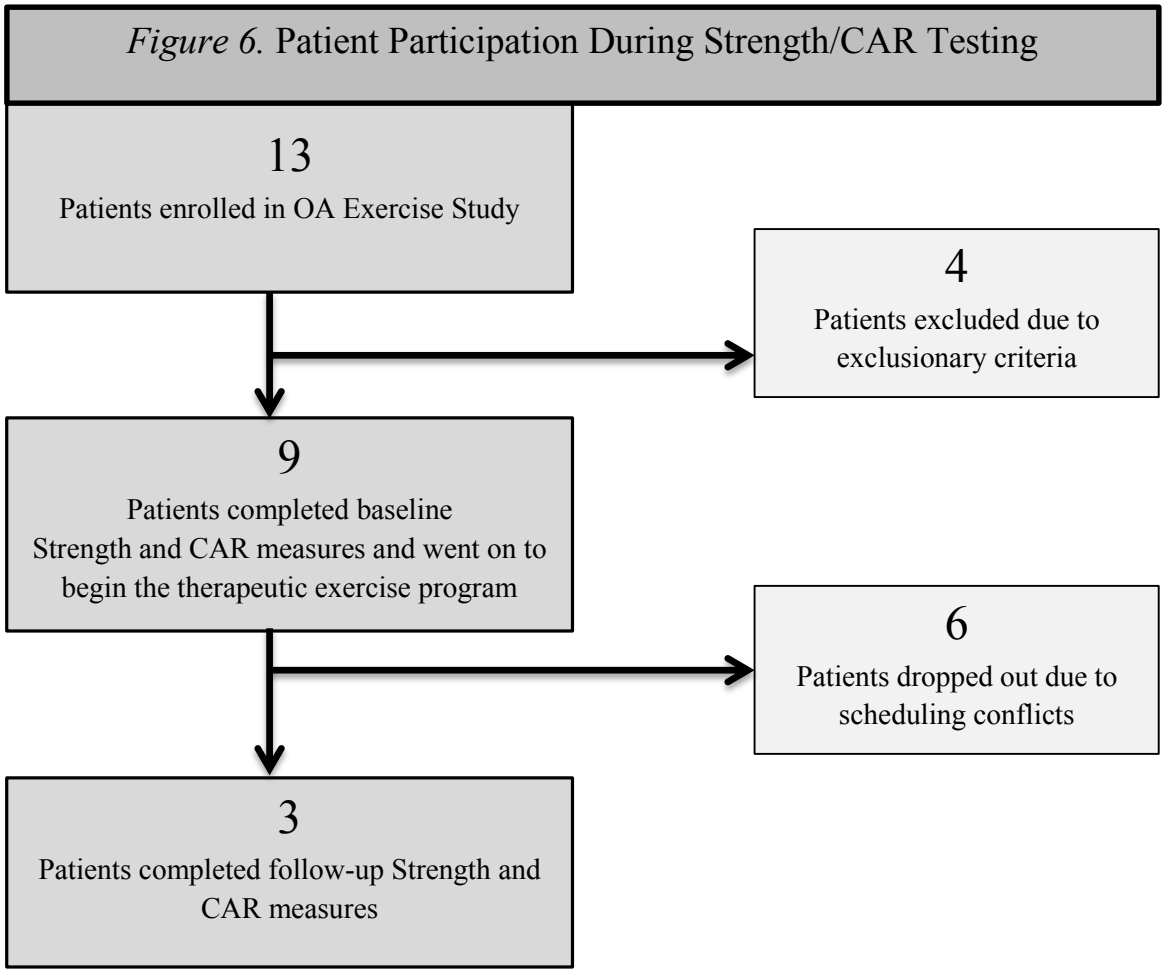
Figure 6. Patient Participation During Strength/CAR Testing
13
Patients enrolled in OA Exercise Study
4
Patients excluded due to exclusionary criteria
9
Patients completed baseline Strength and CAR measures and went on to begin the therapeutic exercise program
6
Patients dropped out due to scheduling conflicts
3
Patients completed follow-up Strength and CAR measures

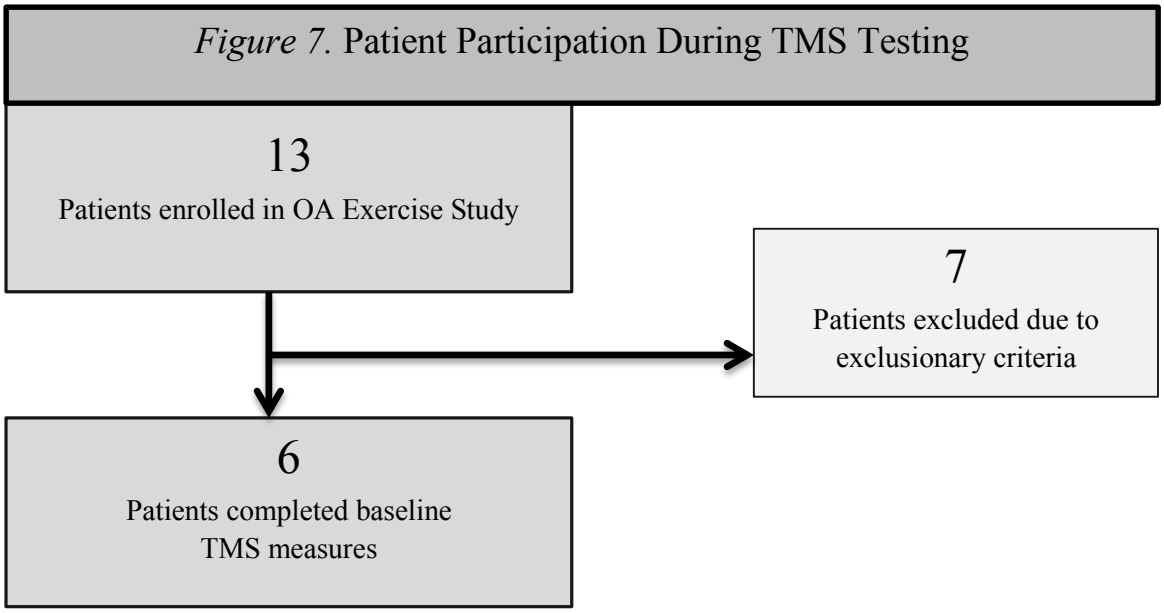
Figure 7. Patient Participation During TMS Testing
13
Patients enrolled in OA Exercise Study
7
Patients excluded due to exclusionary criteria
6
Patients completed baseline TMS measures

