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Beth E. Fisher
University of Southern California, bfisher@usc.edu

Ya-Yun Lee
National Taiwan University

Todd E. Davenport
University of the Pacific, tdavenport@pacific.edu

Stephen F. Reischl
University of Southern California

Elizabeth Ruckert
George Washington University

See next page for additional authors

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Within-day Test-retest Reliability of Transcranial Magnetic Stimulation Measurements of Corticomotor Excitability for Gastrocnemius and Tibialis Anterior Muscles

Beth E. Fisher, PT, PhD, FAPTA[1]
Ya-Yun Lee, PT, PhD[1]
Todd E. Davenport, PT, DPT, OCS[2]
Stephen F. Reischl, PT, DPT, OCS[1]
Elise Ruckert, DPT[1]
Kornelia Kulig, PT, PhD, FAPTA[1]

[1]Division of Biokinesiology and Physical Therapy, Herman Ostrow School of Dentistry, University of Southern California, Los Angeles, CA
[2]Department of Physical Therapy, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA

ABSTRACT

Background: Manual therapy interventions targeting the talocrural joint can improve gait and balance functions in individuals following ankle sprains. Less is known about the underlying mechanisms of functional improvements after manual therapy. One hypothesis involves change in corticomotor excitability (CE) following manual therapy procedures. Transcranial magnetic stimulation (TMS) is a brain imaging method that could provide important information regarding potential changes in CE associated with manual therapy techniques applied to the talocrural joint. However, within-day reliability of TMS to measure CE must first be established in order to measure CE changes associated with manual therapy procedures. **Objective:** To determine the within-day test-retest reliability of TMS CE measures for gastrocnemius (GAS) and tibialis anterior (TA) for use in test-retest designs assessing corticomotor excitability in manual therapy and exercise studies. **Method:** TMS measures, including motor evoked potential (MEP) amplitude and cortical silent period (CSP), were completed twice on the same day under resting and active conditions in n = 6 nondisabled participants. The absolute reliability (coefficient of variation), relative reliability (intraclass correlation coefficient), standard error of measures, and minimal detectable change outside the 95% confidence interval were calculated for both GAS and TA muscles in each experimental condition. **Results:** There were no statistically significant differences between the first and second TMS measurements. TMS measurements for GAS and TA demonstrated good absolute and relative test-retest reliability under the active condition, but not the resting condition. **Discussion:** TMS under the active condition can be reliably used to assess CE even in postural muscles with a small cortical representation area, such as GAS.

Key Words: motor evoked potential, cortical silent period, intraclass correlation coefficient

INTRODUCTION

Although the use of manual therapy procedures by physical therapists has been widely documented to improve function and decrease symptoms related to musculoskeletal pathology, studies to document the mechanisms underlying manual therapy interventions are less common. Understanding the potential mechanisms of manual therapy can help physical therapists select and create optimal treatment protocols by showing how manual therapy procedures modulate changes in symptoms and motor behavior. Historically, mobilization and manipulation were thought to reduce a cycle of maladaptive fibrosis.[1,2] However, the relatively rapid improvements in symptoms and disability observed following manual therapy procedures have led some authors to hypothesize and investigate potential neural mechanisms associated with improvements in symptoms and motor behavior after manual therapy procedures. Similarly, recent ultrasonographic findings have indicated short-term changes in abdominal and multifidus muscle thickness in individuals with low back pain following lumbopelvic manipulation.[3,4] These short-term changes in morphology were thought to be mediated by improved trunk muscle recruitment, perhaps by way of a neural mechanism.

Transcranial magnetic stimulation (TMS) has become a commonly used method to investigate experience-dependent neuroplasticity in response to exercise training or skill acquisition.[5-7] Recent studies have suggested the feasibility of using TMS to measure changes in corticomotor excitability after manual therapy. Dishman and colleagues[8,9] identified a significant increase in the lumbar paraspinal and gastrocnemius motor evoked potentials (MEP) following lumbar manipulation in healthy volunteers. Muscle-dependent effects of cervical spine manipulation on sensory and motor TMS measurements also have been identified.[10,11] Although these initial TMS studies are promising, use of the spine as the experimental paradigm may be limited because the relationship between symptoms and their location is unclear, and the lack of localization of treatment procedures.

