Evaluation of Motor Cortical Excitability Using Evoked Torque Responses: A New Tool with High Reliability

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Abstract

Background: Motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) are typically recorded via surface electromyography (EMG). However, another suitable alternative may be recording torque output associated with MEPs, especially when studying multiheaded muscles (e.g. *quadriceps*) for which EMG may not be ideal.

Methods: We recorded the motor evoked torque elicited by TMS along with conventional EMG-based MEPs (MEP_{EMG}) over a range of TMS intensities (100–140% of active motor threshold [AMT]) from twenty healthy young adults on two different days. MEPs were normalized using different normalization procedures (raw, normalized to maximum voluntary isometric contraction [MVIC], and peak MEP). Additionally, motor evoked torque was normalized to TMS-evoked peripheral resting twitch torque. Intraclass correlation coefficients (ICCs) were determined for each of these variables to compute reliability.

Results: Motor evoked torque showed good to excellent reliability (ICC: 0.65–0.90) at TMS intensities ≥ 110% AMT, except when normalized by peak MEP. The reliability of raw MEP_{EMG} and MVIC normalized MEP_{EMG} was fair to excellent only at ≥ 130% AMT (ICC: 0.42–0.82) and

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CONFLICT OF INTEREST STATEMENT
The authors declare no conflict of interest

at ≥ 120% AMT (ICC: 0.41–0.83), respectively. The reliability of both MEP_{EMG} and motor evoked torque generally increased with increasing TMS intensities, with motor evoked torque normalized to the resting twitch torque yielding the best ICC scores.

Comparison with existing methods: When compared with conventional MEP_{EMG}, motor evoked torque offers superior and reliable estimates of corticospinal excitability, particularly when normalized to resting twitch torque.

Conclusions: TMS-induced motor evoked torque can reliably be used to measure corticospinal excitability in the quadriceps muscles.

Keywords

Evoked torque; vastus medialis; vastus lateralis; rectus femoris; knee; input/output curves

INTRODUCTION

The central nervous system (CNS) is a collection of nerve cells in the brain and spinal cord that communicate by excitatory and inhibitory electrochemical signals to process sensory and motor information (Lovinger, 2008). Neurobiological recovery processes after a CNS injury are known to alter these signals by modulating the excitability of the corticospinal pathways (Badawy et al., 2012). Therefore, an understanding of the corticospinal pathways' excitability may provide valuable information regarding the biological processes relevant to the recovery of function after CNS injury.

Transcranial Magnetic Stimulation (TMS) is a noninvasive brain stimulation technique commonly used to assess corticospinal excitability in individuals with and without neurological injuries/disorders (Krishnan et al., 2015; Rossi et al., 2009). TMS uses rapidly changing magnetic fields to stimulate nerve cells in the brain. When a single-pulse TMS is delivered over the primary motor cortex (M1) with adequate intensity, it induces efferent volleys along the corticospinal pathways (Barker et al., 1985). These efferent volleys (i.e., motor evoked responses) can be studied by recording the neuroelectric signals via surface electromyography (EMG) or the neuromechanical signals via force/torque sensors (e.g. isokinetic dynamometer) (Barker et al., 1985; Day et al., 1987; Krishnan, 2019; Lee et al., 2009; Mills et al., 1987; Nuzzo et al., 2016; Rothwell et al., 1987; Todd et al., 2007). The conventional practice is to use EMG-based motor evoked potentials (MEPs) to evaluate corticospinal excitability. While this approach is suitable for single-headed muscles, it may not be ideal for multi-headed muscles (e.g., quadriceps) because it is difficult to optimize the intensity for all the muscles within a group (i.e., finding a suitable intensity that will satisfy the motor threshold requirement across all muscles). As a result, researchers often use a single muscle as a representative sample of the entire muscle group (Bodkin et al., 2019; Brownstein et al., 2018; Lepley et al., 2020; Scheurer et al., 2020; Zarzycki et al., 2020). However, this approach may not always provide a complete picture of the corticospinal excitability of the entire muscle group. In this situation, the torque output associated with the MEPs may serve as a suitable alternative to study the net effect of TMS-induced motor volleys on the muscle group as a whole (Krishnan, 2019). Moreover, unlike EMG responses, torque outputs are inherently stable and may not require conventional normalization procedures (e.g., using M-max or maximum voluntary isometric contractions [MVICs]).