Figure 8. Average Normalized Strength in Females With Knee OA

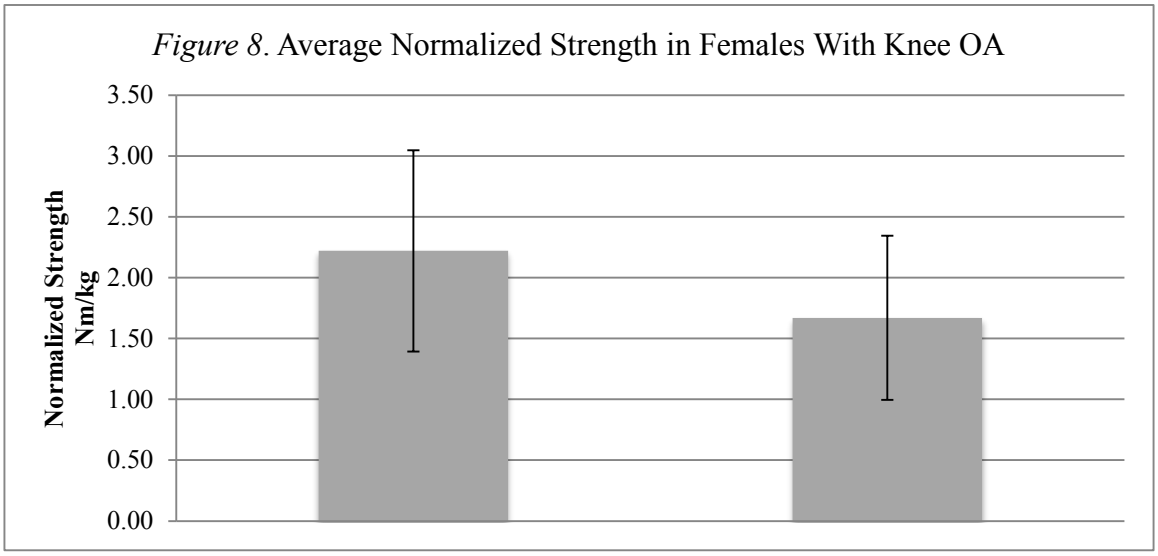

Figure 9. Central Activation Deficit in Females With Knee OA

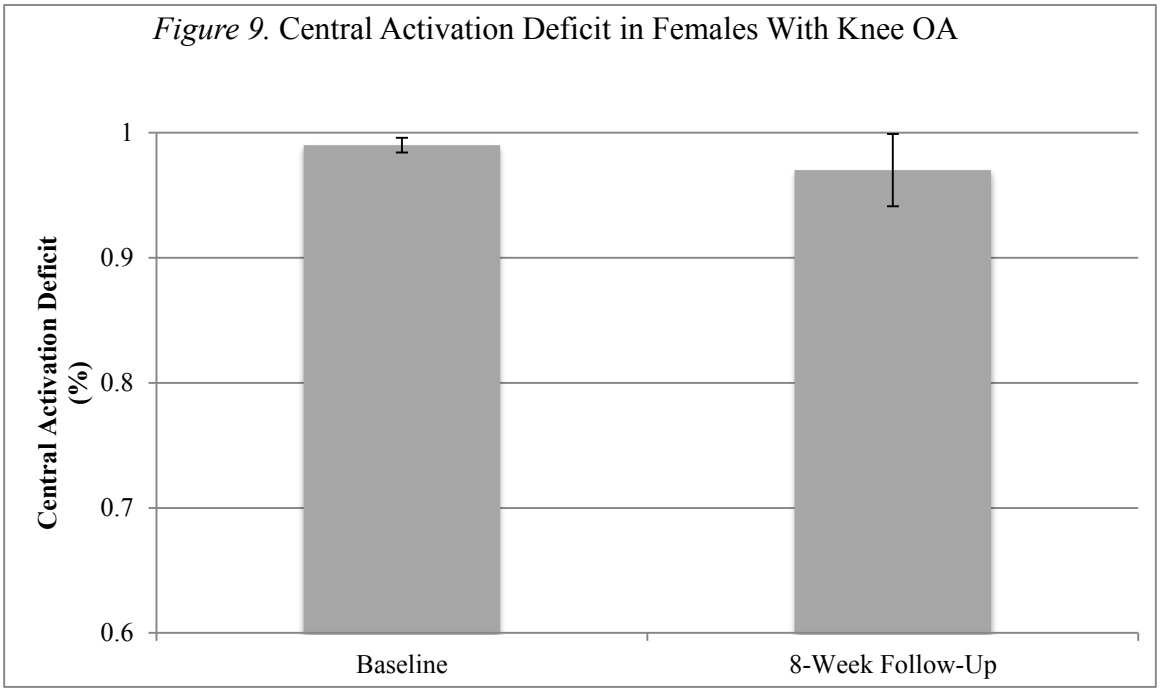

Table 3. *Baseline strength, normalized strength, and CAR.*

DEMOGRAPHICS					BASELINE		
ID	**Age**	**Height (m)**	**Mass (kg)**	**BMI**	**Strength (Nm)**	**Normalized Strength (Nm/kg)**	**CAR (%)**
OA_001	53	1.70	88.45	30.61	184.81	2.09	0.99
OA_002	50	1.60	70.76	27.64	129.24	1.83	0.92
OA_006	65	1.70	72.60	25.12	89.04	1.23	0.99
OA_007	61	1.70	117.90	40.80	61.14	0.52	0.94
OA_008	51	1.80	136.10	42.01	146.96	1.08	0.98
OA_011	58	1.70	74.80	25.88	219.29	2.93	0.99
OA_012	58	1.70	90.30	31.25	118.61	1.31	0.98
OA_013	63	1.70	90.30	31.25	219.25	2.43	0.99
OA_015	55	1.8	73.50	22.69	138.29	1.88	0.99
Mean±SD	57.11±5.28	1.71±0.06	90.52±22.58	30.81±6.69	145.18±54.51	1.70±0.74	0.97±0.03

Table 4. *Strength, normalized strength, and CAR*.												
DEMOGRAPHICS					**BASELINE**				**FOLLOW-UP**			
ID	**Age**	**Height** (m)	**Mass** (kg)	**BMI**	**Pain** (NPRS)	**Strength** (Nm)	**Norm. Strength** (Nm/kg)	**CAR** (%)	**Pain** (NPRS)	**Strength** (Nm)	**Norm. Strength** (Nm/kg)	**CAR** (%)
OA_011	58	1.70	74.80	25.88	6	219.29	2.93	0.99	0	170.68	2.28	0.99
OA_012	58	1.70	90.30	31.25	2	118.61	1.31	0.98	6	85.53	0.95	0.94
OA_013	63	1.70	90.30	31.25	6	219.25	2.43	0.99	0	160.18	1.77	0.99
Mean ±SD	59.67 ±2.89	1.70 ±0.00	85.13 ±8.95	29.46 ±3.10	4.67 ±2.31	185.72 ±58.12	2.22 ±0.83	0.99 ±0.01	2.00 ±3.46	138.80 ±46.43	1.67 ±0.67	0.97 ±0.03

Table 5. *TMS neuromuscular testing*.								
DEMOGRAPHICS					**TMS VARIABLES**			
ID	**Age**	**Height (m)**	**Mass (kg)**	**BMI**	**AMT**	**SICI**	**ICF**	**LICI**
OA_001	53	1.70	88.45	30.61		0.24	3.37	0.07
OA_002	50	1.60	70.76	27.64		0.36	2.78	0.35
OA_006	65	1.70	72.60	25.12	58	0.44	2.31	0.26
OA_009	56	1.60	74.40	29.06	45			
OA_011	58	1.70	74.80	25.88	41	0.93	1.03	0.60
OA_015	55	1.80	73.50	22.69	42	0.60	1.36	0.54
Mean±SD	56.17±5.12	1.68±0.08	75.75±6.39	26.83±2.86	46.50±7.85	0.52±0.27	2.17±0.97	0.36±0.21

Chapter Five

Discussion

The aim of this pilot study was to develop novel theories and a better understanding of how knee OA affects quadriceps activation. Although there was a relatively small sample size, we were able to gain a small understanding of how our participants' quadriceps activation was being affected in the presence of knee OA.

Muscle Strength and Activation at Baseline

It is well known that when an injury occurs, the healthy musculature surrounding a joint becomes less active or not facilitated, and this is known as CAD.[15,18,20] As previously stated, this affects a person's ability to activate motor neurons for recruitment during normal muscular contractions. Women with knee OA typically exhibit impaired quadriceps activation.[15,18,20] It has been reported previously that a CAR≥0.95 is considered healthy.[62] Thus, the group of participants involved in this study did not have decreased quadriceps activation as measured by their CAR.

A number of previous investigators have utilized CAR to quantify quadriceps activation in patients with knee OA.[41,63,64,66,67,68] These previously published data range from CAR of 67-95%. The women enrolled in our study presented with CAR greater than in these previously published studies. A number of explanations for this finding may exist. First, CAR diminishes with the increasing grade of OA. As severity increases, a greater CAR is found.[68] Although we did not quantify KL grade in this study, we believe that based on the strength and activation data collected as well as the magnitude of symptoms present the participants included presented with KL grade 1 knee OA.

Because KL grade 1 is a presence of symptoms without radiographic evidence, our participants would most appropriately fit within this category. Previous studies that also did not quantify KL grade reported CAR measures around 93%,[64,66,67] which is within the range of CAR data collected in the present study. Additionally, BMI plays an important role in the knee OA population. Because obesity is a contributing factor to knee OA, those with an increased BMI are more likely to suffer from this disease. Unfortunately, in patients with a high BMI, there is a large degree of subcutaneous adipose tissue present that diminishes the magnitude of the electrical stimulus delivered to the muscle, which does not allow all previously inactive motor units to be recruited, thereby increasing the CAR value obtained. Therefore, patients with a high BMI are excluded from studies examining quadriceps CAD. This limits the data available. In order to fully understand this population, all those suffering from knee OA, regardless of exclusion criteria, need to be evaluated in order to obtain a better understanding of this patient population.

A number of other studies have used normalized quadriceps strength to evaluate women with knee OA. Previous investigators report quadriceps strength of 1.4-2.0 Nm/kg.[43,64,68] in the affected limb of patients with knee OA, which is similar to the data obtained in the present study as well as strength for healthy adults.[64] Typically, however, patients with knee OA experience up to a 22-36% quadriceps strength deficit when compared to healthy individuals.[66,67] An explanation for this discrepancy would, again, relate to KL grade. Because our patients likely had emergent OA, it is logical that they may have nearly full strength compared to healthy adults. Additionally, as mentioned previously, BMI plays a factor in this and since we were unable to collect data on those with greater BMI, further research is needed. Finally, it is known that a greater

quadriceps MVIC can be achieved within the midrange (50-70°) of knee flexion;[63] therefore, if this measure would have been tested within this range, different values may have been obtained. However, testing strength at 90° of knee flexion was used because it is most accurate when completing the other subsequent tests and allows for the most direct comparison to strength obtained in other studies.[63,68] Lastly, because most of the exercises performed within the therapeutic exercise program were targeted to improve gross lower extremity strength, the quadriceps may not have been sufficiently exercised in order to see strength gains.

