A Thesis

entitled

The Intrarater Reliability and Agreement of Transcranial Magnetic Stimulation in Lower Extremity Musculature

by

Brittney A Luc, ATC

Submitted to the Graduate Faculty as partial fulfillment of the

requirements for the Masters of Science Degree in Exercise Science

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Dr. Brian Pietrosimone, Committee Chair

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Dr. Phillip Gribble, Committee Member

_____

Dr. Michael Tevald, Committee Member

_____

Dr. Patricia R. Komuniecki, Dean
College of Graduate Studies

The University of Toledo

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An Abstract of

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Objective: To determine the intrarater reliability of transcranial magnetic stimulation (TMS) in both the quadriceps muscles and the fibularis longus muscles. Long term assessment of reliability and agreement between measures was conducted through two separate testing sessions with four weeks from baseline to follow-up. Design and Setting: Interclass Correlation Coefficients (ICCs) and Bland-Altman plots were created to assess the reliability of the dependent variables of Active Motor Threshold (AMT) and Motor Evoked Potential (MEP) wave size normalized to the M-wave. All data were collected in a research laboratory. Subjects: Twenty participants were initially included in this study; however two were deemed to be outliers and were removed during data analysis. Eighteen healthy subjects (8 male, 10 female; 22.35 + 2.3yrs; 1.71 + 0.11m; 73.61 + 16.77kg) were included in the final analysis. Measurements: The MEPs were elicited using the Magstim Rapid (Magstim Company, Wales, UK) via a double cone coil

(Magstim Company, Wales, UK). AMT was defined as the lowest output required to elicit 5 positive waves > 0.1μV, with 6 negative waves < 100 μV recorded at the output 1% less. After threshold was found, 5 MEPs were recorded at both 120 and 140% of AMT. The average of these 5 MEPs was calculated then divided by the maximal muscle output, which was found through stimulating the mixed nerve controlling the muscles being examined and increasing the stimulus until a maximal muscle reflex was achieved. Results: For AMT, the dominant and nondominant quadriceps showed good reliability ($ICC_{3,1}$ = 0.873 and 0.828, respectively), but showed a lesser degree of agreement through Bland-Altman plot analysis. Conversely, MEP measurements at both 120 and 140% of AMT showed excellent reliability ($ICC_{3,5}$ = 0.917 and 0.975, respectively) for the dominant quadriceps and also acceptable agreement between sessions. The nondominant quadriceps showed excellent reliability at both 120% ($ICC_{3,5}$ = 0.954) and 140% ($ICC_{3,5}$ = 0.982) of AMT. Nondominant quadriceps also showed strong agreement between sessions. For the AMT of the dominant fibularis reliability was poor ($ICC_{3,1}$ = 0.522) but agreement was good. Nondominant fibularis AMT has good reliability ($ICC_{3,5}$ = 0.763) and also good agreement. While all MEP measurements for the fibularis longus showed good or excellent reliability (Dominant 120% = 0.863; Dominant 140% = 0.939; Nondominant 120% = 0.919; Nondominant 140% = 0.726) Bland-Altman plot analysis showed poor agreement between the two sessions. Conclusions: TMS is a reliable tool for measuring levels of cortical excitability in the quadriceps and fibularis longus muscles over time. However, not all outcome measures are reliable for all four muscles that were studied. When looking at the quadriceps muscles, AMT should not be used as the outcome measure to be studied. MEP amplitude at 120 or 140% of AMT should be used

for comparisons. Conversely AMT should be used when assessing cortical excitability in the fibularis longus muscles, not MEP at either 120 or 140% of AMT.

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Chapter One

Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive technology that allows for the study of neural excitability of the human motor cortex.[1,2] TMS involves directing an electric current through a hand held copper-stimulating coil with the consequent production of a transient magnetic field.[2,3] When held over the scalp, the rapidly changing magnetic field induces a small electric current in underlying brain tissue. This stimulation produces a depolarization of nerve cells that is transmitted via the corticospinal tract to contralateral peripheral muscles where a motor response can be monitored through surface EMG electrodes.[2] TMS is used to evaluate corticomotor excitability and to measure central nervous system (CNS) adaptation and its relationship to changes in neural control and function.[4] Different aspects of corticomotor excitability are assessed with TMS by evaluating active motor threshold (AMT), motor evoked potentials (MEPs), cortical silent periods (CSPs), voluntary activation measures, and motor neuron excitability.[1-3,5-7]

TMS can be an important tool in detecting cortically inhibition in patients suffering from a variety of different neuromuscular pathologies. Neural inhibition has been shown to be present in the quadriceps muscle following anterior cruciate ligament reconstruction (ACLr) and in the peroneals following ankle injury, and is denoted by a

diminished ability to volitionally contract a muscle.[8] This is thought to occur as a natural response, designed to protect the injured knee joint by discouraging its use and creating a diminished motor drive to the muscles surrounding the knee, helping to prevent painful movements. [9,10] Using TMS to discover the causes of cortically driven neural inhibition and new treatment options will be beneficial to creating a more innovative rehabilitation program following injury.

The intersession reliability of TMS must be determined before TMS can be deemed a useful in the clinical setting to assess the effect of an intervention. Typical treatments usually last for more than a single session, and therefore TMS must not only be reliable in a single session but over multiple sessions. TMS is typically used to treat and observe changes in injured patients who have altered levels of cortical inhibition. Due to these changes that occur, the reliability of TMS should first be established with healthy subjects.

1.1 Statement of the Problem

TMS has been documented to produce strong, repeated reliability measures over time when tested in the anterior tibial muscle and upper extremity muscles.[1,3,6,11-20] However, there are few investigations that have established the reliability of TMS in other lower extremity muscles, including the quadriceps and peroneal muscles.[4,7,21] The previous investigations completed in lower extremity musculature were only completed over two separate sessions ranging from two days to thirty one days between sessions, and time between sessions was not standardized in any session.[4,7,21] In order for TMS to be useful in the investigation of lower extremity pathologies, this technique must be shown to produce reproducible data over multiple testing sessions, specifically in the

quadriceps and peroneals. Reproducible measures in healthy subjects will allow future research to apply this knowledge in pathological populations, specifically patients following ACLr and ankle injury, and further the understanding of neural inhibition.

1.2 Statement of Purpose

Reproducibility of outcome measures is extremely important, regardless of the field of research study. TMS has the ability to provide information regarding cortical level pathways and proper muscle function. However, if one is to investigate a longitudinal study with measures of lower extremity cortical excitability, it is essential to ensure the reliability of the tool. Therefore, the purpose of this investigation was to determine the interrater reliability of TMS measurements, specifically AMT and peak to peak MEP amplitude, over two separate sessions four weeks apart in the quadriceps and peroneal muscles.

1.3 Research Hypothesis

The current study was not hypothesis driven research. While current literature has reported strong, repeated reliability measures over time, these investigations have focused mainly on upper extremity musculature.[1-3,5,6,12,13,15,19] The lack of literature on this subject in lower extremity musculature, specifically the quadriceps and fibularis longus muscles, has led us to complete this investigation to determine the reliability of TMS in lower extremity musculature over a four week time period.

1.4 Limitations

As with any research investigation, this study was not without limitation. The amount of activity the participant engaged in outside of the study could not be controlled. While subjects were asked to refrain from any increase or decrease in physical activity

level during the study, it was difficult to control for this. However, in order to monitor activity level, participants completed the GODIN activity level questionnaire. Since this study was only looking at a healthy population, this can be a limitation in itself. The overall goal of using TMS is directed towards a pathological population; but it may be difficult to translate results from a healthy population to a pathological population. However, TMS reliability must be established in a healthy population first before it can be established in a pathological population.

1.5 Significance of the Study

This investigation is significant in that it is one of the first to investigate reliability of TMS in the quadriceps and fibularis longus muscles. If TMS is proven to yield high reliability measures in the quadriceps and fibularis longus muscles, investigators could reliably use these measures in longitudinal studies assesing quadriceps and fibularis longus cortical excitability. Eventually, TMS can be utilized to asses subjects who show inhibition after injury and the effect cortical level pathways play on neural inhibition. If found reliable, TMS can be used in the future to assess neural inhibition as well as possible treatment options that last for a longer duration of time.

1.6 Operational Definitions

TMS = Transcranial Magnetic Stimulation

EMG = Electromyography

AMT = Active Motor Threshold

MEP = Motor Evoked Potentials

SR = Stimulus Response

CSP = Cortical Silent Period

ICC = Intraclass Correlation Coefficient

LOA = Limits of Agreement

Chapter Two

Literature Review

2.1 Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive means to study the human motor cortex.[1,2] TMS involves directing an electric current through a hand held copper-stimulating coil with the consequent production of a transient magnetic field.[2,3] When held over the scalp, the rapidly changing magnetic field induces a small electric current in underlying brain tissue. This excitation produces a depolarization of nerve cells that is transmitted via the corticospinal tract to contralateral peripheral muscles where a motor response can be monitored through surface electrodes.[2] Cortical maps of voluntary muscles can be examined for location, extent, and stimulus response characteristics that can provide insight into the functions of the motor system as well as plasticity of the primary motor cortex.[1,2] TMS can also be used to assess motor evoked potentials (MEPs), cortical silent periods (CSPs), voluntary activation measures, and motor neuron excitability.[1,3,5-7] The CNS can be measured to assess adaptation and its relationship to changes in neural control and function.[4] TMS can also be used as a treatment option for patients eliciting quadriceps-activation deficits after menisectomy.[22] Stimuli given to patients with quadriceps-activation deficits during maximal contraction can increase central activation ratios when compared to participants receiving no magnetic stimuli.[22]

Magnetic stimulation causes excitation of neural tissue which is then transmitted to the muscle, however the neural mechanisms that contribute to muscle activation in inhibited quadriceps after TMS is still unknown.[22] Further investigations involving TMS as treatment for activation deficits are warranted, specifically treatments that are longer in duration.

The process of TMS is begun with the subject positioned in a Biodex chair, or similar chair, and a swim cap placed on their head to allow for marking of the coil. Electromyography (EMG) electrodes are placed over the belly of the muscle that is being studied. The stimulus created from TMS then evokes a contraction, or twitch, in that muscle and the twitch is recorded through EMG. This wave that is seen is the motor evoked potential (MEP).[18]

The stimulating coil is then placed over the cortical motor area and location of the optimal stimulation site, or "hotspot" is determined.[18] The hotspot is the defined as the location that yields the largest MEP peak-to-peak amplitude.[18] Once this is identified, the stimulator is secured and traced to ensure the coil does not move during testing and allows for exact placement for later testing sessions. After the hotspot is located and the coil is secures, motor threshold (MT) can be determined. The MT is defined as the lowest stimulation intensity that evoked MEPs greater than 50μV in 5 out of 10 trials.[1,2,4,14,18] Participants can either be assessed for active motor thresholds (AMT), in which they actively contract their muscle during testing, or resting motor thresholds (RMT), in which the muscle is completely relaxed. After MT is determine, a stimulus response (SR) curve is completed to display the change in MEP size as a function of stimulus intensity.[18]

TMS can be used to detect changes in corticospinal excitability after injury to the knee.[23] When pain becomes chronic, or lasts for a long period of time, complex mechanisms become involved in the perception and expression of the pain.[24] The longer this pain persists, the greater chance it can lead to multiple functional or pathological adaptations at the level of the brain, spinal cord, and peripheral nerves.[24] When comparing patients with patellar femoral pain syndrome (PPS), On et al. (2004), noted that subjects with chronic PPS showed TMS evoked greater MEP amplitudes in the vastus medialis oblique muscle, which demonstrate an increase in motor cortex excitability. However when compared to healthy subjects PPS subjects showed statically significant lower MVC measures. While research is leading towards higher levels of inhibition and excitability, more research is still needed to determine if and why this phenomenon occurs.

Reliability provides an indication of the expected error and statistical power of a measured outcome, and provides confidence that any changes observed in the measure are due to physiological changes within the subjects and not due to the variability in the measure itself.[13] In order for TMS to be useful in the research setting, this technique must be shown to produce reproducible data over multiple testing sessions and for multiple muscle representations.[1] When looking at the quadriceps muscle following knee pathology, TMS must be deemed as a reliable measurement to ensure the data being collected is a true representation of the desired measures.