The raw EMG signals are known to be highly variable and sensitive to several factors, such as the placement, orientation, and contact quality of the sensors as well as the physiological, anatomical, and biochemical characteristics of the muscles (Chowdhury et al., 2013; Reed et al., 2013). As a result, normalization techniques are often incorporated into the data collection and processing to account for the variability introduced by EMG recordings and allow for meaningful interpretation of the MEP data (Zellers et al., 2019). A variety of methods have been utilized (e.g. normalization to MVIC, maximum peak MEP amplitude, M-max, etc.) without a consensus on which of these procedures produce the highest repeatability when measuring MEPs (Ball and Scurr, 2013; Zellers et al., 2019). While several existing studies have investigated the effects of TMS induced MEP via EMG recordings, no studies have examined the repeatability of motor evoked torque responses or how the various normalization techniques affect the reliability of motor evoked responses in the quadriceps muscle.

Therefore, this study was performed to primarily investigate the test-retest reliability of TMS-induced motor evoked torque responses and compare it with MEP EMG- responses (MEP_{EMG}) in the quadriceps muscles. A secondary aim of this study was to investigate the effect of various normalization procedures on the test-retest reliability of TMS-evoked torque and EMG responses. These aims were carried out by simultaneously recording motor evoked EMG responses of the vastus medialis, rectus femoris, and vastus lateralis muscles along with motor evoked knee extensor torques as participants were given a series of TMS pulses across different TMS intensities. Data was also analyzed through several normalization methods. We hypothesized that the MEPs collected via torque would be equally and/or more repeatable than the results obtained from surface EMG recordings, and that the reliability of MEP measurements would be affected by the normalization method used in the analysis.

METHODS

Participants

Twenty healthy individuals (12 males, 8 females, 21.5 ± 4.7 years, 172.0 ± 10.0 centimeters, 71.2 ± 12.2 kilograms, 18 right footed, 2 left footed) volunteered to participate in this study. All participants were free from neurological or orthopedic injuries. Participants were excluded if they: (1) were pregnant, (2) were taking medications that are likely to alter cortical excitability, (3) had ear or metal implants in the skull, (4) had a cardiac pacemaker, or (5) had a history of unexplained recurrent headaches, seizures, recent head injury, significant adverse reaction to TMS, or a major medical or heart condition that would likely affect the outcomes of the study. Participants reviewed a brief description of study protocols approved by the University of Michigan Institutional Review Board and provided written informed consent for participation in the study.

Experimental Approach

The repeatability of TMS-induced MEPs of the *quadriceps* muscles was assessed on the dominant leg (as determined by the participant's preferred leg for kicking) (Krishnan and Williams, 2014, 2009; Ranganathan et al., 2016) on two separate test days that were separated by at least 48 hours. A schematic of the experimental paradigm utilized to assess TMS-induced MEPs is provided in Figure 1. The participant was comfortably seated on an isokinetic dynamometer (Biodex Medical Systems, Inc., Shirley, NY, USA) after attaching surface EMG electrodes on the muscle bellies of the *vastus medialis* (VM), *rectus femoris* (RF), and *vastus lateralis* (VL) according to the SENIAM guidelines (www.seniam.org) (Hermens et al., 2000; Washabaugh et al., 2016; Washabaugh and Krishnan, 2018). Prior to affixing surface EMG electrodes (Trigno, Delsys, Inc., Natick, MA, USA) tightly to the skin with self-adhesive tapes and elastic bandages, the skin was cleaned with alcohol pads to ensure adequate skin contact. The hip and knee of the participant's dominant leg was fixed at ~85° and 60° of flexion, respectively. The hip and knee angles along with the participant-specific dynamometer chair settings were held constant between sessions to ensure that the lower limb position was reliably replicated across test sessions. After a brief warm-up with submaximal isometric contractions (2 × 50%, 2 × 75%), the participant performed two MVIC trials (MVIC) while receiving strong verbal encouragement from the experimenters. Visual feedback of their torque curves was also provided to ensure that the participant was giving their best effort.

Transcranial Magnetic Stimulation Protocol

TMS pulses were delivered at random intervals over the primary motor cortex (M1) using a Magstim® 200^2 stimulator (Magstim Company Ltd, Whitland, UK) via a standard double cone coil (110 mm – diameter) while the participant maintained a small background contraction of their quadriceps muscle (5% of MVIC). The TMS coil was oriented to induce a posterior-anterior current flow in M1 and was stabilized by a coil holder. A linen cap was secured tightly over the participant's head to assist in locating the quadriceps hotspot for TMS. We identified the vertex by determining the intersection of the lines connecting the two auditory tragi and the nasion and inion. An initial stimulation location that was 2 cm lateral and 2 cm posterior to the vertex was then marked on the cap after accounting the offset of the TMS coil dimensions (Rossini et al., 2015). Thereafter, the coil was systematically moved to determine the location that produced the largest and most consistent knee extensor twitch torque at the lowest TMS intensity (Krishnan, 2019; Krishnan et al., 2019; van de Ruit et al., 2015). This location was registered digitally as the quadriceps hotspot using a custom-developed frameless stereotaxic camera system (NeuRRoNav) (Rodseth et al., 2017). The coil was then secured to this location using an adjustable coil holder, and the feedback from NeuRRoNav system was used to maintain the position and orientation of the coil over the hotspot throughout the experiment.