The major difference between this pilot study and other studies done is the self-reported diagnosis of osteoarthritis. Our participants subjectively reported their diagnoses of OA regardless of whether they have been diagnosed by a physician or not. Additionally, radiographic evidence of each person's disease would have allowed us to further relate our data to other data, and to also take the severity of one's disease into consideration. All of these factors would have been helpful in analyzing our data, however the American College of Rheumatology Clinical Criteria for Knee Osteoarthritis is a valid scale for identifying patients with knee OA and has been previously used. Furthermore, determining a participant's true CAR and MVIC values are very challenging. The participant has to maximally contract their quadriceps in order to get a valid reading, which may frighten some individuals. With the fear of producing more pain upon maximal contraction, the CNS input to the alpha-motor neuron pool is reduced, which results in an impaired activation.[19] Finally, participants may not want to completely contact due to existent pain within the knee joint itself.

Exercise Group

The secondary aim of this pilot study was to determine if a group-based exercise intervention could augment CAD in women with knee OA. As stated previously, the 3 women who completed follow-up testing after the exercise program experienced a strength and CAR deficit when comparing their baseline and post-measures. Because their activation was already so high (0.97±0.74), it is easy to see why they did not improve. However, these participants demonstrated a reduction in muscle strength following the intervention, when we hypothesized strength should have increased. Why this occurred is unclear; however, it is possible that factors such as knee pain and training adaptations may have influenced muscle strength.

Of the 3 participants who completed follow-up measures, 2 of them experienced a decrease in pain, while the third reported follow-up pain 3 times greater than at the beginning of the study. Because of the great discrepancy in results seen here, strength loss is likely due to other factors.

The therapeutic exercise intervention employed in this study was targeted to improve gross lower extremity muscle strength. Although a quadriceps strength loss was seen, these patients reported feeling 'better'. As this pilot study was part of a larger study, WOMAC scores were assessed. All subcategories, as well as the total score for the WOMAC assessment improved following the 8-week therapeutic exercise intervention. An explanation for not seeing strength improvements is the fact that the strengthening exercises were solely with the participant's bodyweight. No external weight or force was used to strengthen the lower extremity. The intention behind not using external weight was that the participant could complete the exercises at home and

continue them long-term following the conclusion of the study. Although each participant progressed throughout the course of the study, pure strength may not have been challenged because added demands (extra weight) were not added to the exercises. The body will adapt to what is placed upon it, but only the specific adaptation needed will occur; therefore, the adaptation to exercise is directly related to the type of training stimulus.[69] Since this study required high repetitions with low force, the capacity to perform prolonged work increased. However, this does not necessarily mean that strength would have to increase. A study done by Hickson et al. compared strength and endurance training (concurrent training) to strength training alone and endurance training alone. This study found a 44% increase in thigh girth in the strength training group, a 25% increase in the concurrent training group, and no increase in the endurance group. The strength group performed each exercise with as much weight as they could handle, which was typically around 80% of their maximal contraction. An interesting finding was that the strength group continued to see increases throughout the entire 10-week program, while the concurrent training group only saw increases in the first 8 weeks, and then saw a decrease in weeks 9 and 10. It would have been interesting to measure strength each week throughout our pilot study to see how our participants' strength was changing, especially when it started declining. One additional thing that made the concurrent training group different than our group was the rest period between strength and endurance bouts. Our study completed the walking portion immediately after strength training was completed; however, Hickson et al. completed the bouts of exercise 2 hours apart from each other, which is consistent in the literature for providing the greatest physical improvement.[69] Because our study did not necessarily train for strength

because weight was not added, it may be that the therapeutic exercise program was training more for an endurance improvement. Although bodyweight training may initially improve strength, strength training alone results in the greatest strength gains when compared to endurance training alone and concurrent training.[70] The strength loss seen could be attributed to this theory.

An additional explanation why strength may have decreased is because strength was measured isometrically in a 90° position. This is fairly consistent in the literature; however, the only time that the participants acted in a 90° position was in the rest position during the sit-to-stand exercise. If the participants are not exercising in the specific position that they were tested in, strength gains may not have been seen. If our participants performed the strength assessment within the mid-range of motion, there may have been strength gains noted. However assessing MVIC at 90° of knee flexion allowed for strength comparison to previous literature.

A final possible explanation of our inconclusive results could be because these participants did not seem to have all of the major signs and symptoms of knee OA. Although these participants reported suffering from knee OA, it seemed as though that they were in the very beginning stages of the disease. The disease was not progressed enough to see major neuromuscular deficits, but rather just pain and the beginning stage of function loss.

TMS at Baseline

The final aim of this study was to record baseline TMS measures for individuals with knee OA. This information is desired because there is a large gap in the literature

pertaining to these data. This information will propel researchers forward into further understanding how knee OA affects intracortical excitability and what can be done to prevent this disease from worsening.

This pilot study's baseline TMS data, as well as unpublished data performed in the MHMS Laboratory can be compared. The unpublished study tested reliability and validity between 2 investigators on young, healthy adults. Based on these findings, the 6 participants that participated in our pilot study experienced decreased SICI, increased ICF, increased AMT, and decreased LICI when compared to healthy controls. This means that the OA population experienced a decreased $GABA_A$ inhibition, which was expected; an increased NMDA facilitation, which was not expected; a decreased $GABA_B$ inhibition, which was expected; and an increased stimulus required to activate the motor cortex, which was expected.

If the osteoarthritic population truly suffers from altered intracortical inhibition and facilitation, SICI and LICI would be decreased and would result in smaller numbers. This would indicate a greater inhibition. ICF would be increased and would result in larger values signifying a greater facilitation. Following a therapeutic exercise intervention, inhibition would be expected to decrease (larger SICI and LICI values), while facilitation would be expected to increase (larger ICF values). However, it is unclear as to how this data compares with other populations, and amongst the OA population, because of the lack of data. This pilot study is one of the first to quantify these measures. Therefore, more research is warranted in order to fully understand the deficits seen in knee OA.

Limitations

As previous stated, up to ~30% of participants are not able to participate in TMS and CAR testing.[18] Only 6 out of 9 participants were able to complete baseline TMS and CAR assessments. Two participants were excluded due to BMI being greater than 40kg/m^2. The other participant was excluded due to a neurologic condition predisposing her to seizures. Because of these factors, we may have not been able to accurately test TMS and CAR measures. Women with a higher BMI are more likely to suffer from knee OA due to the added stress on their tibiofemoral joint. We are unable to measure an accurate EMG signal on individuals with a greater BMI because the TMS stimulus would be too great, therefore not allowing us to get a true reading on this population.

Assessor blinding could not take place due to the nature of this study. Because the assessors supervised each exercise intervention with the treatment group, blinding was not possible, resulting in a possible bias in follow-up strength measures. However, by supervising the exercise intervention, we were able to ensure that the participants were accurately performing the exercises.

Since we ultimately could not control what the participants did outside of our study, an additional limitation could account for the strength loss measured in strength testing. Participants were asked to keep track of the exercises completed during the week in order for us to record this information during the following visit. Because we were not able to physically be present every time they exercised, we are unsure as to whether or not they actually completed these exercises.

During strength and CAR testing, participants were instructed to maximally contract against the Biodex, and it is possible that they were not contracting as hard as they could. To help encourage the participants, verbal and visual cues were given.

A final limitation of this study is the small sample size. Differences may not be seen with this population because of the small number of the people included. Although we exhausted our recruitment methods, additional participants are absolutely needed in order to see differences and truly understand the influence of knee OA on quadriceps strength and central activation.

Future Research

Since we were unable to see how a bodyweight therapeutic exercise program affected TMS values, further research is warranted. Initially, it would be important to recruit a larger group of women with knee OA in order to ensure that some would still be present to measure following the exercise program. A power analysis previously completed revealed a need for 17 participants per group (OA treatment vs. OA control). Next, it would be important to compare this population with a control group. This could include a group of women with knee OA who do not participate in the exercise program, and an additional group that would include healthy individuals going through the same exercise program. This would allow the assessors to see differences and compare measures between and within all groups.