2.2 Reliability of TMS and Plastic Changes in the Central Nervous System

Within the athletic population, strength training and skill acquisition are often combined in order to optimize performance. During initial strength training and

preliminary motor skill development, it is well documented that neural adaptations and plastic changes occur in the central nervous system.[20] In humans, TMS has shown that motor skill training induces changes in the organization of movement representations in the primary motor cortex.[20] A study conducted by Jensen et al. (2005) assessed the excitability of corticospinal projections in the biceps brachii after four weeks of strength training. Twenty-four subjects were included in the study and were assigned to either a strength training intervention or visuomotor skill-learning group. Thirteen training sessions were performed over a four-week training period. TMS was used to record MEPs from the biceps brachii and triceps brachii through EMG and cortical excitability was measured through MEP amplitudes, motor threshold, and stimulus response curves. Results showed that participants within the strength-training group displayed a significant increase in both maximal isometric and dynamic muscle strength. TMS measurements showed a significant effect of the first training session. MEPs were facilitated after training, which was reflected by a significant increase of MEPmax.[20] MEPmax also increased during tonic contraction in response to training and MEP threshold decreased.[20] After a six month detraining period, results from four subjects yielded measurements similar to their own pre-training measurements. Overall, this study has demonstrated that several weeks of skill learning can increase cortical excitability and that these changes seem closely related to the acquisition of new visuomotor skills. In contrast, strength training was associated with decreased cortical excitability at rest.[20] With the acquisition of a new motor skill, there appears to be an increased cortical drive to the spinal motor neurons. When the body is exposed to a new challenge, the brain must work harder in order to accomplish the task and therefore this abundance of new information must be

processed by the brain leading to an increase in excitability.[20] Since these results show that subjects partaking in new activities or activities at increased levels it is important to consider the overall effect of these cortical changes on the reliability of TMS. For subjects partaking in a study involving TMS reliably, it is important to ensure the amount of physical activity the subjects participate in should not change. If a subject decides to increase their activity levels, it can lead to an increase in excitability, resulting in different measures assessed at different testing time points. This in turn would cause a decrease in reliability of the measure. This is both important in this current research investigation, and any investigation utilizing TMS to elicit outcome measures of interest.

2.3 Reliability of TMS in Measuring Motor Evoked Potentials

When an area of the motor cortex is stimulated through TMS, the magnetic stimulus results in the activation of descending corticoneurons.[19] The stimulus depolarizes interneurons of the brain and other neurons that subsequently synapse onto corticospinal neurons. The stimulation of these fibers cause activation of motor neurons, resulting in motor unit recruitment and muscle excitation.[19] The resulting response, called a motor-evoked potential (MEP), can be recorded using conventional EMG electrodes placed over the appropriate muscle group.[4,6,19] The TMS output measured using MEP represents the net excitatory and inhibitory influences on corticospinal cells.[11,19]

2.3.1 Upper Extremity Musculature

TMS reliability has previously been established in a plethora of upper extremity muscles, including the first dorsal interosseous (FDI), abductor pollicis brevis (APB), exstensor digitorum communis (EDC), and flexor carpi radialis (FCR). However, each investigation used slightly different outcome measures, providing different means to

interpret each conclusion. Carroll et al. (2001) demonstrated the reliability of TMS in recording MEPs on three separate days. Eight healthy subjects were included to elicit MEPs of the FDI muscle, while torques were exerted up to 50% of their maximum capacity. Two separate ICCs were ran to assess reliability from the first session and then to assess the reliability across all three sessions. During passive trials, the ICC for an individual session ranged between 0.47 and 0.81. The ICC across the three passive trials was higher, ranging between 0.73 and 0.96. During the active trials, ICC for TMS was 0.50 and 0.53. From this investigation, it appears that the strongest reliability in TMS measures occurs across trials rather than across separate sessions, however all ICC values represented strong correlations.

TMS has also be used to investigate motor system plasticity, which can underline motor recovery after stroke.[1] A study conducted by Malcolm et al. (2006) used TMS to determine motor threshold, map tomography, and stimulus-response curves for the FDI, APB, EDC, and FCR muscles in twenty healthy subjects. Their aim was to determine the reliability of these TMS measurements for these forearm and hand muscles.[1] The four primary TMS outcome measures examined were motor map area, motor threshold, location of the center of gravity (CoG) of the motor map, and the slope of the stimulus response curves. All assessments were performed during two separate testing sessions separated by two weeks. Data was analyzed using an ICC to assess reliability. Results showed ICC values of 0.97 and 0.90 for optimal position of the coil and motor threshold respectively, while stimulus response curve results yielded only moderate test-retest reliability with ICC values ranging from 0.60 in the FCR to .83 in the EDC muscle. Forearm muscle representations (EDC and FCR) demonstrate a higher reliability when

reproducing measurements of motor map area when compared to the intrinsic hand muscles.[1] Overall TMS measures of motor cortex organization and excitability produced good test-retest reliability, specifically for positioning the coil and determining motor threshold between sessions.

The abductor digiti minimi (ADM) muscle has also been used to test the reliability of motor-evoked potential amplitudes both within and between sessions using TMS. Unlike the investigations above, the study conducted by Christie et al. (2007) looked at differences found between two sessions that were held only twenty minutes apart. MEPs were evoked at rest at intensities of 1.1, 1.3, and 1.5 times MT.[13] High ICCs were found at all three intensities for the overall group, with females producing higher correlation values than males. This study also concluded that the number of trials per intensity was very important when determining reliability. When using only two averaged trials per intensity, the ICC was only 0.07, and when averaging five trials per intensity the ICC increased dramatically to 0.97. Test-retest reliability coefficients ranged from 0.65 to 0.83 which is just below strong.[13] This investigation demonstrates that it is important to elicit at least five MEPs at a given intensity to achieve a reliable measure for that participant.

Longitudinal reliability of test-retest TMS sessions have also been demonstrated in the literature. Livingston et al. recorded MTs, and MEP latencies and amplitudes on six occasions over fifteen days in the abductor pollicis brevis (APB), first dorsal interosseous (FDI), and abductor digiti minimi (ADM).[14] Lower thresholds and upper thresholds were determined by finding the maximum intensities in which ten stimuli evoked no response and ten stimuli evoked a positive response.[14] Peripheral nerve

stimulation was then used to find maximum muscle response (M) amplitudes from the median and ulnar nerves.[14] Subjects were tested for five additional sessions that occurred 1) within twenty-four hours of the first testing session, 2) within forty-eight hours of the first session, and sessions four, five, and six occurred on five, ten, and fifteen days after the initial session, respectively. Intra-rater and inter-session reliability were estimated using ICCs for MTs, MEP latency and amplitude, central motor conduction time (CMCT), and MEP:Mmax amplitude ratio. Moderate to high reliability was found for MTs (0.58-0.94), MEP latencies (0.85-0.92), and CMCT (0.48-0.76) over the six testing sessions. Median nerve MEP latencies presented ICCs of 0.87 and 0.92 for the left and right, respectively and ulnar nerve MEP latencies present left and right ICCs of 0.87 and 0.85.[14] Interestingly, this study suggests that not only does side of body play a factor in reliability, but also the nerve conducting the stimulus. Also, it appears that normalizing MEP amplitude to a maximal M wave is another way to standardize the reliability between measures.

Magnetic stimulation has also been utilized at the cervical and peripheral levels.[6] Lefebvre et al. (2004) included nine subjects in which transcranial, spinal, and peripheral magnetic stimulation was delivered to stimulate MEPs in the opponens pollicis muscle with either eyes open or eyes closed and either mental activity that was controlled or not controlled to produce a total of four experimental conditions. To control for mental activity subjects were instructed to count backwards from 101 by three.[6] At the cranial site, the stimulator was positioned over the vertex and then was placed between the fifth and sixth cervical vertebrae at the spinal level. To stimulate at the peripheral site, the stimulator was placed over the median nerve at its most superficial location at the anterior

aspect of the elbow, medial to the distal tendon of the biceps. MEPs were standardized by reporting the MEPs as a ratio of the Mmax which was reported to remove unwanted variability associated with subjects and the technique and allow for comparisons between subjects, trials, and conditions.[6] ICCs were calculated, resulting in high reliability measures at 0.94, 0.98, and 0.91 for transcranial, cervical and peripheral stimulation, respectively.[6] Testing conditions in which subjects had their eyes closed and mental activity was controlled allowed for allowed for the highest MEP amplitudes to be produced.

MEP amplitudes measured from the biceps brachii on three separate occasions separated by at least 24 hours yielded ICCs ranging from 0.95 to 0.99.[19] While each testing session was completed at the same time of day, MEP amplitudes increased from the first session to the second and third, which could be present because the administration of TMS can produce plasticity in cortical neurons that persists for at least 24 hours.[19]

The literature above suggests many factors that account for variability in TMS measurements. It is therefore important to try and minimize variability in measurements through averaging at least five MEP amplitudes normalized to M-waves, understand the nerve conducting the stimulus and control for external distractions that may alter cortical information.

2.3.2 Lower Extremity Musculature

MEP amplitudes have shown a high variability when repeatedly assessed.[11] The aim of the study completed by van Hedel et al. (2007) was to evaluate the test-retest reliability of several MEP parameters recorded from the anterior tibialis muscle (TA) of

healthy patients and patients with incomplete spinal cord injury (iSCI).[11] Single pulse TMS was used for MEP analysis and an intraclass correlation coefficient (ICC) was calculated for the variance associated with the variability of MEP measures for healthy subjects and iSCI subjects. A two-way repeated measures ANOVA was used to determine MEP differences between static and dynamic conditions. Results showed good test-retest reliability for the static condition at 40% of maximal contraction. Torque and task controlled MEPS allowed for reliable follow up recording of amplitudes and latencies. The reliability calculated for the difference in dynamic and static MEP amplitude was only fair.[11] Other MEP reliabilities shown in the TA have shown moderate to high interrater ICCs for MEP threshold (0.73), plateau (0.75), and max amplitude (0.93) and intrarater ICCs of moderate strength for the same three variables (0.65, 0.68, 0.79).[18]

Wheaton et al. (2009) looked at the test-retest reliability of motor threshold (MT) and MEP amplitudes in the quadriceps of twenty three patients who had previously suffered a stroke. Initial testing included measurements of MT expressed as %-stimulator output, latency, and peak to peak MEP amplitudes. Subjects returned seven to ten days later and testing was conducted at the same time of day to account for diurnal variations.[4] ICCs were below criteria for demonstrating strong reliability (0.80) at 0.65-0.79 for MEP latencies, and MEP amplitudes produced values ranging from 0.21-0.87.[4] The greatest reliability measure was shown for motor thresholds at 0.98 showing that TMS is highly reliable for this outcome measure. This shows that healthy subjects may be more suitable for reliability investigations.

2.4 Reliability of TMS and Cortical Voluntary Activation Measurement

Voluntary activation describes the level of neural drive to a muscle during contraction and is most commonly estimated using twitch interpolation.[7] To quantify voluntary activation the size of the superimposed twitch evoked during a contraction is compared with the force produced by the same stimulus delivered to the resting potentiated muscle.[7] In order to elicit a superimposed twitch a single supramaximal stimulus must be delivered during MVC.[21] If extra force is then elicited greater than the MVC through stimulation, voluntary activation is then quantified by expressing the extra forced evoked by maximal stimulation as a percentage of the force produced by the same stimulus at rest according to the formula ([1-SIT/RT] x 100%).[21] TMS has been used to quantify voluntary activation because it allows for further localization of the site of impairment and the determination that the presence of a superimposed twitch produced by TMS during MVC suggests that drive from the motor cortex is suboptimal.[7]

The site of neural drive impairment responsible for incomplete voluntary activation can be identified and localized through the use of TMS. Reliably predicting voluntary activation was tested in the knee extensors by Goodall et al. (2009) in which the vastus lateralis was examined both between sessions on the same day and between sessions separated on average by nineteen days. Motor nerve stimulation was first conducted using peripheral stimulation of the right femoral nerve and Mmax was found. TMS was then conducted to find MT by decreasing the stimulator output from 80% by increments of 5% until the MEP response was below 0.05 μV in more than half of the eight stimuli given at the output level.[7] A total of four trials during two separate visits were conducted with trials one and two separated by thirty minutes on the first day and the second two on a separate day. Repeated measures ANOVA was conducted to

compare SIT, MEP, and ERT amplitudes between trials and ICCs were calculated to determine measurement errors when assessing maximal cortical activation. There were no systematic differences between maximal voluntary contraction either within day or between days and TMS was concluded to reliably provide estimates of maximal voluntary activation and that it can be useful for monitoring muscle function, movement disorders, and disease progression.[7] Reliability of TMS to quantify the degree to which the motor cortex drives muscles during activation was again proven in the knee extensors by Sidhu et al. (2008) in which ICCs resulted in 0.95 and 0.97 measures for contractions at 25-100% MVC and 50-100% MVC, respectively.[21] Eight subjects participated in this study in which two identical experiments were conducted at least 48 hours apart. A total of four trials were performed during each section. Not only is the superimposed burst technique reliable in testing the knee extensors it can also yield an ICC of 0.96 in the wrist flexors over several days.[15]