Our group recently recommended the talocrural joint as a novel region to investigate potential changes in TMS measurements associated with manual therapy procedures.[12] This recommendation was based on the size of the joint, relative localization of pathology and treatment procedures to the region, and high prevalence of injury to this joint. However, the reliability and sensitivity to change of TMS measurements following manual therapy interventions has yet to be established for muscles crossing the talocrural joint. Many factors can contribute to the inherent noise of TMS measurements, including artifact and interference of electromyographic (EMG) signal when stimulating over primary motor cortex (M1). Additionally, variability in TMS measurements can be introduced by variable coil positioning during stimulation, electrode placement on the muscle between stimulation time points, and a subject's level of attention, age, muscle fatigue, or hormonal fluctuations.[13-16] The relatively deep location of ankle and foot muscle motor representation in the central sulcus further complicates potential problems related to coil placement.

The purpose of this study was to determine the within-day test-retest reliability of TMS measurements of musculature crossing the talocrural joint. Gastrocnemius (GAS) and tibialis anterior (TA) were selected for analysis on the basis of their relatively large size and importance to activities of daily living. In this study, TMS measurements were obtained during two common

experimental conditions, rest and during submaximal active contraction of the target muscle. All subjects were tested on the same day with approximately a one-hour interval between two test sessions. This pre- and post-timing interval (1 hour) is consistent with the common time period for manual therapy applied in the clinic, which includes the time window of pre-treatment assessment, manual therapy and treatment, and post-treatment observation of functional improvement. We hypothesized that TMS measurements would demonstrate adequate test-retest reliability and sensitivity to change.

METHOD

Participants

Six nondisabled young adults with mean age 24.17 ± 0.98 years old (5 female and one male) participated in this study. Participants were excluded if they had lower extremity injury in the past 12 months, a history of lower extremity or low back surgery, lower extremity neuropathy, vestibular dysfunction, diabetes, or active arthritis. Based on the TMS safety guidelines,[17] other exclusion criteria include neurological disorders; psychological problems; history of significant head trauma; any electrical, magnetic, or metal device implanted in the body (ie, cardiac pacemakers or intracerebral vascular clip); pregnancy; history of seizures or unexplained loss of consciousness; immediate family member with epilepsy; use of seizure threshold lowering medication; current use of alcohol or drugs; history of schizophrenia; or history of hallucinations.

Procedure

After informed consent was obtained, all participants completed a TMS safety questionnaire before participating in the study. Two TMS assessments of TA and GAS were conducted with one hour between the conclusion of the first test and initiation of the second test. The entire study protocol was completed within 4 hours for each participant. All TMS testing was conducted over the TA and GAS representational areas of left M1. This study was approved by the University of Southern California's Health Sciences Institutional Review Board.

TMS measurement

All the TMS assessments were carried out with a single-pulse magnetic stimulator (Magstim 200^2). A Double Cone 110 mm coil was used to generate the TMS pulse because it can provide stimuli with sufficient depth of penetration to activate the cortical representational areas of lower extremity muscles. The skin over the designated muscles of the right lower extremity was prepared with cleansing gel and alcohol to decrease impedance for applying surface EMG electrodes. Surface EMG electrodes (Ag-AgCl, 12 mm diameter, inter-electrode distance: 17 mm) were attached over the muscle belly of TA and GAS, and the ground electrodes were placed over the medial and lateral femoral epicondyle, respectively for each muscle. The electrodes remained in place between the two TMS test sessions. The EMG signals were filtered with 1-1000 Hz bandwidth filter, amplified, and digitized at 2000 Hz. The data were displayed and stored with customized MATLAB module (dwaq; dataWizard acquisition, ADW) in 600-ms samples beginning 100 ms before TMS stimulus.