It would also be interesting to compare the bodyweight exercise program to a strength training exercise program where actual weights would be used during the

activities. Maybe then, an improvement in strength would be seen because the participants would not be training for endurance, but strength instead.

This research could lead to many more studies on the effects of therapeutic exercise on neuromuscular measures in women with knee OA. This study could be done with a larger population over a longer time period in order to collect proper baseline and follow-up measures on numerous individuals. In order to fully understand how knee OA affects a person's neuromuscular measures, it is imperative to be able to collect this information from beginning to end.

Conclusion

This investigation found baseline TMS values, strength values, and CAR values for women with knee OA. Additionally, this study found that isometric quadriceps strength decreased following an 8-week body weight therapeutic exercise program, which is counterintuitive. These results did not support our hypothesis that strength would increase following the exercise program. Additional participants with knee OA are needed to further test strength and neuromuscular measures in order to better understand the effect this disease has on these measures. Although we did not see a statistical improvement in strength, the participants reported having a greater ability and confidence to perform activities of daily living. Additional studies are required to further understand the role of quadriceps central activation in the osteoarthritis process so that appropriate interventions can be developed and implemented.

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Appendix A

Institutional Review Board

UT IRB # 108105
ICF Version Date: 05/05/2014

THE UNIVERSITY OF TOLEDO

Department of Kinesiology
2801 W. Bancroft, MS 119
Toledo, Ohio 43606
(p) 419-530-4467
(f) 419-530-2477

ADULT RESEARCH SUBJECT INFORMATION AND CONSENT FORM

Exercise To Improve Knee and Hip Pain in Adults

Principal Investigator.	Patricia Hogue, PhD, PA-C
Other Staff (identified by role)	Abbey Thomas, PhD, ATC (Co-investigator) David Sohn, MD, JD (Co-investigator) Michelle McLeod, MA, ATC (Coordinator) Devon Eley, ATC (Coordinator) Allison Schultz (Coordinator) Bradley Stempky, ATC (Coordinator)
Contact Phone number(s).	(419) -383-4807

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 of exercise for people with knee and hip osteoarthritis. The purpose of the study is to learn if a series of muscle strengthening exercises and walking in a group setting can improve pain and symptoms in people suffering from osteoarthritis This information will help the researchers determine the best way to treat knee and hip osteoarthritis.

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NO TEXT THIS PAGE

You were selected as someone who may want to take part in this study because you have knee or hip osteoarthritis Up to 75 people from the University of Toledo and surrounding community will participate in this study

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 Sciences Laboratory at the Unviersity of Toledo on 2 occassion, once at the beginning and once at the end of the study. Each visit will last approximately 3 hours. Friendship Baptist Church in Toledo, OH on up to 9 occasions (once per week for 9 weeks) Each session will last approximately 1 hour Your participation in this study will last 9 weeks

Each session may include the following exercises to treat pain associated with osteoarthritis.
1) Symptom and activity level assessment
2) Gait assessment
3) Strength and neuromuscular activation assessment
4) Functional assessment
5) Muscle strengthening
6) Walking

Symptom and Activity Level Assessment
You will be asked to complete a series of questionnaires regarding your knee or hip symptoms. The questionnaires ask about any pain you may be experiencing and how that pain influences your daily activities and overall function. You will also be asked to disclose any medications you are taking for knee or hip pain. Lastly, you will be asked to complete a brief survey indicating your current level of physical activity This will take approximately 5 minutes.

Gait Assessment
Prior to performing these tasks, a series of joint markers will be placed on your legs and trunk. Joint markers are Styrofoam balls covered in tape They allow researchers to recreate your joint motion on a computer You will be asked to walk approximately 30 ft on a level floor As you walk, you will step on a force plate (scale). A force plate allows researchers to understand the loads being placed on your joints as you walk. You will be asked to perform this task at two different speeds, your comfortable walking pace and a speed equivalent to normal, human walking speed You will also be asked to go up and down a custom-made staircase. This staircase has four steps You will be asked to go up at a comfortable pace You will pause briefly at the top and then be asked to go down the stairs at a comfortable pace. These tasks will take approximately 30 minutes to complete.

Strength and Neuromuscular Activation Assessment
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.

Muscle Activation Testing
This test helps researchers determine if you are using your thigh muscles to their full potential This test is similar to the strength testing, except you will have two electrodes (stickers) placed over your thigh muscles. These electrodes will deliver a brief, mild electrical stimulus to your leg while you contract your thigh muscles as hard as possible 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.

Electromagnetic Stimulation of the Brain to Measure Muscle Activity
This test helps researchers understand how your brain is controlling your thigh muscles The researchers will use a strong magnetic coil to deliver a brief electromagnetic stimulus to your scalp The output of this coil is similar to what is delievered during an MRI. By using this electromagnetic stimulus, the researchers can selectively activate your thigh muscles to better understand how they are functioning During this testing, you will be asked to sit in a chair and you may be asked to contract your thigh muscles at up to 20% of their maximal strength. The bullet points below describe the four steps to this testing process.

- Brain Mapping
  This process helps the researchers find the spot on your scalp that best corresponds to your thigh muscle. This spot is called your optimal stimulating point and it is where researchers will place the coil for the rest of the testing. For this test, you will sit quietly in a chair and the coil will be moved around on your scalp until the researchers generate a consistent contraction in 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 stimuli will be delivered 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 30 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. 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 tell 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 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.

Functional Assessment
You may be asked to complete a series of activities to measure your physical function These tests will be similar to things you do every day, including rising from a chair and walking down a hallway These tests may be timed. These tests will take approximately 10 minutes to complete.

Muscle Strengthening

When you report to Friendship Baptist Church, you will be asked to perform a series of exercises to strengthen your leg muscles. A member of the study team will demonstrate the exercises to you and talk you through the process of performing them Exercises will be performed using your own body weight to provide resistance You will perform up to 6 different exercises. Up to 4 sets of 20 repetitions of each exercise may be performed. You will be provided a warm-up period and ample rest time between sets These exercises are standard physical therapy exercises for people with osteoarthritis These exercises will take approximately 20 minutes to complete

Walking
A member of the study team will accompany you as you walk in the church building or around the property. You will walk at a comfortable pace for up to 45 minutes.

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

Likely Risks

- Muscle soreness as a result of strengthening exercises
- Mild, temporary discomfort in the scalp

Less Likely Risks

- Muscle soreness as a result of strength testing
- Mild, temporary skin irritation from the electrodes
- Minor discomfort from noise associated with the TMS pulse. To minimize this risk, you will be offered 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
- Mild headache lasting a few hours after testing If you have a history of headache disorders, magnetic stimulation may aggravate your headaches

Unlikely Risks

- There is a risk for seizures with magnetic stimulation of the brain, especially if you have had a seizure before or are taking medication that increases your seizure risk. Seizures have only been reported in people given repetitive magnetic stimulation. You will not be receiving repetitive magnetic stimulation.
- Loss of confidentiality
- There may be risks that are unknown to the researchers at this time

Exercise is the standard of care treatment for osteoarthritis But, your condition may not get better or may become worse while you are in this study Magnetic stimulation of the brain is safe for most people, however, it may have short or long-term risks associated with it that are not presently known or suspected If you become pregnant, the particular procedures involved in the study may involve risks to the embryo or fetus that are currently unknown.

POSSIBLE BENEFIT TO YOU IF YOU DECIDE TO TAKE PART IN THIS RESEARCH

As a result of participating in this study, you may notice less pain in your knees or hips Also, you may notice that the muscles you exercised are stronger and your overall fitness is improved. However, we cannot and do not guarantee or promise that you will receive any benefits from this research.

COST TO YOU FOR TAKING PART IN THIS STUDY

There is no cost to you for taking part in this study

PAYMENT OR OTHER COMPENSATION TO YOU FOR TAKING PART IN THIS RESEARCH
You will not receive financial compensation for participating in this study

ALTERNATIVE(S) TO TAKING PART IN THIS RESEARCH
This study is designed to relieve pain in your knees or hips related to osteoarthritis Physical therapy, including exercises that are a part of this study, combined with pain relieving medications prescribed by your physician are the current standard of care for people with osteoarthritis. Your alternative to participating in this study is not to participate.

CONFIDENTIALITY - (USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION)
The researchers will make every effort to prevent anone who is not on the research team from knowing that you provided this information, or what that information is. The consent forms with signatures will be kept separate from the information we collect, which will not include names and which will be presented to others only when combined with other responses Although we will make every effrt to protect your confidentiality, there is a low risk that this might be breached.