2.5 Reliability of TMS and Motor Mapping Characteristics

TMS motor mapping is important because the approach can provide indexes of cortical change after insult to the brain.[2] Motor mapping is completed by placing a cap on the subjects head with a 1 cm plotted grid so the simulating coil could be accurately positioned.[2] The coil is then systematically moved over the grid and the motor evoked response was plotted after stimulation of each relevant grid location.[17] The motor evoked response was determined to be positive if the peak to peak amplitude was 50 μV or higher.[2,17] The grid position that elicits the maximal motor potential amplitude with the lowest stimulation intensity in 5 of 10 trials was defined as the "hotspot".[2,17] Active sites are then identified and mapping is considerd complete when locations adjacent to the

active sites are identified as nonreactive by demonstrating less than 5 out of 10 positive responses.[2] While studies have been completed showing good reliability of motor mapping between hemispheres in healthy subjects over time, few have been completed to demonstrate intra- and intersubject reliability. When the abductor pollicis brevis was tested for reliability measures using motor mapping techniques, results showed it to be reliable when testing sessions occurred at a median interval of 27.5 days.[2] Wolf et al. (2004) looked at cortical mapping of the extensor digitorum communis across three sessions from both hemispheres. All three sessions were spaced in approximate intervals and all sessions were separated by 7-14 days. A two-way repeated measures ANOVA was used to explore the difference between sessions, hemispheres, hotspots, and center of gravity distances with no significant difference between sessions for any parameter measured.[17] This information shows that longer periods of time in between TMS session can yield high levels of reliability as well.

2.6 Reliability of TMS and Excitability Changes

Motor responses in the muscles being studied can be recorded through EMG as previously discussed, and can allow for determination of motor neuron excitability at a subcortical level.[5] When using the hotspot technique as for stimulating the motor cortex to a given muscle, the optimal location to generate excitatory impulses is reliable when repeated over multiple testing sessions.[5] The stimulating coil must be placed in the exact same location every time for results to be reliable and hotspots must be located on swim caps to allow for exact placement each time. When using eight subjects and testing over two sessions ICC values ranged from high to moderate in all parameters that were tested within and across sessions.[5]

A cortical silent period (CSP) is an interruption of EMG activity in the corresponding muscle after TMS is administered to the motor cortex.[3] The length of the CSP is reflective of cortical excitability and is thought to represent GABA-B receptor mediated inhibition of cortical excitability.[3,16] Longer duration CSP is associated with motor neglect and shorter CSP is associated with spasticity.[3] Kimberly et al. (2009) took nine healthy subjects and six subjects with focal hand dystonia and measured CSP to assess the inter-rater reliability of CSP calculation. Two raters who were naïve to CSP obtained 10 CSP measurements in a single session for each subjects. ICCs were calculated using an ANOVA to quantify inter-rater reliability showing that reliability between the raters was very high at 0.976. Being able to record a reliable silent period can give clinicians the confidence that the CSP they are receiving are reflective of the true values from patients. This information can lead to further investigations on treatment options for TMS. The reliability of TMS in lower extremity muscles, specifically the quadriceps and peroneals, must be proven to be strong before any advances can be made about treatment options through TMS and assessments of cortical inhibition through TMS. After injury to the knee such as ACL tear and reconstruction, neuromuscular function and strength are often the focus of initial rehabilitation. However this process can be hindered by an inability to voluntarily contract the musculature around the joint.[25] This inhibition, or the diminished ability of a muscle to contract, is known as arthrogenic muscle inhibition (AMI).[9,10] AMI is considered a natural injury response that it designed to protect the injured joint by discouraging its use. In effect, this helps to prevent painful movements by creating a diminished motor drive to the muscles surrounding the injured joint.[9]

AMI is caused by disruption in the neural pathways that innervate the motor neuron pool of the effected muscle. This effects the excitability of spinal interneurons and the muscles' ability to produce appropriate motor output.[26] After injury there are many neuromuscular consequences due to the disruption of communication to the CNS and reorganization of afferent sensory information such as somatosensation, muscle activation, strength, and function.[27] It is important to consider the neurophysiological factors associated with AMI after joint injury. The afferent pathways of the peripheral nervous system send sensory signals from the peripheral nerves in the body back to the spinal cord and CNS to be processed.[28] When this process becomes interrupted, the body must then make adaptations to these changes. TMS can be used to detect changes in corticospinal excitability after injury to the knee.[23] When pain becomes chronic, or lasts for a long period of time, complex mechanisms become involved in the perception and expression of the pain.[24] The longer this pain lasts leads to multiple functional or pathological adaptations at the level of the brain, spinal cord, and peripheral nerves.[24] When comparing patients with patellar femoral pain syndrome (PPS), On et al. (2004), noted that subjects with chronic PPS showed TMS evoked greater MEP amplitudes which demonstrate an increase in motor cortex excitability. However when compared to healthy subjects PPS subjects showed statically significant lower MVC measures. While research is leading towards higher levels of inhibition and excitability, more research is still needed to determine if and why this phenomenon occurs.

Overall TMS has been proven to be reliable both within a single session and over time with high ICCs from both inter-rater and intra-rater experiments in predominately upper extremity musculature. When looking at the ability of TMS to be reliable it is

important to make sure the stimulating coil is placed in exactly the same location each time. Placement of the coil should be traced on the subject's swim cap to make sure the coil is placed in the exact same location. Consideration should be made that testing is done at the same time each day to account for diurnal variations and the possibility that TMS can increase plasticity in the motor cortex for up to 24 hours.[19] Sessions should occur more than 24 hours apart to ensure effects of TMS on cortical excitability have diminished completely. There is only one article that describes the reliability of TMS in the quadriceps muscle in which the measures are taken on two days separated by ten days.[4] While ICCs yielded high reliability measures in patients who had previously suffered a stroke, no healthy participants were studied. Further research is needed to conclude that TMS can produce high reliability in lower extremity muscular over a longer period of time than sessions completed only a few days apart. Subjects should be healthy to control for changes in cortical excitability that happen after injury.

Chapter Three

Methodology

3.1 Research Design

Study Design: Descriptive laboratory study.

The independent variables in this study included time (baseline and four weeks post) and muscle (quadriceps of the dominant and nondominant limbs, and fibularis longus of the dominant and nondominant limb). The dependent variables were the outcome measures retrieved through transcranial magnetic stimulation (active motor threshold, and peak to peak MEP amplitude normalized to the M-wave). The outcome measures for peak-to-peak MEP amplitude were assessed according to the stimulus recruitment (SR) curve, and were taken at, 120 and 140 percent of active motor threshold.

3.2 Experimental Design

A repeated measures procedure was used to assess outcomes of reliability for achieving TMS outcome measures over two different time periods, separated by four weeks. Testing was completed at the same time of day, within one hour, and occurred at a baseline testing session, and four weeks post baseline.

3.3 Participants

Twenty participants between the ages of 18-35 were recruited from all races and both sexes. Participants were excluded if they had a history of: concussion or head injury in the past 6 months, history of stroke, cardiac condition, epilepsy, cranial neurosurgery, migraines, cancer in the brain or thigh musculature, diagnosed psychiatric disorder; or has a cardiac pacemaker, implanted cardiac defibrillator or intracranial metallic clips. We also excluded all pregnant females for protection of the fetus from electrical and magnetic stimuli. Since this study was looking at a healthy population only, all participants with previous lower extremity pathology, injury, or surgery were also excluded. Current levels of physical activity had to be maintained throughout the entire time of the study, and the GODIN leisure time questionnaire was administered to monitor physical activity levels.[29] Participants were also to refrain from coffee or caffeine intake prior to testing on the day testing was taking place to prevent increased neural excitability effects from caffeine.

3.4 Randomization

Outcome measures were measured on two separate days, with twenty eight days between the sessions. Both sessions took place at the same time of day within one hour of the baseline testing session. During the first testing session it was randomly determined which muscle would begin testing for each subject. That order was then repeated for each of the remaining sessions.

3.5 Instrumentation

3.5.1 Muscle Response

We collected muscle response measurements with surface electromyography (MP100C BIOPAC Systems, Inc Goleta, CA). Analog to digital signal conversion was

processed with a 16 bit converter (MP150, BIOPAC Systems Inc). The Acqknowledge BIOPAC Software (BIOPAC Version 3.7.3, BIOPAC Systems, Inc.) was used to visualize the signals as well as manipulate the stimuli. Signals were sampled at 1024 Hz and electromyography (EMG) amplification was set at a gain of 1000 (EMG100C BIOPAC Systems, Inc.). The common mode rejection ratio of our EMG amplifier was 100 dB and the input impedance was 2MOhms. The disk-shaped electrodes used to acquire signals were disposable, 10 mm pre-gelled Ag/AgCl (BIOPAC Systems, Inc).[13] The electrodes were positioned 2 cm apart over the muscle belly of both the vastus medialis and fibularis longus.[13] Muscle reflex responses were elicited using the BIOPAC stimulator module (STIM100A, BIOPAC Systems, Inc.), a 200 volt maximum stimulus isolation adaptor (STIMSOC BIOPAC Systems, Inc), a 2 mm shield disk stimulating electrode, (EL254S BIOPAC Systems, Inc.) and a 7 cm carbon impregnated dispersive pad.

3.5.2 Cortical Motor Evoked Potentials

The motor evoked potentials were elicited using the Magstim Rapid (Magstim Company, Wales, UK) via a double cone coil (Magstim Company, Wales, UK). The magnetic stimulation did not exceed 1.4 Tesla. All motor evoked potentials were measured in the peripheral muscles using a shield disk electrode. The disk-shaped electrodes used to acquire signals were disposable, 10 mm pre-gelled Ag/AgCl (BIOPAC Systems, Inc). The before mentioned Acqknowledge BIOPAC Software (BIOPAC Version 3.7.3, BIOPAC Systems, Inc.) was used to visualize the signals.

3.6 Procedures

3.6.1 Muscle Response

Participants were positioned supine on a padded Biodex System II chair with their arms comfortably placed at their side with their head in a neutral position. The head of each participant rested comfortably and their knee was slightly flexed (~10-15º). The hair over the collection sites on the legs was shaved and the skin over the recording electrode site will be debrided and cleaned with alcohol.[14] Two 10mm, pre-gelled Ag-AgCl (EL503, BIOPAC Systems Inc) surface electromyography electrodes were positioned 2cm apart over the muscle belly of the vastus medialis (when measuring quadriceps excitability) and over the muscle belly of fibularis longus. A 2mm shielded disc stimulating electrode (EL2524S, BIOPAC Systems Inc) was positioned over the femoral nerve (when measuring quadriceps excitability) and over the tibial nerve (when measuring fibularis longus excitability) and secured with hypoallergenic tape and a 7x13cm self-adhesive electrode was positioned over the hamstring and used as a dispersive electrode. A 1ms square wave stimulus was produced with a BIOPAC stimulator module (STM100A, BIOPAC Systems, Inc) and a 200 volt maximum stimulus adaptor (STMISOC, BIOPAC Systems Inc) and was delivered to the appropriate nerve.

During testing, participants were instructed to maintain a constant head, eye and hand position by focusing on a spot on the ceiling. The stimulus was given at a low intensity initially so that the participant became familiarized with the stimulus. The stimulus continued to increase until the maximum muscle response (M-wave) was found. Maximum M-wave was found when the amplitude of the M-wave did not increase while the stimulus intensity continued to increase. Three maximal responses were recorded and

averaged. The M-wave was used to normalize each MEP amplitude recorded during the TMS testing.

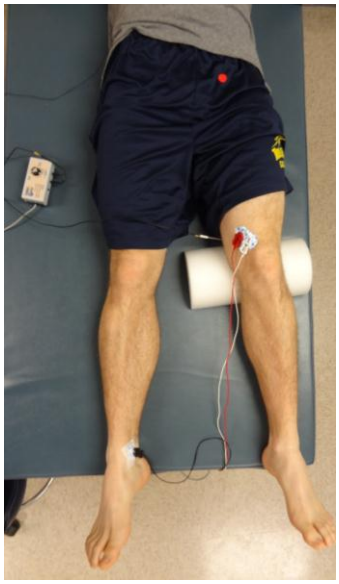

Figure 3-1: Patient positioning for quadriceps muscle response testing. The knee was positioned in 10° of flexion.