To determine the optimal TMS stimulus point ('hotspot'), the participants were required to wear a swim cap with 1 cm × 1 cm grid. The coil was initially placed on a potential spot for the target muscle, and then systematically moved in 1 cm increments in each direction to find the point that induced the most consistent and prominent MEPs with the shortest latency.[18] After the hotspot was determined, the stimulation intensity was gradually adjusted until MEP amplitude was minimum 50μV evoked 5 out of 10 trials (50%).[18,19] This stimulation intensity was established as the resting motor threshold (RMT). For testing purposes, stimulation intensity is set as a percentage of each individual subject's motor threshold, enabling comparison among subjects. Since the biological response to stimulation varies greatly across subjects depending on unique, individual characteristics, normalizing stimulation intensity can greatly decrease variability between subjects.[17] To control TMS coil positioning variability, a stereotactic image guidance system (Brainsight Frameless, Rogue Research Inc, Montreal, Canada) was used. The hotspot of each muscle was marked on a 3D reconstruction of a standard magnetic resonance image of the brain in the first test session, and the same point of stimulation was used for the second test session.

For both TA and GAS, TMS stimuli were applied under two conditions: with the subject at rest (resting condition) and during voluntary contraction of the muscle (active condition). We used the active contraction condition in order to obtain measurement of cortical silent period (CSP), which would provide a method by which to differentiate between peripheral and central responses. During the resting condition, participants were asked to completely relax their legs while 10 TMS pulses were applied over the hotspot at 120% of motor threshold. For the active contraction condition, the TMS pulse was delivered as participants actively contracted TA and GAS by performing ankle dorsiflexion and plantar flexion respectively through a small amount of range. The dorsiflexion and plantar flexion ranges were controlled at 50% of the participant's maximal active range of motion. The movement range was controlled by placing a ruler in front of the ankle. Participants were instructed to consistently dorsiflex (for TA) to touch the ruler with the toe or plantarflex (for GAS) to touch the ruler with the instep (Figure 1). Ten TMS pulses at 100% of RMT were delivered with an interstimulus interval of approximately 5 to 10 seconds.

Figure 1. Experimental setup. A double cone coil was used to evaluate corticomotor excitability of tibialis anterior (TA) and gastrocnemius (GAS). In the resting condition, TMS data were collected while the subject was relaxed. In the active contraction condition, TMS stimuli were applied while the subject voluntarily dorsiflexed (for TA) to touch the ruler with the toe or plantarflexed (for GAS) to touch the ruler with the instep.

Data analysis

Data were analyzed off-line with a customized MATLAB (Mathworks, Natick, MA) software, dataWizard (version 08.11, A.D.W., USC) by the same rater.[20] The MEP amplitude for both resting and active conditions was determined as the difference between peak-to-peak envelope of the EMG signal output (Figure 2). The cortical silent period, the period of EMG silence following an MEP[21] generated with pre-contraction of the target muscle, was also analyzed. To calculate CSP, the period from the TMS pulse to the sustained return of rectified, integrated EMG signals of at least two standard deviations of background EMG amplitude following EMG silence was measured (Figure 3).[21] The average of 10 trials for each testing condition was calculated and used for data analysis. Distribution of the data was screened resulting in the application of nonparametric Wilcoxon signed rank test to compare the means between the two TMS assessments.

The intraclass correlation coefficient ($ICC_{(3,k)}$) of each muscle under each condition was analyzed with SPSS (Version 16, SPSS Inc., Chicago, IL) to determine the consistency of the TMS data obtained.[22] In this study, ICC values above 0.90 were considered excellent reliability, between 0.75 and 0.90 were indicative of good reliability, while values below 0.75 were considered moderate to poor reliability.[22] Standard error of measurement (SEM) was calculated from the ICC results to determine the standard deviation of systematic measurement error. The SEM is the product of the standard deviation (SD) and the square root of one minus the correlation coefficient [$SEM = SD*\sqrt{(1-ICC)}$].[22] In addition to SEM, the coefficient of variance of typical error (CV_{TE}) was calculated (CV_{TE} = 100%* SD of the difference ÷ $\sqrt{2}$ ÷ mean of all trials). The CV_{TE} assesses the standard deviation in proportion to the mean, and it enables the comparison of the response stability across different TMS measurements.[22] The minimum detectable change (MDC) outside the 95% confidence interval was also calculated in order to provide a reference for future studies to determine whether the amount of observed change is due to actual experimental manipulation or due to measurement error. The MDC_{95} was calculated as $1.96*\sqrt{2}*SEM$, while 1.96 represents the 95% confidence interval of SEM from the normal distribution, and $\sqrt{2}$ is used to account for the additional uncertainties introduced by repeated measurement errors between two time points.[23]