Under some circumstances, the Institutional Review Board, or the Research and Sponsored Programs of the University of Toledo may review your information for compliance audits. If you receive any payments for taking part in this study, your personal information and limited information about this study will be given to The University of Toledo's accounts payable department as necessary to process payment to you We may also disclose your protected health information when required by law, such as in response to judicial orders.

The University of Toledo is required by law to protect the privacy of your health information, and to use or disclose the information we obtain about you in connection with this research study only as authorized by you in this form There is a possibility that the information we disclose may be re-disclosed by the persons we give it to, and no longer protected. However, we will encourage any person who receives your information from us to continue to protect and not re-disclose the information.

Your permission for us to use or disclose your protected health information as described in this section is voluntary However, you will not be allowed to participate in the research study unless you give us your permission to use or disclose your protected health information by signing this document

You have the right to revoke (cancel) the permission you have given to us to use or disclose your protected health information at any time by giving written notice to Patricia Hogue, PhD, PA-C However, a cancellation will not apply if we have acted with your permission, for example, information that already has been used or disclosed prior to the cancellation. Also, a cancellation will not prevent us from continuing to use and 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.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U S Law This Web site will not include information that can identify you At most, the Web site will include a summary of the results You can search this Web site at any time


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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, contact the investigators for this study· Patricia Hogue, PhD, PA-C at 419-383-4807

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.

TEXT CONT. 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 the investigators for this study, Patricia Hogue, PhD, PA-C at 419-383-4807

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
Relationship to the Subject (Healthcare Power of Attorney authority or Legal Guardian)		Time a.m p m
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.

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Appendix B

Data Collection Documents

IRB # PI Thomas, AC Date 10/23/12

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

11. Have you ever suffered a serious head injury (including concussion)? Yes No

    If yes, please answer the following questions

    a. When did your head injury occur?

    _____

    b. Did you lose consciousness? _____

    c. Do you suffer from any memory loss as a result of your head injury? Yes No

12. Do you currently, or have you ever, had a condition that increases the pressure within your brain? Yes No
13. Do you have a history of illicit drug use, alcohol abuse, or are you currently withdrawing from any substance? Yes No
14. What medications are you currently taking? Please list all prescription and over the counter medications. _____

    _____

    _____

    _____

    _____

Investigator performing screening _____

To be collected only if participant is eligible

Name _____ Date _____

Date of birth _____ Age _____

Phone _____ Alternate Phone: _____

Email _____

Participant ID

BASELINE

Demographics			
Age			
Height			
Mass		BMI	#DIV/0!

Functional Performance	
GUG	
6MW	

Symptoms			
WOMAC pain			
WOMAC stiffness			
WOMAC disability		WOMAC total	0
NPRS			
GRS			
UCLA			

Weeks 1-8 Symptoms Left		
Week 1	NPRS	
Week 2	NPRS	
Week 3	NPRS	
Week 4	NPRS	
Week 5	NPRS	
Week 6	NPRS	
Week 7	NPRS	
Week 8	NPRS	
Week 9	NPRS	

Weeks 1-8 Symptoms Right		
Week 1	NPRS	
Week 2	NPRS	
Week 3	NPRS	
Week 4	NPRS	
Week 5	NPRS	
Week 6	NPRS	
Week 7	NPRS	
Week 8	NPRS	
Week 9	NPRS	

Exercise (days/week)	
Week 1	
Week 2	
Week 3	
Week 4	
Week 5	
Week 6	
Week 7	
Week 8	
Week 9	

FOLLOW-UP

Demographics			
Age			
Height			
Mass		BMI	#DIV/0!

Functional Performance	
TUG	
6MW	

Symptoms			
WOMAC pain			
WOMAC stiffness			
WOMAC disability		WOMAC total	0
NPRS			
GRS			
UCLA			

Central Activation Ratio Data Collection Form

Subject # _____ Date _____ Leg Tested First _____

Practice MVIC		
	Right Leg	Left Leg
Trial 1		
Trial 2		
Trial 3		
Trial 4		
Trial 5		
Trial 6		
Mean Threshold		

CAR Testing				
	Right Leg		Left leg	
	Pre Trigger Average	Peak Torque	Pre Trigger Average	Peak Torque
Trial 1				
Trial 2				
Trial 3				
Trial 4				

Participant ID:_____ Date: _____ Session _____

Left Leg Mapping Template

(-2,2) _____μV _____μV _____μV	(-1,2) _____μV _____μV _____μV	(0,2) _____μV _____μV _____μV	(1,2) _____μV _____μV _____μV	(2,2) _____μV _____μV _____μV	(3,2) _____μV _____μV _____μV	(4,2) _____μV _____μV _____μV
(-2,1) _____μV _____μV _____μV	(-1,1) _____μV _____μV _____μV	(0,1) _____μV _____μV _____μV	(1,1) _____μV _____μV _____μV	(2,1) _____μV _____μV _____μV	(3,1) _____μV _____μV _____μV	(4,1) _____μV _____μV _____μV
(-2,0) _____μV _____μV _____μV	(-1,0) _____μV _____μV _____μV	**(0,0)** _____μV _____μV _____μV	(1,0) _____μV _____μV _____μV	(2,0) _____μV _____μV _____μV	(3,0) _____μV _____μV _____μV	(4,0) _____μV _____μV _____μV
(-2,-1) _____μV _____μV _____μV	(-1,-1) _____μV _____μV _____μV	(0,-1) _____μV _____μV _____μV	(1,-1) _____μV _____μV _____μV	(2,-1) _____μV _____μV _____μV	(3,-1) _____μV _____μV _____μV	(4,-1) _____μV _____μV _____μV
(-2,-2) _____μV _____μV _____μV	(-1,-2) _____μV _____μV _____μV	(0,-2) _____μV _____μV _____μV	(1,-2) _____μV _____μV _____μV	(2,-2) _____μV _____μV _____μV	(3,-2) _____μV _____μV _____μV	(4,-2) _____μV _____μV _____μV
(-2,-3) _____μV _____μV _____μV	(-1,-3) _____μV _____μV _____μV	(0,-3) _____μV _____μV _____μV	(1,-3) _____μV _____μV _____μV	(2,-3) _____μV _____μV _____μV	(3,-3) _____μV _____μV _____μV	(4,-3) _____μV _____μV _____μV

PI Thomas, AC

Version Date 10/24/12

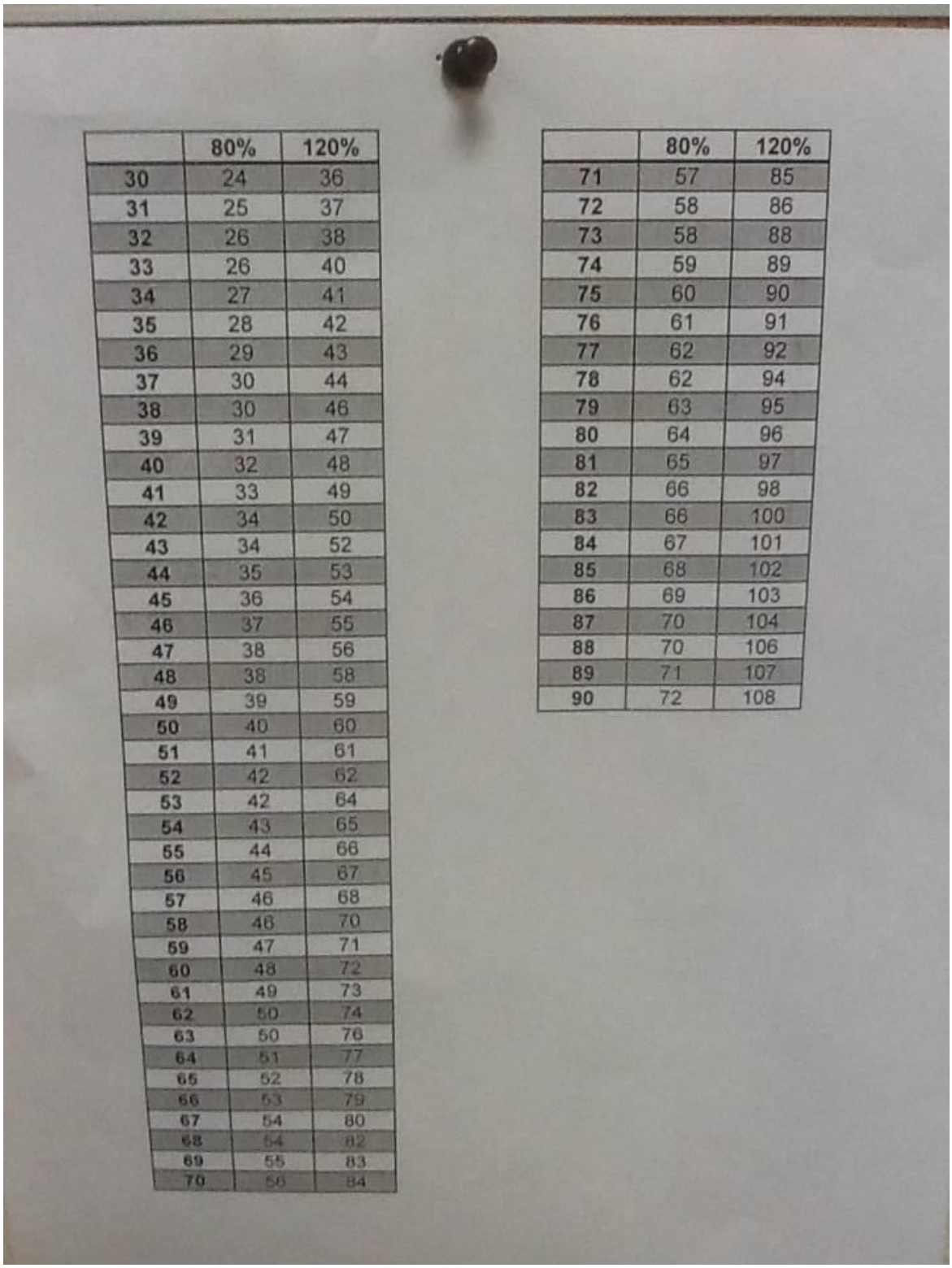
Participant ID _____ Date _____ Session _____