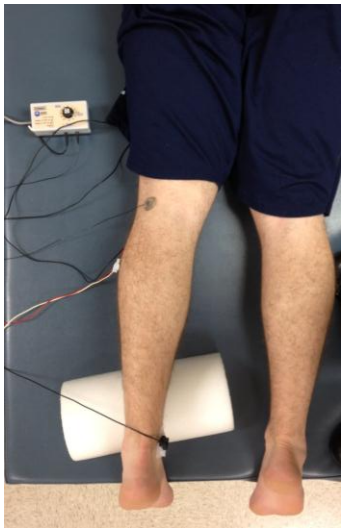

Figure 3-2: Patient positioning for fibularis longus muscle response testing. The knee was positioned in 10° of flexion.

3.6.2 Cortical Motor Evoked Potentials and Active Motor Threshold

Participants were positioned in a seated position in the Biodex System II dynamometer. During quadriceps testing, the dominant knee was placed at 90 degrees of flexion. For testing of the fibularis longus, the knee was placed in 10 degrees of flexion and the ankle in 10 degrees of dorsiflexion. A lycra swim cap was placed on the participant's head to allow for location of the motor cortex.[30] Perpendicular lines were then drawn vertically on the swim cap and connected from the center of the occiput and nose, and from each external auditory meatus.[30] Where the lines intersect denoted the optimal location of the motor cortex.[30] Formable disposable ear plugs were given to the participants for comfort from an audible noise that is heard during magnetic stimulation.[30]

For the quadriceps measurement, participants were instructed to give a maximal voluntary isometric contraction (MVIC). To achieve this, the shank of the leg was secured to the arm of the isokinetic dynamometer, and the participant was instructed to try and straighten their knee with as much force as possible against the stationary arm. For fibularis longus MVIC measurement, the plantar side of the foot was placed on the foot plate of the isokinetic dynamometer and instructed to push against the stationary plate using as much force as possible. Five percent of the maximal isometric contraction was used as a standardized volitional muscle contraction during active motor threshold/MEP testing. To elicit an MEP, a double cone coil (Magstim Company, Wales, UK) was positioned over the vertex of the cranium and the Magstim rapid (Magstim Company, Wales, UK) was used to produce a maximum magnetic stimulus of 1.4 Tesla. Initial stimuli was given at 50% of the max stimulator output in order to locate the optimum coil placement to produce MEPs. The coil was moved approximately 1cm in an

anterior-to-posterior direction over the vertex until a MEP response was found and marked on the swim cap by the investigator.[2,17] The area producing the greatest MEP wave amplitude was noted as the hot spot and was marked on the swim cap.[2,17] The stimulator was then be secured on to that spot using an adjustable camera mount and the inside of the coils were traced on the swim cap to ensure exact replication of placement for each of the following testing sessions. At the follow-up session the coil was first lined up with the tracings of the coil from the first session to begin locating the optimal cortical stimulation location.

Active motor threshold (AMT) was defined as the lowest TMS intensity required to evoke a measurable MEP (> 100 μV) in the quadriceps and fibularis longus muscles. In order to establish threshold, a total of 5 out of 10 measurable MEP waves must be elicited at the respective intensity. Once 5 out of 10 waves were found, the intensity level was decreased by 1% until a total of 6 out of 10 negative waves are produced, meaning that the 6 waves elicited peak to peak measured less than 100 μV.

Participants were instructed to sit still with their arms crossed over their chest, and remain focused and relaxed. They were then instructed to extend their knee to 5% of their maximum voluntary isometric quadriceps contraction and hold until the stimulus is given when testing the quadriceps. For fibularis longus testing, the participant was required to push into plantar flexion at 5% of their maximum voluntary output. A real time, visual feedback representation of their contraction was provided on a computer screen to control for variance in muscle contractions. After the stimulus was given, the participant was able to relax until the next stimulus was ready to be given. Surface electromyography

electrodes were positioned on the vastus medialis muscle and fibularis longus as described above to collect the signal elicited by the magnetic stimulation.

A stimulus response curve was then generated based on the level of active motor threshold that is determined. 120, and 140% of active motor threshold stimulus was determined.[26] At 120 and 140% of active motor threshold, an additional 5 stimuli were given.[26] The peak-to-peak amplitude of each MEP generated from the stimulus was recorded, saved, averaged and then normalized to the M-wave found from the above spinal reflex testing.

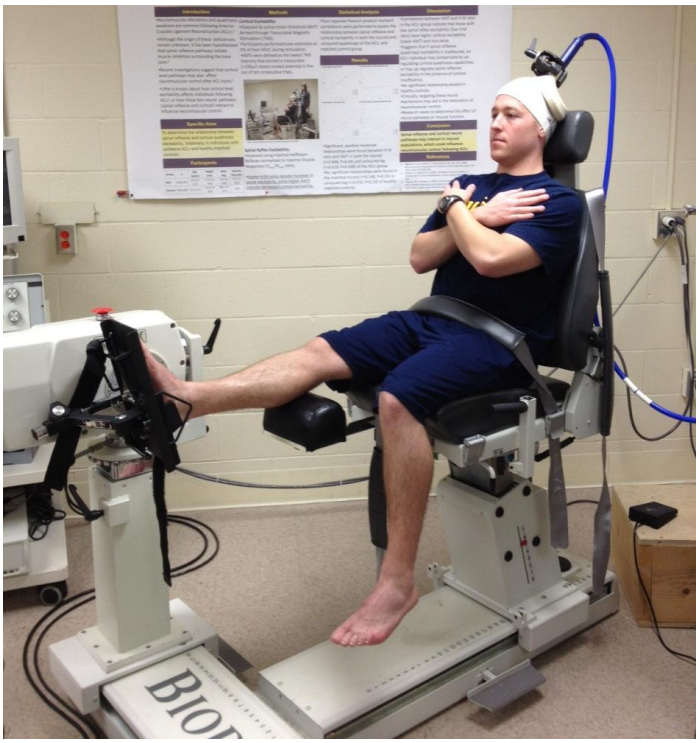

Figure 3-3: Patient positioning for TMS corticospinal excitability testing. The knee was flexed to 10° and ankle positioned in 10° of plantar flexion.

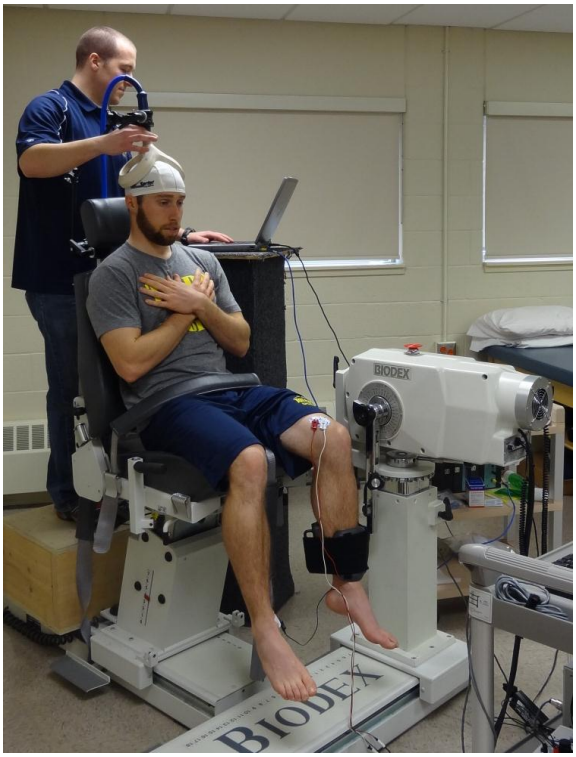

Figure 3-4: Patient positioning for TMS corticospinal excitability Testing of the quadriceps. The knee was flexed to 90°.

3.7 Statistical Analysis

An interclass correlation coefficient (AMT ICC 3,1; MEP ICC 3,5) will be used to determine the differences between testing sessions in order to determine the interrater reliability of TMS outcome measures in the quadriceps muscle and peroneals. ICCs were run using a two-way mixed analysis for absolute agreement. Bland-Altman plots were constructed to demonstrate agreement between TMS outcome variables in the quadriceps and peroneals over two separate testing sessions. Limits of agreement (LOA) were used to evaluate variability in mean differences associated with overall mean scores included in the Bland-Altman plots. Bland-Altman plots were constructed plotting mean difference against the average of the two means. LOA were identified as 1.96 times the standard deviation of the variable. An ideal Bland-Altman plot depicts all data points lying within

the LOA. In order for agreement to still be deemed acceptable no more that 5% of all data points should lie outside of the LOA.

Chapter Four

Results

4.1 Participants

Twenty participants were initially recruited between the ages of 18 and 35. Two were removed from data processing because their changes in AMT for all four muscles fell more than two standard deviations away from the group means and were determined outliers. Demographic data from the remaining participants is located in Table 1. All participants completed both of the testing sessions which lead to a dropout rate of 0%.

4.2 Active Motor Threshold

ICCs were calculated for all four muscles at the four week time point. If AMT was not able to be reached during the first session, the subject data was removed from that specific analysis. This occurred for one participant in both the nondominant quadriceps and fibularis longus muscle, and for three participants in the dominant fibularis. Dominant quadriceps yielded the highest ICC for the eighteen included subjects (Table 3). Bland-Altman plot showed one data point, or 5%, of all data points falling outside the limits of agreement (Figure 1). The mean difference was 2.5 and the range between upper and lower limits was 15.92. The nondominant quadriceps reliability was lower than dominant quadriceps ($ICC_{3,5}$ =.828) and 0% of the seventeen data points on the Bland-Altman plot were outside the limits of agreement (Figure 2). Mean difference and range are shown in Table 2.

Both dominant and nondominant fibularis muscles yielded lower reliability compared to the quadriceps (Table 3). Thirteen percent of the 15 data points fell outside of the limits of agreement for the dominant fibularis (Figure 3). The Bland-Altman plot for nondominant fibularis showed 6% of the 16 data points outside of the limits of agreement (Figure 4). The dominant fibularis yielded the smallest mean difference and also had the greatest range between limits of agreement (Table 2). The nondominant fiblularis mean difference and range is shown in Table 2.

4.3 Motor Evoked Potentials

MEPs were collected at 120 and 140% of AMT for each muscle studied. ICCs were calculated and Bland-Altman Plots were constructed comparing week 1 MEPs to week 4 MEPs. If MEPs were not able to be recorded during the first session, the subject was removed for that muscle analysis. All four muscles yielded strong ICCs at both 120 and 140% of AMT (Table 3). For dominant quadriceps, six percent of the data points fell outside of the limits of agreement for both 120 and 140% AMT (Figures 5 and 6). Nondominant quadriceps ICCs were higher than dominant quadriceps (Table 3). Bland-Altman plot analysis showed 100% of the sixteen data points for 120% AMT falling within the limits of agreement (Figure 7). Six percent of the fifteen data points fell outside the limits of agreement for nondominant quadriceps (Figure 8).

Dominant quadriceps at 120 and 140% AMT both had small mean differences (Table 2). However, the ranges for both were large indicating a lesser degree of agreement between the two testing sessions. Nondominant quadriceps had small mean difference scores at both 120 and 140% AMT (Table 2). Dominant fibularis analysis showed high ICCs at 120 and 140% AMT (Table 3). One hundred percent of the data

points fell within the limits of agreement for both 120 and 140% AMT Bland-Altman plots (Figures 9 and 10). Nondominant fibularis ICCs were strong at 120% AMT and good at 140%. 100% of the ten data points fell within the limits of agreement for 120% AMT (Figure 11). Fourteen percent of the seven data points fell outside of the limits of agreement for nondominant fibularis MEPs at 140% AMT (Figure 12).

Although ICCs were high, and all data points fell within the limits of agreement for the dominant fibularis at both 120 and 140% AMT, MEP mean difference at 120% AMT was small and the range between limits of agreement was large (Table 2). The same is true at 140% AMT with a mean difference of 0.001 and a range of 0.06. For the nondominant fibularis, mean differences were small at 120% and 140% and both ranges were large (Table 2).