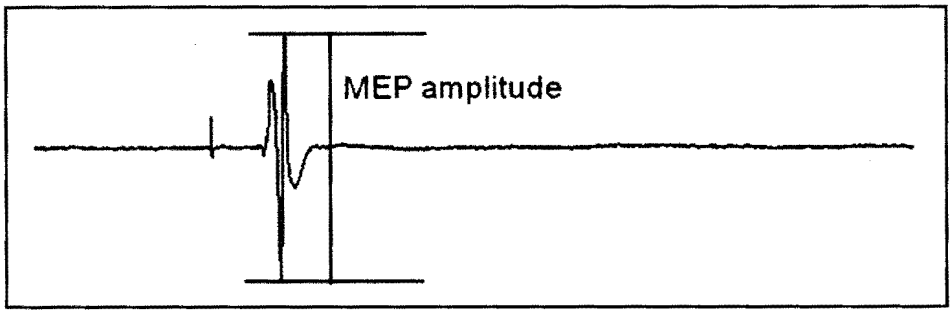

Figure 2. Motor evoked potential amplitude determination at resting condition.

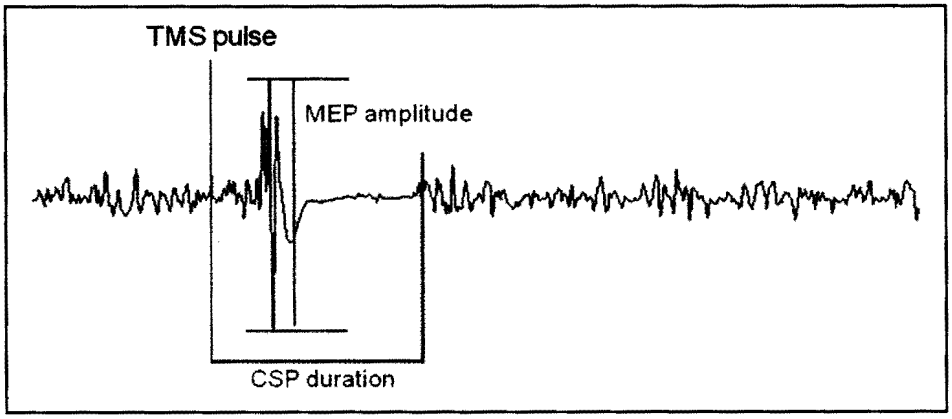

Figure 3. Motor evoked potential amplitude and cortical silent period determination at active condition.

RESULTS

There were no statistically significant differences between the first and second test sessions in any of the TMS measurements (Table 1). The relative and absolute reliability for all the TMS measurements are presented in Table 2. The $ICC_{3,k}$ values of both muscles were good to excellent for MEP amplitude and CSP measured during the active contraction condition (r = 0.84 – 0.99). However, the $ICC_{3,k}$ values for MEP amplitude during the resting condition were poor to moderate (r = 0.27 – 0.46). Similarly, absolute reliability (CV_{TE}) demonstrated lower percentage errors in MEP amplitude and CSP during the active contraction condition (5.28 – 26.19%) compared to the resting condition (32.23 – 38.35%). The SEM and MDC_{95} values are also provided in Table 2. Changes within ± 2 SEM were considered within systematic measurement error and further calculation of MDC_{95} provided a reference value for detecting 'true changes' that were independent of the variations associated with repeated measurements.[23]

DISCUSSION

This study established the within-day reliability of TMS measurements for GAS and TA, thus providing data for future investigation of potential corticomotor changes after a single session of manual therapy. Test-retest reliability of TMS measurements previously had been well-established for upper extremity muscles,[13,24-26] with only a few studies investigating corticomotor excitability (CE) of lower extremity muscles. However, until this study, reliability of TMS measurements for GAS had not been established. Commonly, TMS reliability studies were conducted across several days[27,28] with less known about within-day variability. This study was the first to establish high within-day test-retest reliability of MEP amplitude and CSP duration measurements in both TA and GAS.