Right Leg Mapping Template

(-4,2) _____μV _____μV _____μV	(-3,2) _____μV _____μV _____μV	(-2,2) _____μV _____μV _____μV	(-1,2) _____μV _____μV _____μV	(0,2) _____μV _____μV _____μV	(1,2) _____μV _____μV _____μV	(2,2) _____μV _____μV _____μV
(-4,1) _____μV _____μV _____μV	(-3,1) _____μV _____μV _____μV	(-2,1) _____μV _____μV _____μV	(-1,1) _____μV _____μV _____μV	(0,1) _____μV _____μV _____μV	(1,1) _____μV _____μV _____μV	(2,1) _____μV _____μV _____μV
(-4,0) _____μV _____μV _____μV	(-3,0) _____μV _____μV _____μV	(-2,0) _____μV _____μV _____μV	(-1,0) _____μV _____μV _____μV	**(0,0)** _____μV _____μV _____μV	(1,0) _____μV _____μV _____μV	(2,0) _____μV _____μV _____μV
(-4,-1) _____μV _____μV _____μV	(-3,-1) _____μV _____μV _____μV	(-2,-1) _____μV _____μV _____μV	(-1,-1) _____μV _____μV _____μV	(0,-1) _____μV _____μV _____μV	(1,-1) _____μV _____μV _____μV	(2,-1) _____μV _____μV _____μV
(-4,-2) _____μV _____μV _____μV	(-3,-2) _____μV _____μV _____μV	(-2,-2) _____μV _____μV _____μV	(-1,-2) _____μV _____μV _____μV	(0,-2) _____μV _____μV _____μV	(1,-2) _____μV _____μV _____μV	(2,-2) _____μV _____μV _____μV
(-4,-3) _____μV _____μV _____μV	(-3,-3) _____μV _____μV _____μV	(-2,-3) _____μV _____μV _____μV	(-1,-3) _____μV _____μV _____μV	(0,-3) _____μV _____μV _____μV	(1,-3) _____μV _____μV _____μV	(2,-3) _____μV _____μV _____μV

PI Thomas, AC

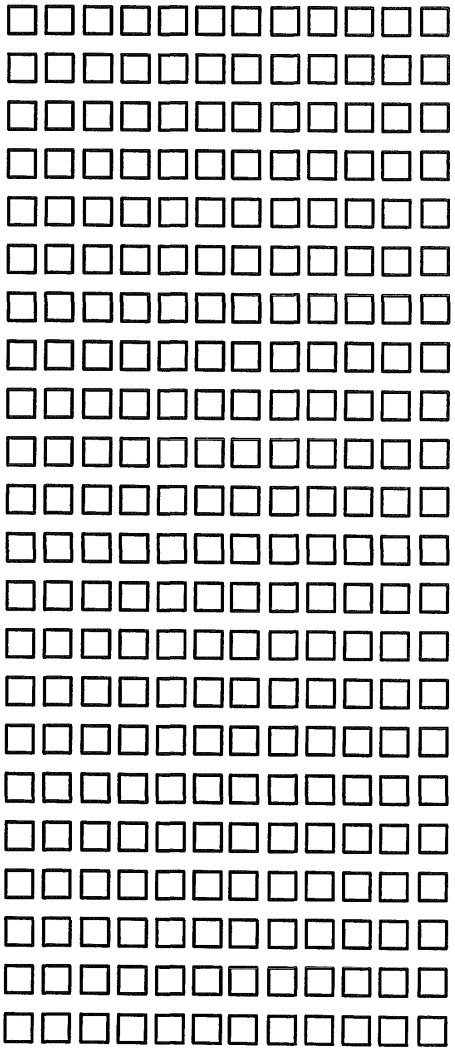
Version Date 10/24/12



	80%	120%
30	24	36
31	25	37
32	26	38
33	26	40
34	27	41
35	28	42
36	29	43
37	30	44
38	30	46
39	31	47
40	32	48
41	33	49
42	34	50
43	34	52
44	35	53
45	36	54
46	37	55
47	38	56
48	38	58
49	39	59
50	40	60
51	41	61
52	42	62
53	42	64
54	43	65
55	44	66
56	45	67
57	46	68
58	46	70
59	47	71
60	48	72
61	49	73
62	50	74
63	50	76
64	51	77
65	52	78
66	53	79
67	54	80
68	54	82
69	55	83
70	56	84

	80%	120%
71	57	85
72	58	86
73	58	88
74	59	89
75	60	90
76	61	91
77	62	92
78	62	94
79	63	95
80	64	96
81	65	97
82	66	98
83	66	100
84	67	101
85	68	102
86	69	103
87	70	104
88	70	106
89	71	107
90	72	108

Participant ID _____ Date _____ Session _____

Paradigm	Results
_____	

+ = MEP; - = too low to be MEP; ↑=value higher than average; ↓= value lower than average

Appendix C

Therapeutic Exercise Intervention

Arthritis 101 Exercises   Dr Abbey Thomas

Instructions:

1 Perform exercises 8-10 times for each leg (when applicable)
2 Repeat 2-3 times throughout the day
3 Complete exercises 3 days per week

~~~~~~

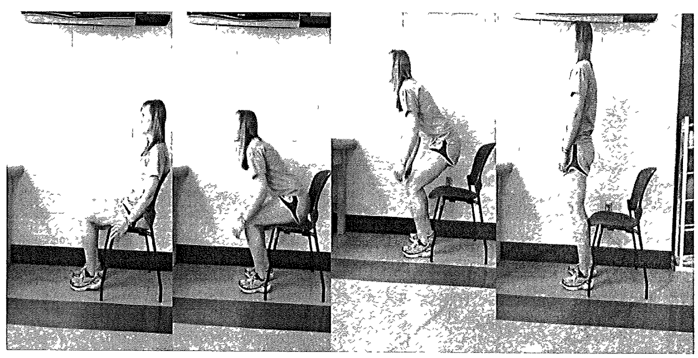
Seated Exercises

Knee extension

1 Sit in a chair
2 Slowly straighten your knee
3. Hold for 3-5 seconds
4. Slowly return to start position

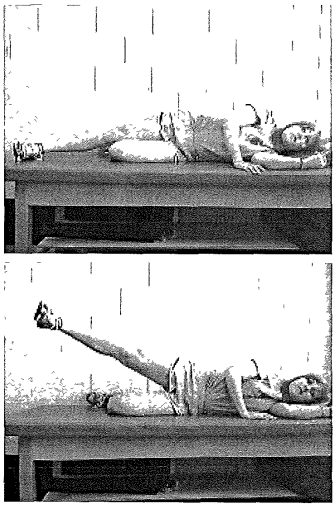
Sit-to-Stand

1 Sit in a chair
2 Slowly rise to a standing position
3 Slowly sit down in the chair



CENTER FOR SUCCESSFUL AGING
THE UNIVERSITY OF TOLEDO
~~~~~~