Table 4.1: Subject Demographics

Table 1. Subject Demographics	
Number	18
Males	8
Females	10
Age	22.35 $\pm$ 2.3
Height (M)	1.71 $\pm$ 0.11
Weight (Kg)	73.61 $\pm$ 16.77

Table 4.2: Bland-Altman Plot AMT and MEP Data

Outcome Measure	Mean Difference	SD*1.96	Lower Limit of Agreement	Upper Limit of Agreement	Range	% of Data Points Outside of LOA
AMT Dom Quad	2.5	7.96	-5.46	10.46	15.92	5
AMT NDQuad	-1.47	5.63	-7.11	4.16	11.27	0
AMT Dom Fib	-0.87	32.37	-33.23	31.50	64.73	13
AMT NDFib	1.13	13.50	-12.38	14.63	27	6
MEP DomQuad 120%	0.01	0.09	-0.08	0.10	0.186	6
MEP DomQuad 140%	0.01	0.01	-0.12	0.14	0.256	6
MEP NDQuad 120%	-0.009	0.04	-0.05	0.03	0.087	6
MEP NDQuad 140%	-0.004	0.04	-0.04	0.03	0.076	6
MEP DomFib 120%	0.004	0.03	-0.02	0.032	0.055	0
MEP DomFib 140%	0.0007	0.03	-0.03	0.03	0.057	0
MEP NDFib 120%	-0.003	0.03	-0.04	0.03	0.069	0
MEPNDFib 140%	-0.02	0.13	-0.15	0.11	0.254	0

Dom = Dominant; ND = Nondominant; LOA = Limits of Agreement

Table 4.3: AMT and MEP ICC Results

Muscle	AMT ICC	MEP 120% ICC	MEP 140% ICC
Dominant Quadriceps	.873	.917	.975
Nondominant Quadriceps	.828	.954	.982
Dominant Fibularis	.522	.862	.939
Nondominant Fibularis	.763	.919	.726