Interestingly, MEP amplitude and CSP duration during active contraction for both GAS and TA showed good to excellent reliability compared to the resting condition. These findings are consistent with previous research involving TMS measurements obtained during TA active contraction.[27-29] There are two possible explanations for this

Table 1. Mean (SD) Values of Each TMS Measurements in Two Test Sessions

TMS variables	First test	Second test	P value
TA rest MEP (μV)	231.40 (68.73)	288.63 (109.37)	0.249
TA active MEP (μV)	1286.14 (487.50)	1349.30 (483.11)	0.600
TA CSP (ms)	136.41 (44.17)	127.22 (43.80)	0.075
GAS rest MEP (μV)	186.32 (93.51)	168.92 (66.35)	0.917
GAS active MEP (μV)	613.20 (246.33)	676.37 (376.20)	0.917
GAS CSP (ms)	136.60 (36.26)	141.04 (46.52)	0.753

Abbreviations: TA, tibialis anterior; GAS, gastrocnemius; MEP, motor evoked potentials; CSP, cortical silent period

Table 2. Relative and Absolute Reliability Results of TMS Measurements

	ICC	SEM (units)	CV_{TE} (%)	MDC_{95} (units)
TA rest MEP (μV)	0.27	77.88	32.23	215.87
TA active MEP (μV)	0.94	114.85	12.03	318.34
TA CSP (ms)	0.99	5.02	5.28	13.90
GAS rest MEP (μV)	0.46	59.85	38.35	165.90
GAS active MEP (μV)	0.84	128.77	26.19	356.92
GAS CSP (ms)	0.98	6.04	6.05	16.75

Abbreviations: TA, tibialis anterior; GAS, gastrocnemius; MEP, motor evoked potentials; CSP, cortical silent period

result. First, volitional muscle contraction may preactivate corticomotor excitability to a more consistent level across trials. Second, the requirement of performing an active contraction may increase the focus of the subjects' attention throughout testing.[24] We suggest that changes in TMS measurements for TA and GAS under the active contraction condition may more reliably reflect treatment effects than resting condition.

There are two potential limitations of this study. First, the muscle contraction level during the active condition was controlled by movement range of motion instead of muscle contraction force. The muscle contraction level was controlled by actively dorsiflexing or plantar flexing through 50% of each subject's available active range. By controlling ankle movement range instead of contraction force, participants can maintain a relatively easy movement throughout testing. Moving the ankle through 50% of active range of motion requires less than 20% of maximal voluntary contraction;[30] hence, muscle fatigue throughout testing would not be a major concern in this study. In this study, good to excellent reliability was found during the active contraction condition in the present study, which suggests that controlling muscle contraction level by movement range is both feasible and reliable. A second limitation of this study is that only nondisabled young adults were recruited into this study. Thus, the reliability results may not generalize to other age groups or individuals with pathology. However, in clinical settings, young adults with sport-induced ankle injuries often require re-training for gait and balance. The reliability of TMS procedures with healthy young adults in this study will inform future studies examining changes in corticomotor excitability after one session of treatment in young adults with acute ankle sprain.

In summary, for both GAS and TA muscles, testing under an active contraction condition induced more consistent and reliable results than testing under resting conditions. Tibialis anterior and gastrocnemius muscles are the major muscles that may be directly affected by ankle manual therapy. The mechanisms underlying why manual therapy can effectively improve gait and posture are not well understood. This study provided a feasible and reliable method for future investigations into the possible corticomotor changes after a single-session treatment. In addition, the SEM, MDC_{95}, and CV_{TE} values provided in this study can assist researchers in future studies to determine true change in corticomotor excitability due to training or intervention.

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