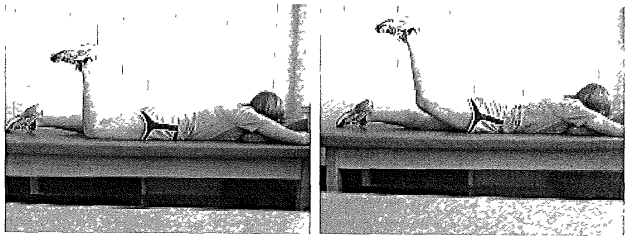
Side-lying Exercises



Hip abduction

1. Lie on your side with trunk and legs in a straight line
2. Bend your bottom knee
3. Keep top knee straight and toes pointing forward
4. Slowly lift top leg toward the ceiling
5. Hold for 3-5 seconds
6. Slowly return to start position

Hip extension



1. Lie on your stomach
2. Bend your knee
3. Slowly raise your thigh off the table
4. Hold for 3-5 seconds
5. Slowly return to start position

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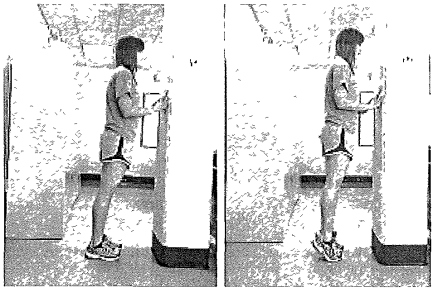
THE UNIVERSITY OF TOLEDO

Standing Exercises

Heel raises



1 Find a chair, wall, or doorway that you can use to help you balance
2 Start with your feet hip width apart and flat on the floor
3. Slowly raise yourself up on your toes
4 Hold for 3-5 seconds
5 Slowly lower yourself to the ground

Balance

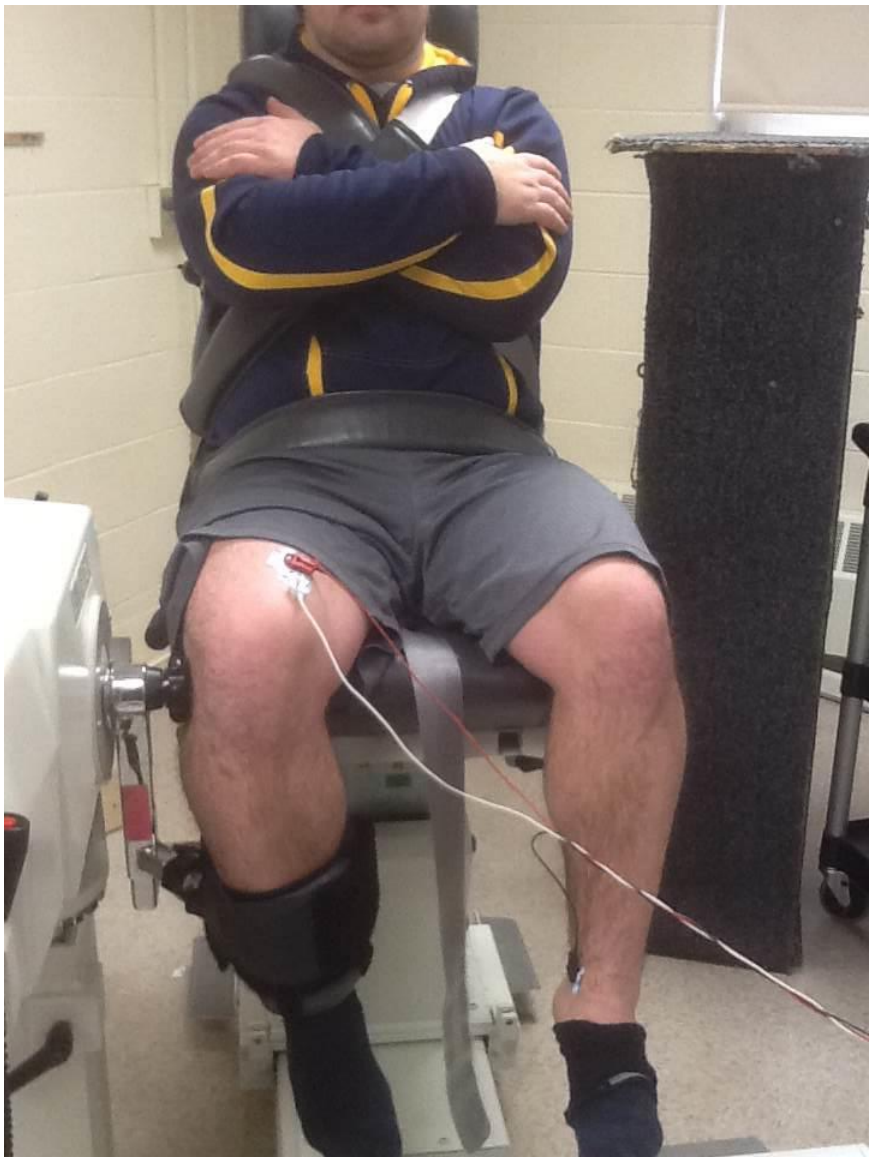
1. Find a chair, wall, or doorway that you can use to regain your balance if necessary
2. Raise one foot off the floor by bending your knee
3 Balance on one leg for 30-45 seconds
4 Lower your foot to the floor

ID _____

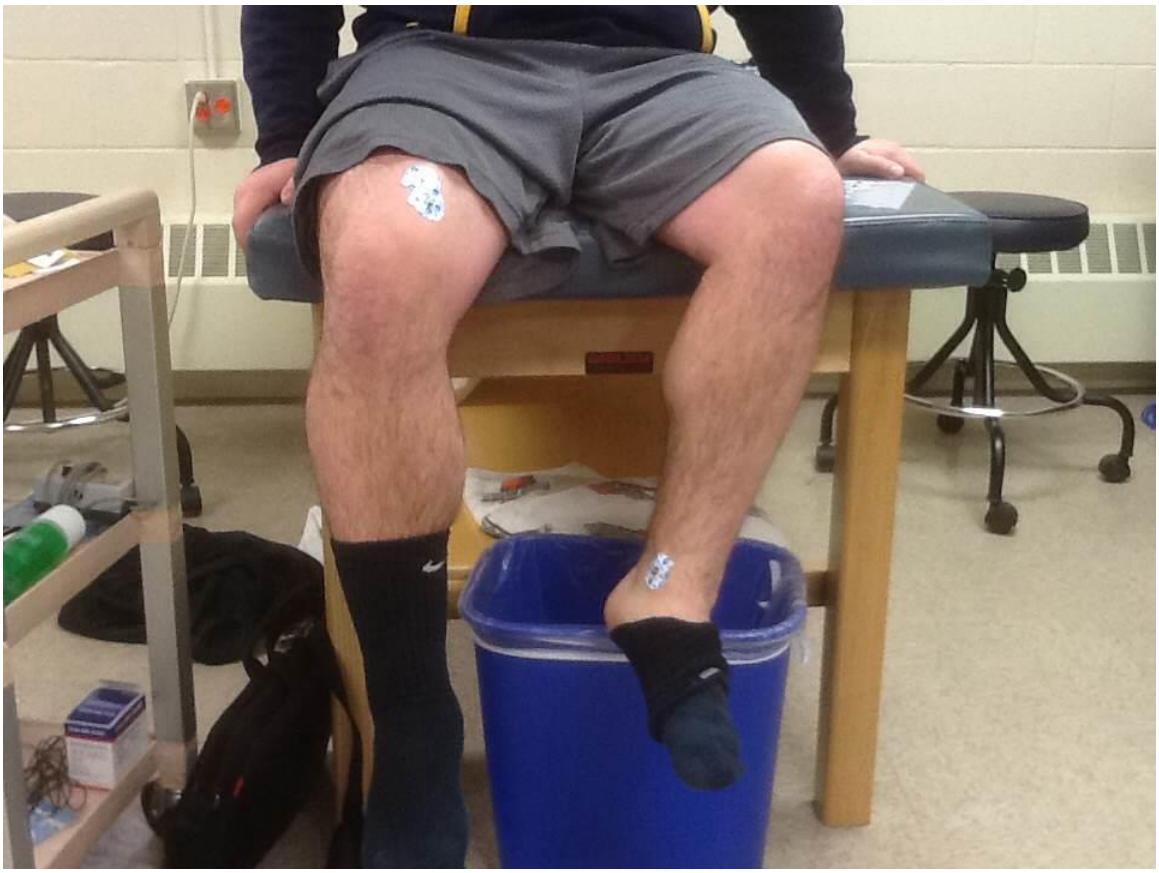
	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9
Knee Ext									
STS									
Hip Abd									
Hip ~~Add~~ Ext									
Calf Raise									
Balance									
Walk									