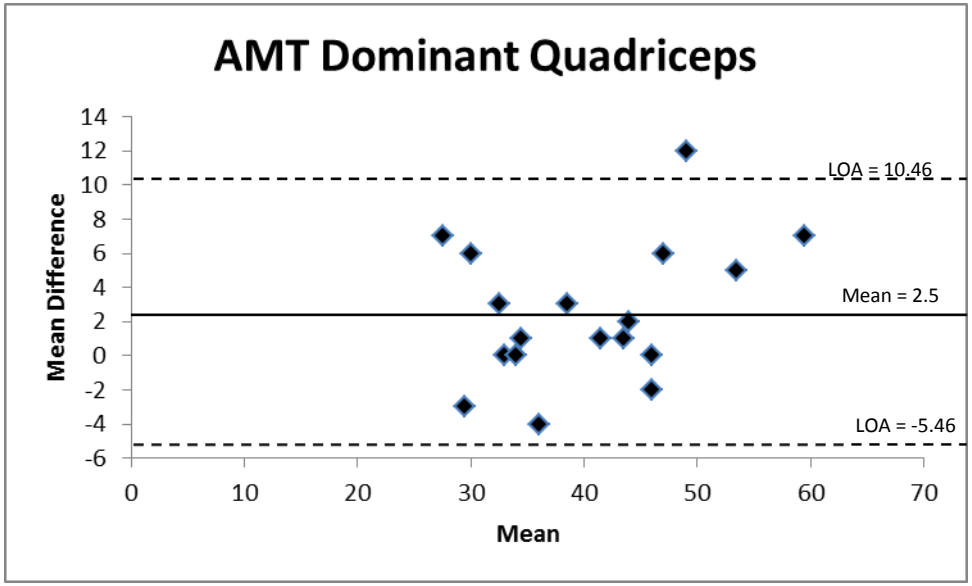

Figure 4-1: Dominant Quadriceps Active Motor Threshold

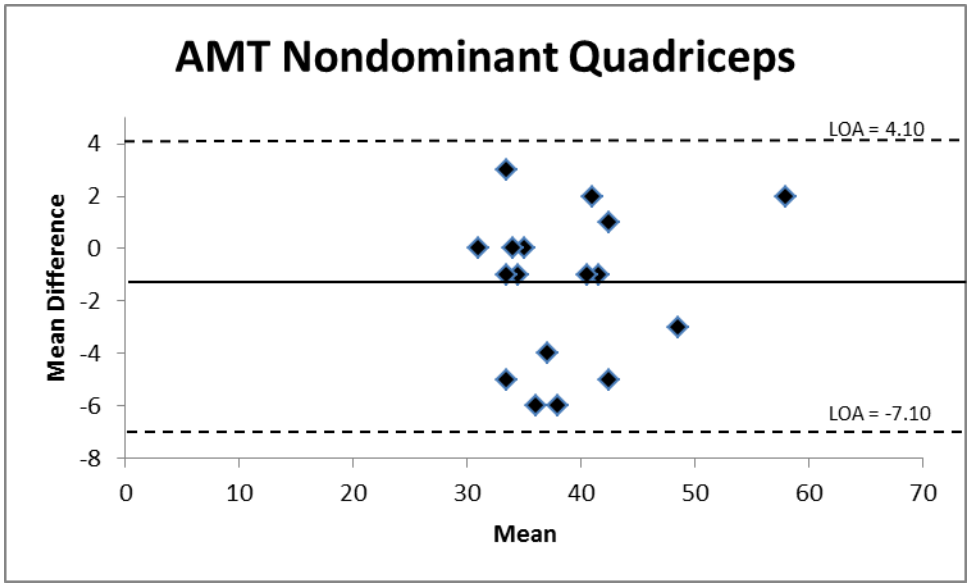

Figure 4-2: Nondominant Quadriceps Active Motor Threshold

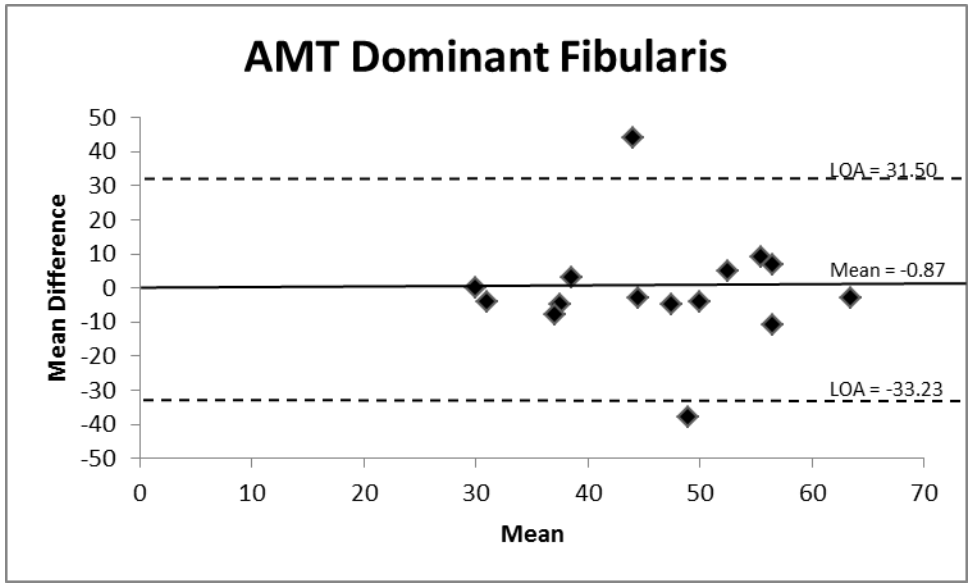

Figure 4-3: Dominant Fibularis Active Motor Threshold

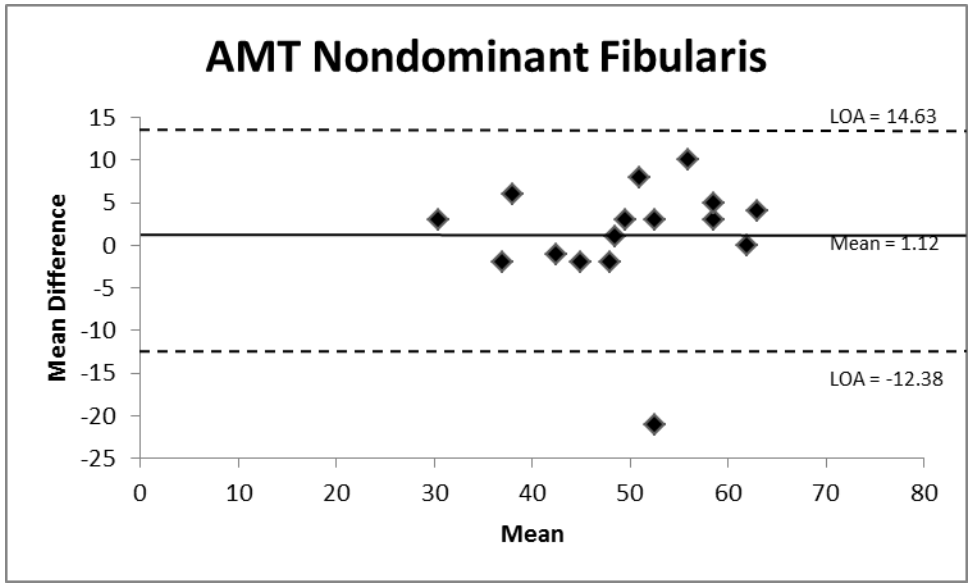

Figure 4-4: Nondominant Fibularis Acvitve Motor Threshold

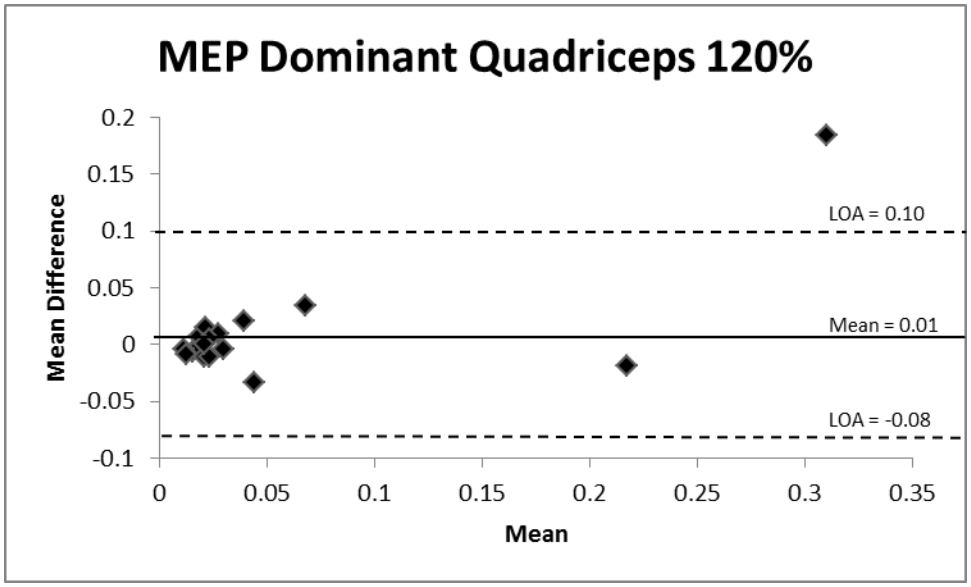

Figure 4-5: Dominant Quadriceps MEP at 120% of AMT

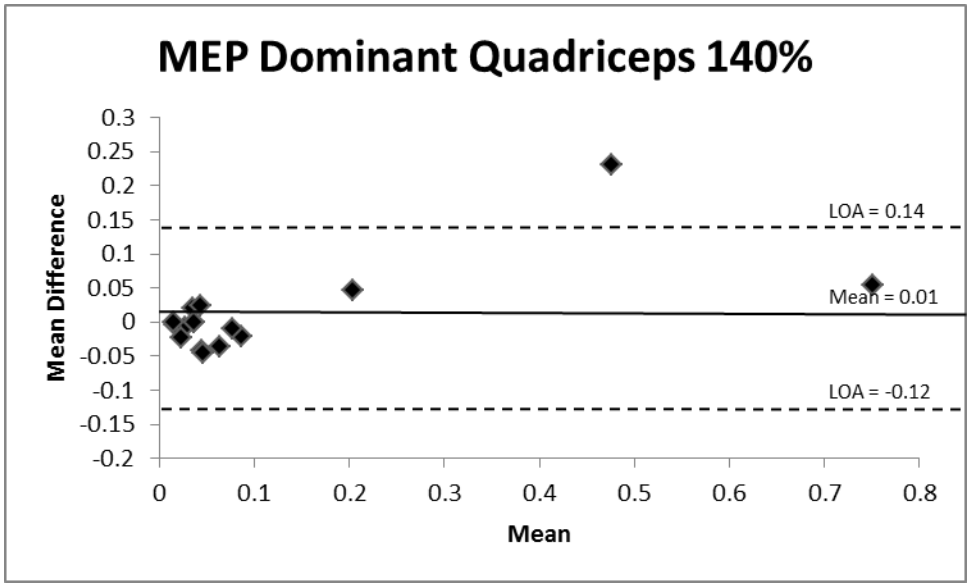

Figure 4-6: Dominant Quadriceps MEP at 140% of AMT

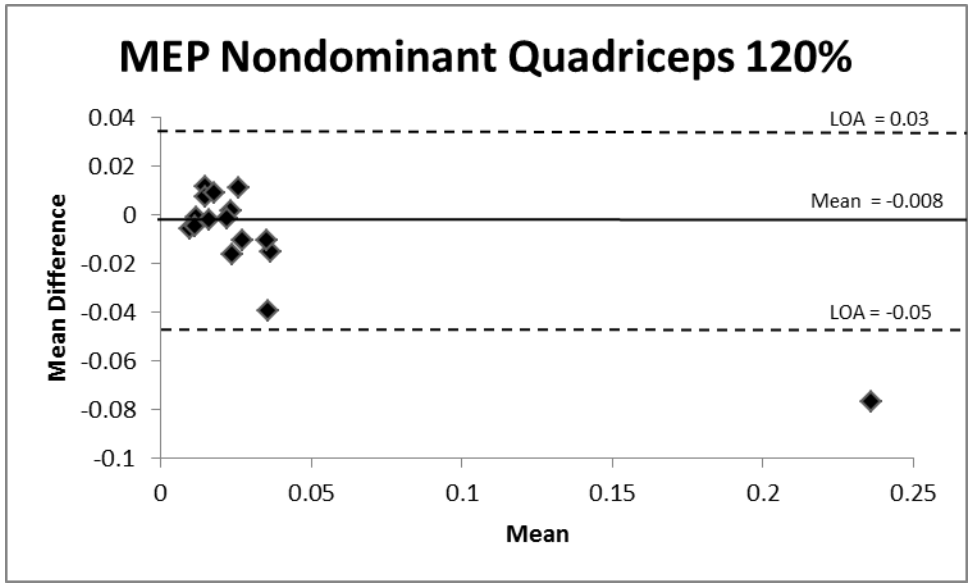

Figure 4-7: Nondominant Quadriceps MEP at 120% of AMT

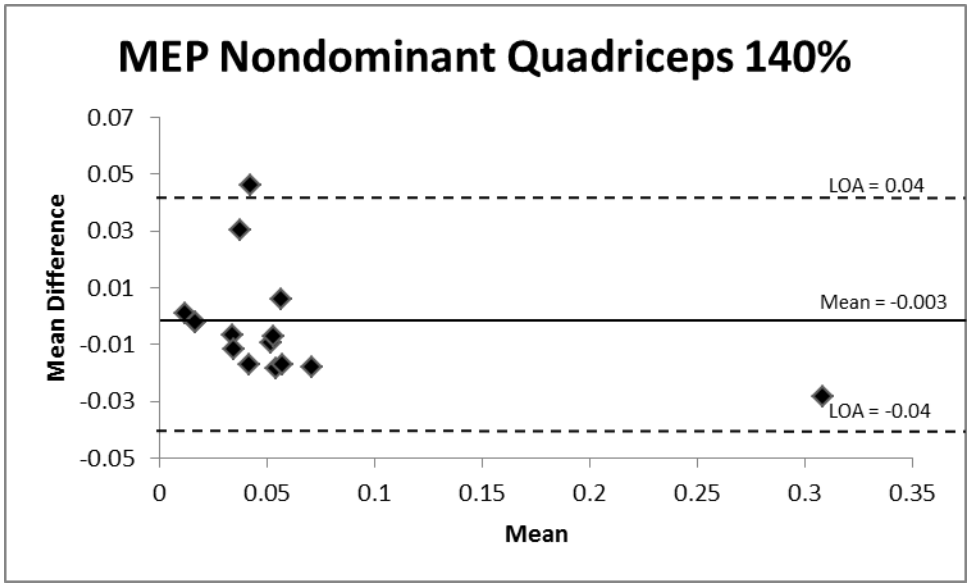

Figure 4-8: Nondominant Quadriceps MEP at 140% of AMT

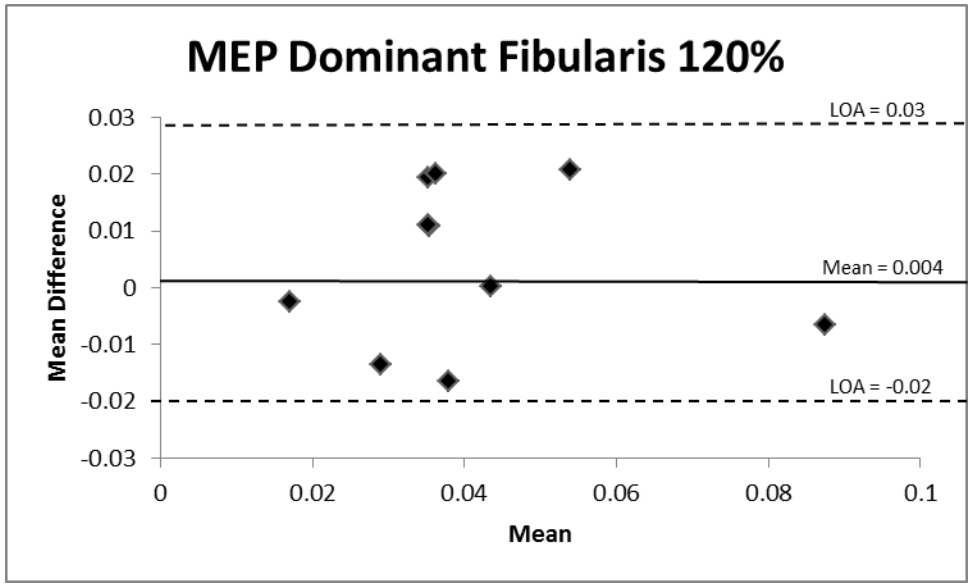

Figure 4-9: Dominant Fibularis MEP at 120% of AMT

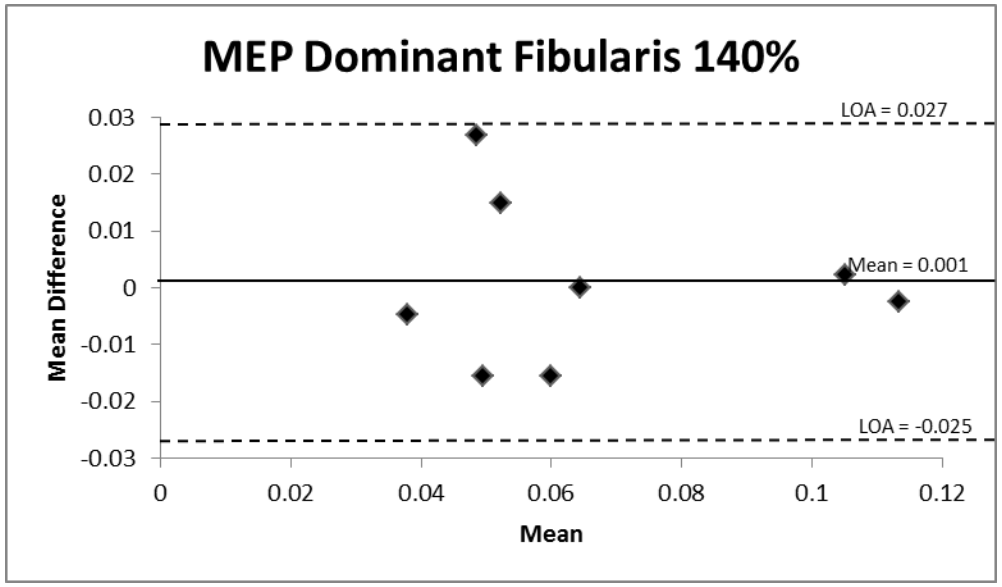

Figure 4-10: Dominant Fibularis MEP at 140% of AMT

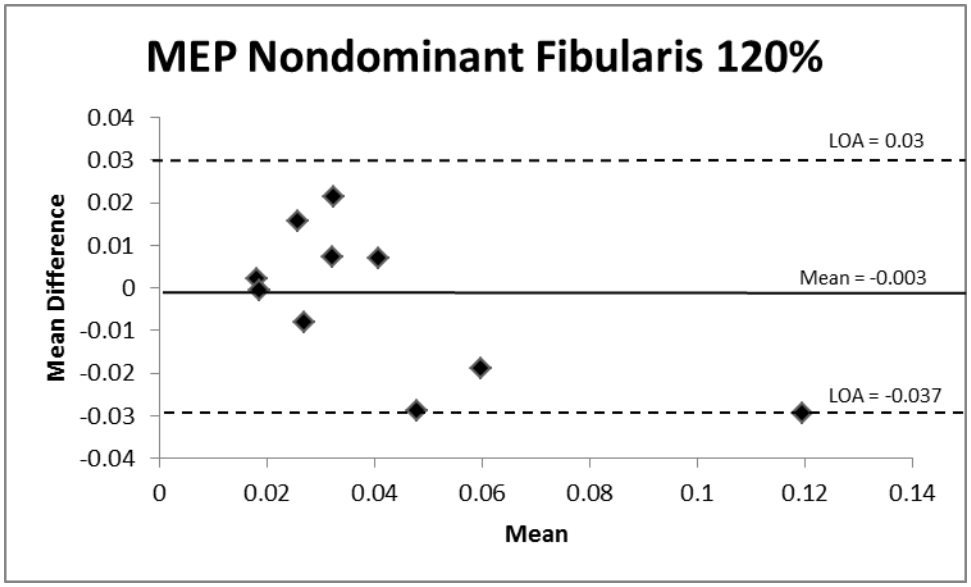

Figure 4-11: Nondominant Fibularis MEP at 120% of AMT

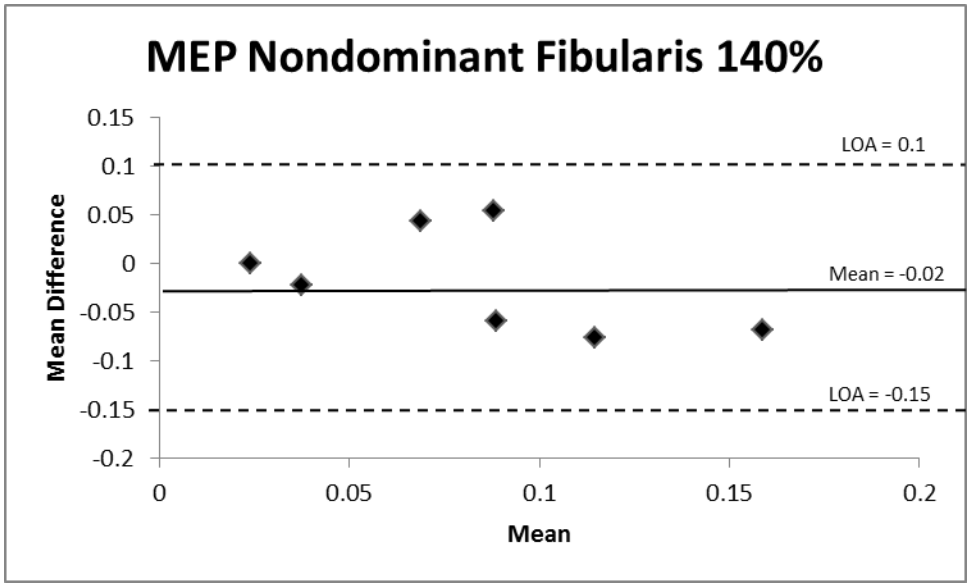

Figure 4-12: Nondominant Fibularis MEP 140% of AMT

Chapter Five

Discussion

The purpose of this study was to determine the intrarater reliability and agreement of Transcranial Magnetic Stimulation in the quadriceps and fibularis longus muscles of both the dominant and nondominant limbs. More specifically AMT and peak to peak MEP measurements were analyzed to determine if TMS can be a reliable measure of cortical excitability over time.