The Active Motor Threshold (AMT) was then established by finding the minimum TMS intensity required to elicit a clear distinguishable MEP in ≥ 50% of the time while the participant maintained a background contraction of their quadriceps muscle. An adaptive threshold-hunting method based on maximum-likelihood parameter estimation by sequential testing (TMS Motor Threshold Assessment Tool, MTAT 2.0, http://

www.clinicalresearcher.org/software.htm) was used to determine the AMT (Borckardt et al., 2006). After determining the AMT, motor evoked responses were collected at five different intensities (100–140% AMT) with five trials at each intensity. Following this, the participant received 5 stimulations at 100% of maximum stimulator output with the TMS coil placed directly over the *quadriceps* (20 cm above the patella) to record their TMS-evoked peripheral resting twitch torque (RTT). The subject was then scheduled for their second visit during which the TMS procedures were repeated in an identical manner to day 1.

Data Analysis

A custom software written in LabVIEW version 11.0 (National Instruments Corp., Austin, TX, USA) was used to collect and process the TMS data. The EMG and torque signals along with the TMS synchronization pulses were low pass filtered at 500 Hz using an 8th order analog Butterworth filter (SCXI 1143, National Instruments) and sampled at 1000 Hz using a Windows desktop computer with an 18-bit high-accuracy M-series data acquisition module (USB 6281, National Instruments). The size of the motor evoked torque response was determined by computing the average peak twitch torque elicited by the TMS at each testing intensity after removing the torque offset associated with background contraction. The size of the MEP_{EMG} was determined by computing the average peak-to-peak MEP amplitude elicited by the TMS at each testing intensity. The MEP_{EMG} and motor evoked torque responses were then evaluated using different normalization procedures: (1) raw data (i.e., without any normalization), (2) normalized to MVIC (eq 1), and (3) normalized to peak MEP amplitude within the range of 100–140% AMT (eq 2). Additionally, the motor evoked torque was normalized to TMS-evoked peripheral resting twitch torque elicited at 100% of maximum stimulator output (eq 3).

$$\text{MVIC Normalization} = \frac{\text{MEP}}{\text{MVIC}} \times 100 \tag{1}$$

$$\text{Peak MEP Normalization} = \frac{\text{MEP}}{\text{Maximum MEP}} \times 100 \tag{2}$$

$$\text{Resting Twitch Torque Normalization} = \frac{\text{Motor Evoked Torque}}{\text{Resting Twitch Torque}} \times 100 \tag{3}$$

Statistical Analysis

All statistical analyses were performed using SPSS version 24 (SPSS Inc., Chicago, IL, USA.). Descriptive statistics were computed to summarize motor evoked torque and MEP_{EMG} obtained at each intensity across the two testing sessions. The test-retest reliability of MEP amplitudes collected across two days was assessed using intraclass correlation coefficients (ICCs). ICC analyses were performed using a two-way mixed-effects model for single measurement and absolute agreement [i.e., ICC (3,1) model] at each TMS intensity for both raw and normalized motor evoked responses. ICC values were interpreted using the guidelines established by Cicchetti: Poor (<0.40), Fair (0.40–0.59), Good (0.60–0.74), and Excellent (0.75–1.00) (Cicchetti, 1994).

RESULTS

TMS-induced MEPs across five TMS intensities

The TMS-induced motor evoked torque responses and MEP_{EMGs} (*vastus medialis*, *rectus femoris*, and *vastus lateralis)* across the two test days are shown in Figure 2 and Figure 3, respectively.

Repeatability of TMS induced MEPs

The ICC values for both the raw and normalized motor evoked torque and MEP_{EMG} data across various TMS intensities are provided in Table 1.