Appendix D

Pictures

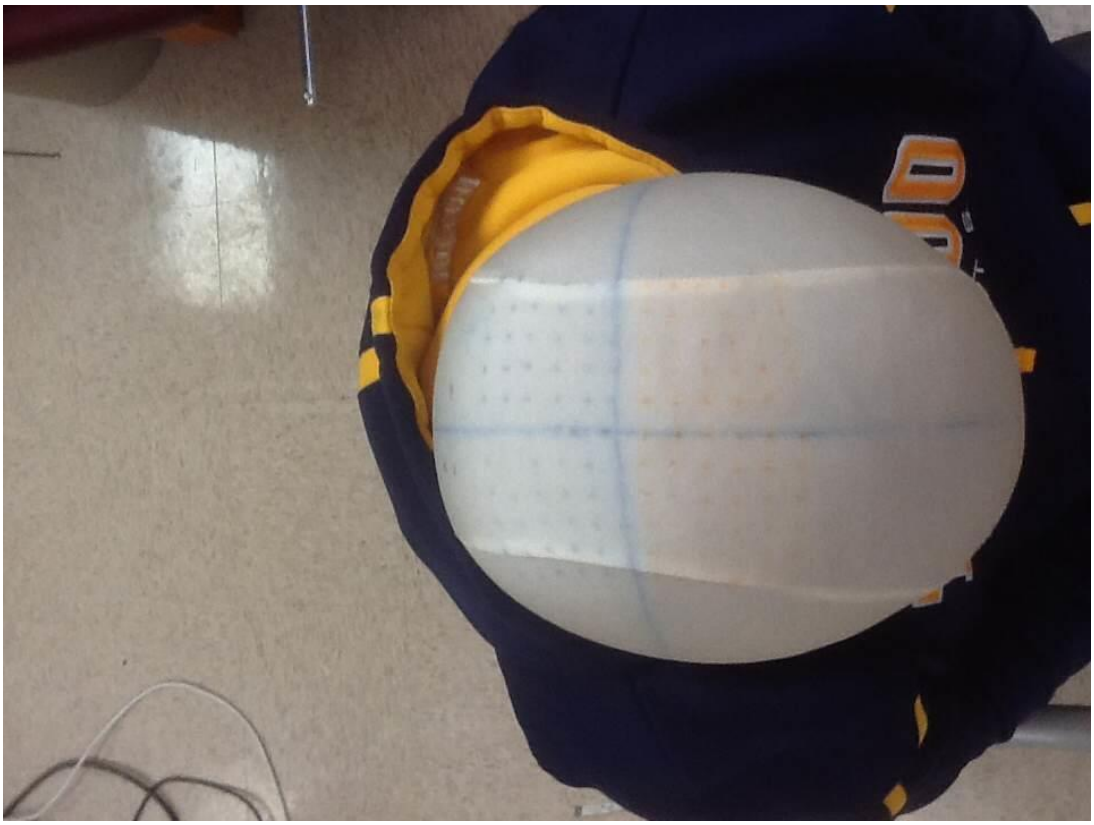


Patient positioning during testing sessions

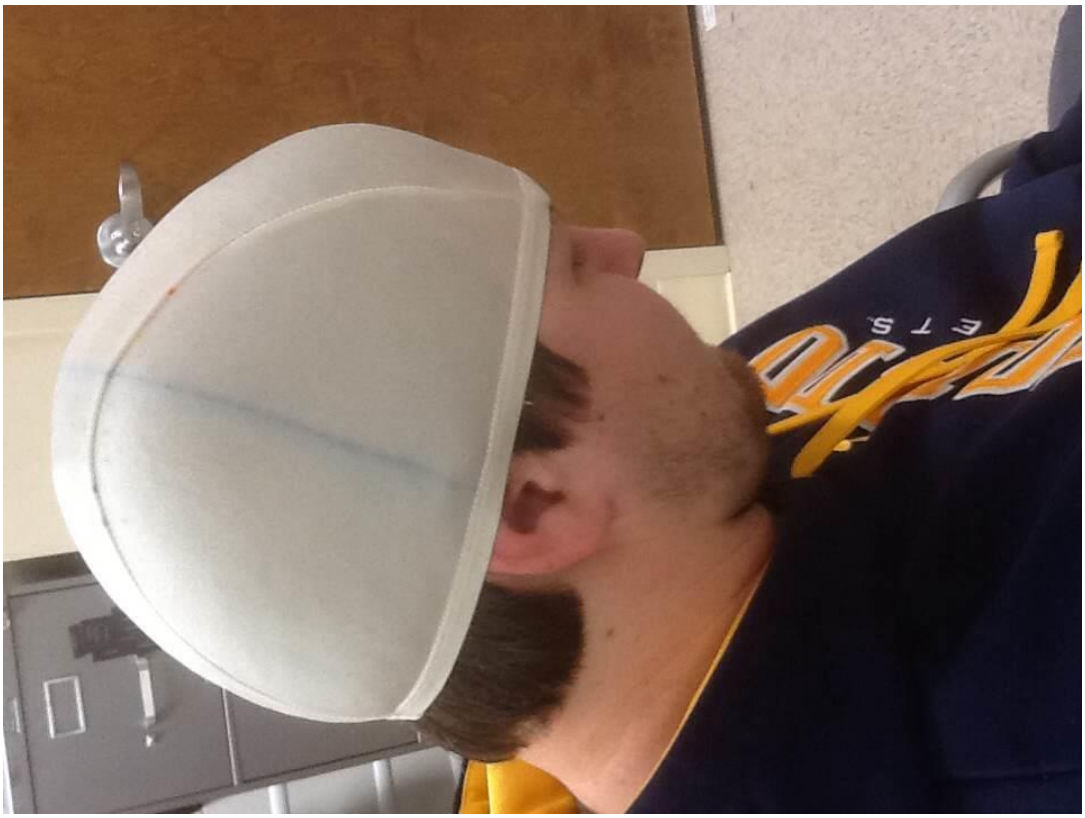


Electrode placement

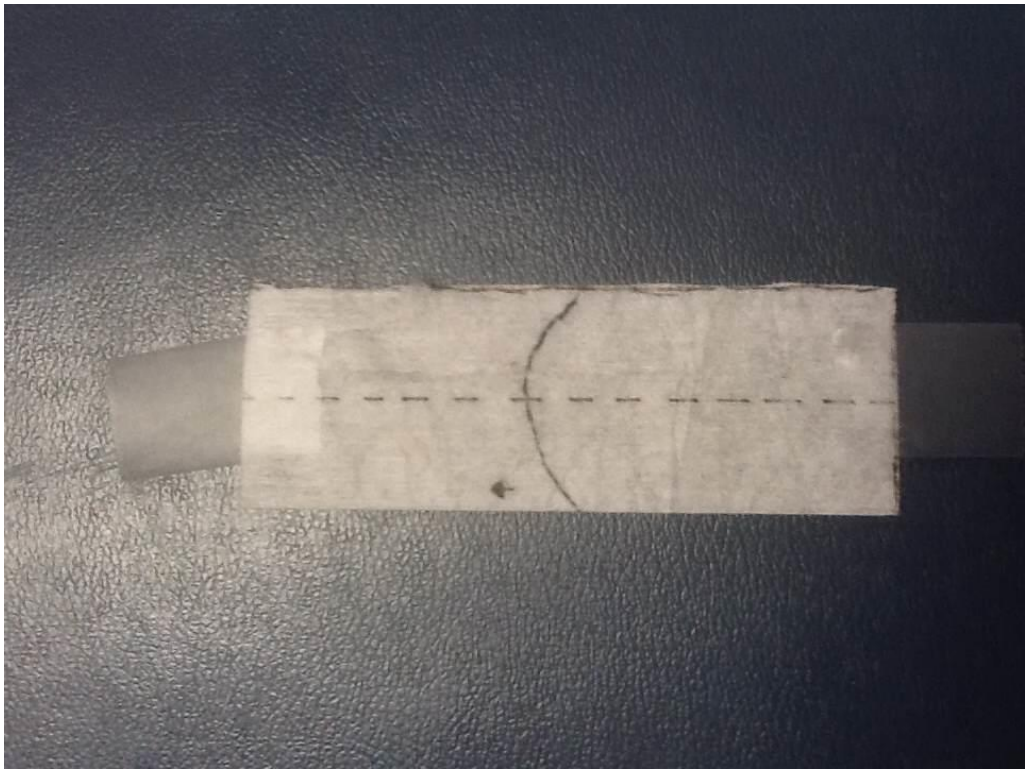
Biopac Setup



Swimcap placement for Brain Mapping



Skin Prep Tools



Brain Mapping Felt