ICC and Bland-Altman plot analyses demonstrated that TMS can be a reliable tool to assess levels of cortical excitability over time in both the fibularis longus and quadriceps muscles. The use of the ICC is the most adequate measure of test-retest reliability, not only because it reflects the degree of association between measurements, but also the strength of association between scores achieved from each data collection session.[12] The use of Bland-Altman plots further demonstrates the strength of agreement between two measures, and reveals further information not gained from ICC measurements. Bland and Altman[31] suggest that analysis through these plots can offer a more robust approach at assessing agreement. Additionally, data can produce high correlations with poor agreement.[31]

Based on previous research, it was determined that TMS can be a reliable measurement of cortical excitability levels in both upper and lower extremity

musculature.[2,6,7,11-13,18,19,30] However, all studies only reported ICCs and did not assess agreement of outcomes. When looking at the reliability of an instrument, it is important to consider not only the correlational relationship but also the level of agreement between each session.

5.1 Active Motor Threshold

Comparing baseline to four weeks post measurements yielded strong ICCs that all showed TMS as reliable in both the quadriceps of the dominant and nondominant limbs and the nondominant fibularis longus over a four week time period. Dominant fibularis assessment yielded fair ICCs. The nondominant quadriceps proved to have more acceptable agreement than the dominant quadriceps when comparing AMT. Even though ICCs were very similar for both the dominant and nondominant limbs, the percentage of data points falling outside of the LOA for nondominant quadriceps was less than the dominant quadriceps and the nondiminant quadriceps also demonstrated a more narrow range. The range between LOA for the dominant quadriceps was also greater when compared to the nondominant quadriceps, which can indicate that measuring the nondominant quadriceps over multiple sessions would increase agreement between scores and would be more accurate at detecting changes in cortical excitability over time. Both dominant and nondominant quadriceps showed a moderate range of limits of agreement without data points clustered towards the mean, but assessing the plot parameters as a whole indicate adequate agreement in both quadriceps and the nondominant yielding a more acceptable level of agreement.

The dominant fibularis yielded the lowest ICC for AMT. When assessing the Bland-Altman plot, the range between the limits of agreement was very large. However,

there were two outliers that could have added to the increased range. All other data points are tightly clustered around the mean difference. If the possible outliers for these specific outcome measures were not present, the range between the LOA would have been smaller, and likely the agreement would have been increased. Based on the Bland-Altman plot, analysis the dominant fibularis may not produce acceptable agreement, as well as the ICC did not reach the threshold to be determined as strong. The nondominant fibularis was shown to be more reliable and produced more acceptable agreement than the dominant fibularis through both ICC comparison and Bland-Altman plot analysis. Even though more than 5% of the data points fell outside the LOA, there were a smaller percentage of data points outside of the LOA compared to the dominant fibularis. The range between the LOA was decreased and data points were clustered around the mean. There was a possible outlier shown for the nondominant fibularis which could have led to an increase in range. Assessing AMT in the nondominant fibularis appears to be a reliable measure.

In future studies, if the fibularis muscle is to be measured for analysis, the nondominant fibularis could produce greater levels of reliability and agreement. Changes could be attributed to actual physiological changes rather than the variability that could be seen using TMS.

5.2 Motor Evoked Potentials

All MEP data elicited higher reliability and agreement than AMT for all muscles that were studied. Not only were the ICCs higher, the percentages of data points outside of the LOA were drastically reduced when compared to each of the individual muscles tested. Overall, MEPs measured at 120% AMT yielded greater ICCs in only the

nondominant fibularis when compared to MEPs measured at 140% of AMT. Since all ICCs were in the excellent range except for the nondominant fibularis, which yielded a strong ICC, it is imperative to analyze the Bland-Altman plots to determine if the measurements taken were actually in strong agreement.

When comparing the Bland-Altman plots of the MEPs from the quadriceps and fibularis longus muscles, it is clear that the data points from both quadriceps are clustered together tightly around the mean and only have a small number of data points lying outside the LOA, which indicate a high level of agreement between the two sessions. The data points for the fibularis muscles are not clustered together and are widely dispersed for the MEP measurements. However the mean differences, range between LOA, and no points lying outside the limits of agreement indicate that both the dominant and nondominant fibularis longus muscles produce acceptable agreement in MEP outcome measures.

When looking specifically at the dominant quadriceps, the Bland-Altman plot for the MEPs at 120%, the range is smaller than that of the MEPs at 140%. The data points are also clustered together more closely than at 140%. For the dominant quadriceps, measures of cortical excitability should be compared through analysis of MEPs at 120% of AMT. For the nondominant quadriceps, measurements should also be compared between sessions based on the MEPs from 120% of AMT. The range between LOA is smaller at 120% and the data points are more closely clustered around the mean difference. Both of these together indicate a higher level of agreement at 120% of AMT.

All Bland-Altman plot analyses for all MEP measurements in both the dominant and nondominant fibularis yielded poor agreement. Ranges between LOA were large and

data points were widely dispersed throughout the graphs. Even though all data points fell within the LOA, both fibularis muscles do not show high levels of agreement using MEPs for analysis. Due to the lack of agreement between scores, MEP measures should not be used for analysis when assessing levels of cortical excitability in the fibularis muscles.

5.3 Limitations

The first limitation of this study is that assessing levels of cortical excitability is highly dependent on the state of the subject being tested. During each session, the participants were instructed to remain quiet, clear their mind and try to relax. This was often difficult to control. If the participant was stressed that day, or wandered with their thoughts, it could affect their neural activity, specifically levels of cortical excitability that could increase or decrease outcome measures on the separate testing sessions. The decrease in reliability, and variability in outcome measures, could possibly be from day to day changes in subject physiology, rather than error from the investigator or the TMS unit. However, this is to be considered as it would still contribute to reliability of TMS measures when using human subjects.

Also, since the sessions were four weeks apart from each other, there was no way to ensure the swim cap was placed in the exact same location or that the electrodes were placed in the exact location over the muscle bellies. The placement of the cap was standardized so that the perpendicular lines were lined up with each external auditory meatus and also the nose and occiput. However, to try to account for any differences in cap placement, the hot spot was reestablished prior to testing. This decreased the risk of testing over a different area of the motor cortex compared to the previous session;

however it was impossible to determine if the spot of stimulation was exactly the same. Motor mapping characteristics have demonstrated the ability to be reliable over time in the upper extremity. [2] We also had a small sample size, which should be taken into consideration when assessing the variability of TMS.

5.4 Clinical Relevance

TMS can be an important tool in detecting cortically driven inhibition in patients suffering from a variety of different neuromuscular pathologies. Neural inhibition has been shown to be present in the quadriceps muscle following anterior cruciate ligament reconstruction (ACLr) and in the peroneals following ankle injury, and is denoted by a diminished ability to volitionally contract a muscle.[8] Determining whether or not TMS is a reliable tool is important before it can be implemented as a clinical tool. Determining reliability gives the clinician confidence that any changes in the levels of cortical excitability are due to the physiological changes that are seen within the person, rather than due to the error associated with using the machine.

5.5 Conclusion

It has been previously demonstrated that TMS is a reliable tool in both the upper and lower extremities.[7,13,16,18,19,30]. This study showed comparable levels of reliability to previous investigations, and not only assessed the correlation between the measures but also the agreement between measures. Assessment of the Bland-Altman plots also allowed for confidence intervals to be constructed through the limits of agreement which enhances our determination of acceptable values of agreement. This study attempted to determine if TMS is a reliable means to study the human motor cortex and its effect on neuromuscular function in lower extremity muscles. Looking specifically at the

quadriceps and fibularis longus muscles, TMS appears to be a reliable method when using the correct outcome measure to detect cortical excitability. When studying the quadriceps muscles, cortical excitability should be measured through MEP at either 120 or 140% of AMT. Conversely, when measuring cortical excitability of the fibularis longus muscles, AMT should be the main outcome measure that is compared for analysis. When studying the fibularis longus muscle, data should only be collected and used from the nondominant fibularis. Through concluding that TMS is reliable in lower extremity musculature, clinicians can continue to target cortically driven forms of neuromuscular deficits in order to decrease the effects of injury and ensure athletes can return to play with full neuromuscular control.

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Appendix A

Informed Consent for Human Research Study

ADULT RESEARCH SUBJECT INFORMATION AND CONSENT FORM

INTERRATER RELIABILITY OF TRANSCRANIAL MAGNETIC STIMULATION IN LOWER EXTREMITY MUSCLES

Principal Investigator:	Brian Pietrosimone PhD ATC
Other Staff (Co-Investigator):	Adam Lepley MS ATC, Brittney Luc ATC, Matthew Harkey ATC
Contact Phone number(s):	(419) 307-9083

What you should know about this research study:

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

- Your participation in this research is voluntary.

PURPOSE (WHY THIS RESEARCH IS BEING DONE)

You are being asked to take part in a research study looking at how well transcranial magnetic stimulation measures what it is intended to measure every time it is used. The purpose of the study is to **determine if transcranial magnetic stimulation can produce the same results when tested on separate days.** You were selected as someone who may want to take part in this study because you are a healthy individual with no previous history of knee injury. There will be approximately 40 people participating in this study at the University of Toledo.

DESCRIPTION OF THE RESEARCH PROCEDURES AND DURATION OF YOUR INVOLVEMENT

If you decide to take part in this study, you will be asked to report to the Joint Injury and Muscle Activation (JIMA) Laboratory in the Healthy Science and Human Services Building (Room 1409). You will be asked to **fill out a questionnaire about your current level of physical activity**. We will then asses your neural excitability through two different methods. These methods will include **Reflex Testing and Motor Cortex Testing.** This study will consist of three sessions lasting approximately one hour.

A history of one the following would exclude you from participating in this study: concussion or head injury in the past 6 months, history of stroke, cardiac condition, cranial neurosurgery, migraines, cancer in the brain or thigh musculature, diagnosed psychiatric disorder; or has a cardiac pacemaker, implanted cardiac defibrillator or intracranial metallic clips. **Any potential participant with a history of a previous seizure or epilepsy will be excluded from this study.** We will also exclude all pregnant females for protection of the fetus from electrical and magnetic stimuli. Since this study will be looking at a healthy population only, all participants with previous lower extremity pathology, injury, or surgery will also be excluded.

Level of Physical Activity Questionnaire

You will be asked to provide us information regarding you current levels of physical activity. You will also be asked to maintain your current level of physical activity throughout the duration of the study.

Reflex Testing

This testing provides an estimate of how well nerves in the lower leg are functioning. You will be instructed to sit in a reclined chair. You will have sticky electrodes placed on your lower legs and thigh. These electrodes are called EMG electrodes which stand for Electromyography which is a recording of the electrical (reflex) activity in skeletal muscle. The sites of EMG electrodes will be shaved and cleaned with alcohol. An electrode that provides a stimulus will be taped behind your knee and in the front of your hip. A few reflex measurements will be taken when you are lying down.

- These measurements will include a 1-millisecond stimulus.
- The intensity of this stimulus will vary depending on the reflex being elicited.
- The stimuli in this study feel similar to static electricity felt as you touch a door knob after walking across a carpet.

Motor Cortex Testing

This testing provides us important information regarding how your brain is sending messages to muscles in your legs. You will be asked to sit in an upright chair with your hands crossed over your chest. We will ask you to wear a bathing cap and ear plugs. We will position a coil over your head and adjust the position until it is in the correct spot. A brief magnetic stimulus will then be produced which will sound like a "click." You will not have any associated pain or discomfort in your head, but rather may feel a brief muscle contraction in the muscles of your leg or thigh. You fill be asked to flex certain leg muscles at a small to moderate intensity while we provide a series of brief magnetic stimuli to your head.

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

Likely Risks

- Mild discomfort for a very brief period during the electrical stimulation.

Less Likely Risks

- Mild, transient skin irritation from the sticky electrodes.

Very Unlikely Risks

- Mild, transient headache following magnetic stimulation
- In people with a history of seizures there is a slight possibility of causing a seizure with the magnetic stimulation, therefore you must tell us prior to testing if you have ever had a seizure so we can exclude you from the study

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

Although information that is gained from this research may be used to asses various ankle and knee injuries, we cannot and do not guarantee or promise that you will receive any benefits from this research.

RISKS TO UNBORN CHILDREN

It is unknown how the electrical stimulation used in this study would affect an unborn fetus; therefore, if you are pregnant you will not be allowed to participate in this study.

COST TO YOU FOR TAKING PART IN THIS STUDY

You are not directly responsible for making any type of payment to take part in this study. However, you are responsible for providing the means of transportation to the Joint Injury and Muscle Activation Laboratory. You will not be compensated for gas for travel or any other expenses to participate in this study.

PAYMENT OR OTHER COMPENSATION TO YOU FOR TAKING PART IN THIS RESEARCH

You will not be compensated for participating in this study.

ALTERNATIVE(S) TO TAKING PART IN THIS RESEARCH

The only alternative is not to participate in this study.

CONFIDENTIALITY - (USE AND DISCLOSURE OF YOUR PROTECTED HEALTH INFORMATION)

By agreeing to take part in this research study, you give to The University of Toledo (UT), the Principal Investigator and all personnel associated with this research study your permission to use or disclose health information that can be identified with you that we obtain in connection with this study. We will use this information to *for the purpose of conducting the research study as described in the research consent/authorization form*.

The information that we will use or disclose includes activity level and muscle activation measurements. We may use this information ourselves, or disclose this information as part of a research study. Under some circumstances, the Institutional Review Board and Research and Sponsored Programs of the University of Toledo may review your information for compliance audits. 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 Dr. Brian Pietrosimone, MS119 2801 W. Bancroft St. Toledo, OH 43606. 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 419-383-3413.

IN THE EVENT OF A RESEARCH-RELATED INJURY

In the event of injury resulting from you 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 the legal rights of your son/daughter/legal charge as a research subject. In the event of an injury, contact Brian Pietrosimone, PhD, ATC (419) 530-4467

VOLUNTARY PARTICIPATION

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

NEW FINDINGS

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

ADDITIONAL ELEMENTS

There is no other additional information for this study.

OFFER TO ANSWER QUESTIONS

Before you sign this form, please ask any questions on any aspect of this study that is unclear to you. You may take as much time as necessary to think it over. If you have questions regarding the research at any time before, during or after the study, you may contact: Dr. Brian Pietrosimone- (419) 530-4467. 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.

Appendix B

TMS Exclusion Criteria

UT IRB #107339

Subject Number_____

TMS Exclusion Form

Joint Injury & Muscle Activation Laboratory

University of Toledo

Please indicate if you have a history of any of the following exclusion criteria.

Yes	No	Concussion or head injury in the past 6 months
Yes	No	Stroke
Yes	No	Cardiac Condition
Yes	No	Epilepsy
Yes	No	Cranial Neural Surgery
Yes	No	cancer in the brain or thigh musculature
Yes	No	Diagnosed psychiatric disorder
Yes	No	A cardiac pacemaker
Yes	No	Implanted cardiac defibrillator
Yes	No	Intracranial metallic clips

APPROVED BY
UNIVERSITY OF TOLEDO IRB

Assigned Version Date: 04/13/2011

Appendix C

Knee Injury History Form

UT IRB #107339

Age_____ Sex_____
Height _____ Mass_____

Knee Injury History Form
Joint Injury & Muscle Activation Laboratory
University of Toledo

Subject Number _____ Date _____

Please Circle (Yes or No) regarding your situation.

Yes	No	Have you had an injury to either leg that has altered you function in the past 6 months?
Yes	No	Have you had a surgery to either leg (knee, ankle, hip) in the past six months (other than meniscectomy)?
Yes	No	Do you have any knee ligaments that have not been reconstructed?
Yes	No	Do you have any nerve injuries in your legs or lower back?
Yes	No	Do you have any known muscular abnormalities?
Yes	No	Do you have a heart condition that would stop you from exercising?
Yes	No	Have you ever been diagnosed with cancer over your knee or thigh?
Yes	No	Do you currently have an infection over your thigh or in your knee?
Yes	No	Do you know of a hypersensitivity to electrical stimulation?

1. Have you ever had a knee injury?

When (month / year): _____

Explain:_____
_____

2. Have you ever had a knee Surgery?

When (month / year): _____

Explain:_____
_____

If ACL Reconstruction, What graft type? _____

3. Did you participate in physical therapy or therapeutic exercise?

When did you start (month / year): _____

For How Long: _____

4. Have you ever had an injury/surgery to you ankle, hip or lower back?
When (month/ year): _____

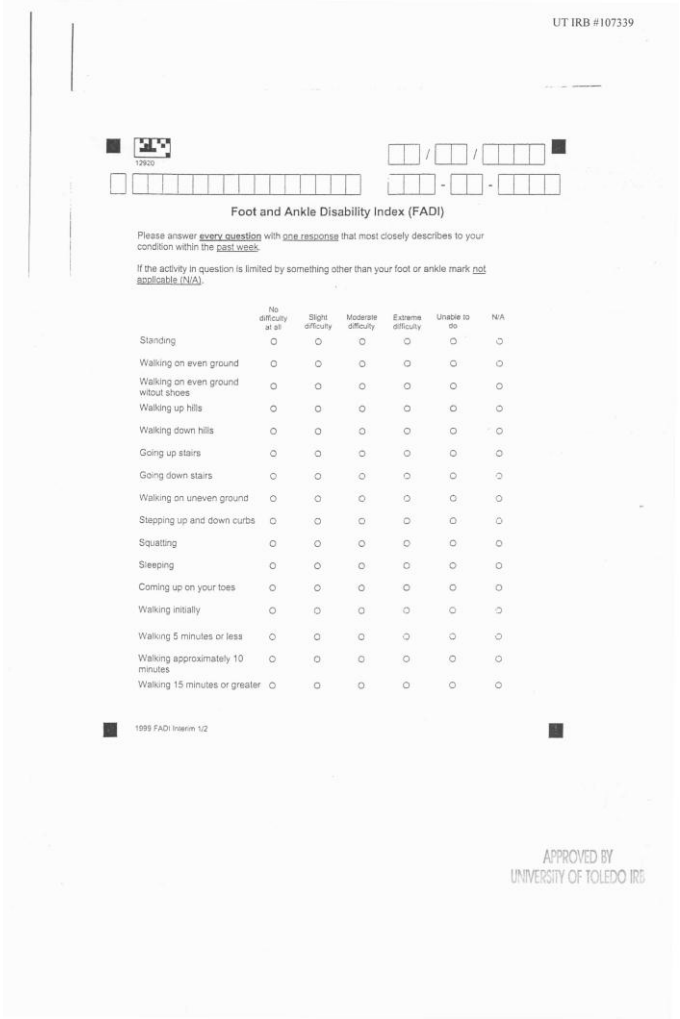
Explain: _____

Assigned Version Date: 04/13/2011

APPROVED BY
UNIVERSITY OF TOLEDO IRB

Appendix D

FADI and FADI Sport Questionnaires



UT IRB #107339

12920

Foot and Ankle Disability Index (FADI)

Please answer **every question** with one response that most closely describes to your condition within the past week.

If the activity in question is limited by something other than your foot or ankle mark not applicable (N/A).

	No difficulty at all	Slight difficulty	Moderate difficulty	Extreme difficulty	Unable to do	N/A
Standing	○	○	○	○	○	○
Walking on even ground	○	○	○	○	○	○
Walking on even ground witout shoes	○	○	○	○	○	○
Walking up hills	○	○	○	○	○	○
Walking down hills	○	○	○	○	○	○
Going up stairs	○	○	○	○	○	○
Going down stairs	○	○	○	○	○	○
Walking on uneven ground	○	○	○	○	○	○
Stepping up and down curbs	○	○	○	○	○	○
Squatting	○	○	○	○	○	○
Sleeping	○	○	○	○	○	○
Coming up on your toes	○	○	○	○	○	○
Walking initially	○	○	○	○	○	○
Walking 5 minutes or less	○	○	○	○	○	○
Walking approximately 10 minutes	○	○	○	○	○	○
Walking 15 minutes or greater	○	○	○	○	○	○

1999 FADI Interim 1/2

APPROVED BY
UNIVERSITY OF TOLEDO IRB

12920

Because of your **foot and ankle** how much difficulty do you have with:

	No difficulty at all	Slight difficulty	Moderate difficulty	Extreme difficulty	Unable to do	N/A
Home resposibilities	○	○	○	○	○	○
Activities of daily living	○	○	○	○	○	○
Personal care	○	○	○	○	○	○
Light to moderate work (standing, walking)	○	○	○	○	○	○
Heavy work (push/pulling, climbing, carrying)	○	○	○	○	○	○
Recreational Activities	○	○	○	○	○	○

Please rate your pain level as it relates to your **foot and ankle**:

	None	Mild	Moderate	Severe	Unbearable
General level of pain	○	○	○	○	○
At rest	○	○	○	○	○
During your normal activity	○	○	○	○	○
First thing in the morning	○	○	○	○	○

FADI Sports Scale

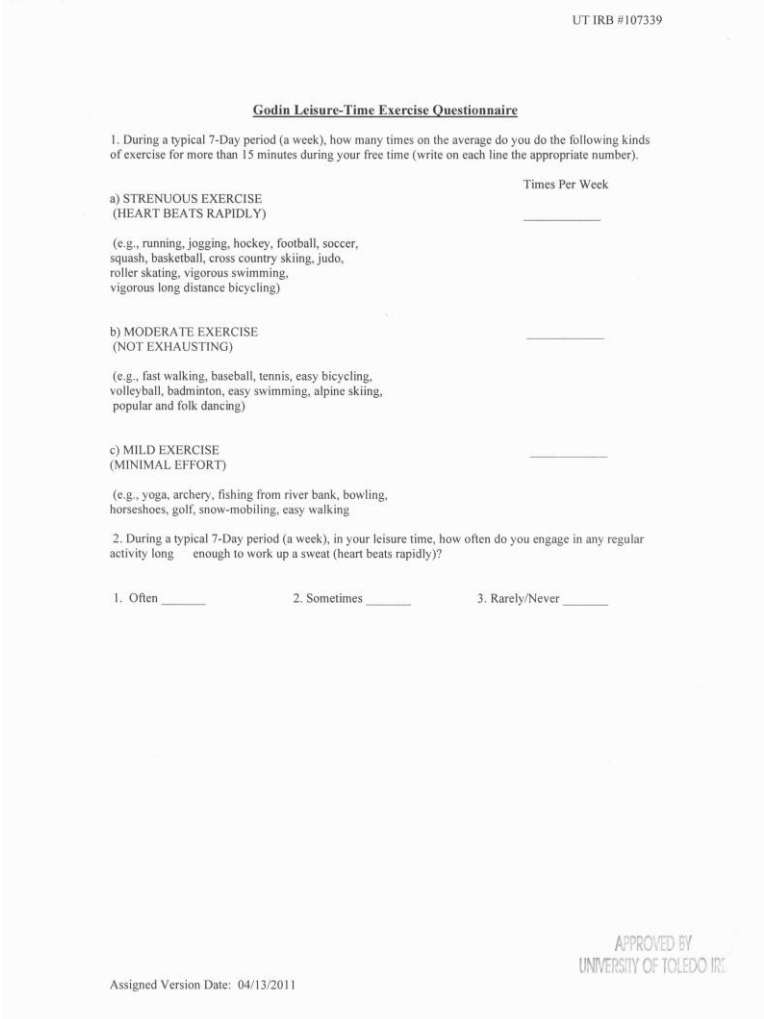
Because of your **foot and ankle** how much difficulty do you have with:

	No difficulty at all	Slight difficulty	Moderate difficulty	Extreme difficulty	Unable to do	N/A
Running	○	○	○	○	○	○
Jumping	○	○	○	○	○	○
Landing	○	○	○	○	○	○
Starting and stopping quickly	○	○	○	○	○	○
Cutting/lateral movements	○	○	○	○	○	○
Low impact activities	○	○	○	○	○	○
Ability to perform activity with your normal technique	○	○	○	○	○	○
Ability to participate in your desired sport as long as you would like	○	○	○	○	○	○

1998 FADI Interim 2/2

Appendix E

Godin Leisure Time Questionnaire



UT IRB #107339

Godin Leisure-Time Exercise Questionnaire

1. During a typical 7-Day period (a week), how many times on the average do you do the following kinds of exercise for more than 15 minutes during your free time (write on each line the appropriate number).

Times Per Week

a) STRENUOUS EXERCISE
(HEART BEATS RAPIDLY) _____

(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) MODERATE EXERCISE
(NOT EXHAUSTING) _____

(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD EXERCISE
(MINIMAL EFFORT) _____

(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking

2. During a typical 7-Day period (a week), in your leisure time, how often do you engage in any regular activity long enough to work up a sweat (heart beats rapidly)?

1. Often _____ 2. Sometimes _____ 3. Rarely/Never _____

APPROVED BY
UNIVERSITY OF TOLEDO IRB

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