The raw motor evoked torque displayed good to excellent reliability at TMS intensities greater than 100% AMT, whereas the raw MEP_{EMG} responses generally demonstrated only poor to fair repeatability (except at high TMS intensities) across testing sessions (Table 1). Normalizing the MEPs to MVIC values generally improved the reliability; however, normalizing the MEPs to peak MEP substantially reduced the test-retest reliability (Table 1). Most noticeably, the motor evoked torque normalized to TMS-evoked peripheral resting twitch torque was very consistent across days, with excellent reliability at TMS intensities greater than 110% AMT (ICC > .75). When comparing the ICC values between the quadriceps muscles, the reliability of the rectus femoris MEP_{EMG} appeared to be better than the other quadriceps muscles. Finally, the reliability of both MEP_{EMG} and motor evoked torque appeared to increase with increasing TMS intensities, suggesting that higher TMS intensities may yield more reliable MEPs.

Discussion

The purpose of this study was to evaluate the test-retest reliability of TMS-induced MEP_{EMG} and motor evoked torque of the quadriceps muscles and to determine how different normalization techniques affect the reliability of these variables. As hypothesized, we found that the motor evoked torque showed good to excellent reliability, except when normalized to the peak motor evoked torque obtained from the recruitment curve. Most noticeably, motor evoked torque normalized to the TMS-evoked resting twitch torque provided the highest ICC values, while MEP_{EMG} normalized to the peak MEP_{EMG} obtained from the recruitment curve provided the lowest ICC values. The reliability of the raw MEP_{EMG} was not as good as the motor evoked torque and approached fair to good repeatability only at high TMS intensities (≥130% AMT). The reliability of the MEP_{EMG} improved when normalized by MVIC but was still lower than the reliability of raw motor evoked torque, indicating that the torque responses were generally more reliable than EMG. The results also indicate that the reliability of the TMS-induced MEPs was generally reduced at low TMS intensities (near AMT) but improved with higher TMS intensities (≥ 120% AMT).

A key finding of this study was that the motor evoked torque, even without any normalization, showed good to excellent reliability. Further, the reliability scores improved when normalizing motor evoked torque to the peripheral resting twitch torque. These findings collectively suggest that TMS-induced motor evoked torque can be used as a reliable alternative to measuring cortical excitability in the quadriceps muscles. It is important to note that normalization of motor evoked torque to resting twitch torque is somewhat equivalent to normalization of MEP_{EMG} to M-wave, which is known to be reliable (Luc et al., 2014; O'Leary et al., 2015; Temesi et al., 2017). This is because both procedures account for any peripheral changes (e.g., electrode locations, skin impedance, differences in positioning, muscle strength, fatigue, etc.) by normalizing the MEPs to their maximal composite muscle activity elicited by a direct stimulus to the peripheral muscle. Thus, any subtle variations in the peripheral torque generating capacity of quadriceps muscle between days were accounted for by normalizing it to the peripheral twitch torque, thereby improving the reliability of the motor evoked torque responses.

The use of raw MEP_{EMG} to quantify corticospinal excitability is very common in TMS studies(Forrester et al., 2006; Kamen, 2004; Ngomo et al., 2012; Sankarasubramanian et al., 2015; Tan et al., 2016; Temesi et al., 2014; Washabaugh and Krishnan, 2016; Wheaton et al., 2009). While the reliability of raw motor evoked torque was good in this study, the reliability of raw MEP_{EMG} was generally not good. Normalizing the raw MEP_{EMG} to the peak MEP_{EMG} amplitude only reduced the reliability scores, even though this method has been regarded as a relatively better method than MVIC normalization (Darling et al., 2006; Hussain et al., 2016). In contrast, the use of MVIC values to normalize MEP_{EMG} improved the reliability scores and is recommended if using motor evoked torque or obtaining M-waves is not feasible. However, there are times when MVIC values may not be a good normalization approach, especially when the MVIC values are expected to change between testing sessions (e.g., during recovery after an injury or after a training intervention). In these situations, the changes in MEP_{EMG} may not reflect true changes in corticospinal excitability but may simply be a byproduct of high (or low) MVIC values that affect the denominator of the normalization equation.

There are several advantages to using torque-based MEP measurements for studying corticospinal excitability of the quadriceps muscle. A key advantage is that the entire muscle group can be studied noninvasively without the need for monitoring each head of the quadriceps muscle (for e.g. vastus intermedius, which requires fine wire or needle electromyography). Furthermore, torque measurements, unlike EMG, are not affected by various peripheral factors such as electrode placements, skin-electrode interface, impedance, subcutaneous fat, etc. More importantly, motor evoked torque eliminates the need for M-wave to normalize MEP_{EMG}, making this approach more comfortable than electrical stimulation and easier to obtain in all participants (due to less intrusive electrode placement). Additionally, the reliability of MEP_{EMG} was found to be greatest only at 140% AMT—a finding that is consistent with previous research (Luc et al., 2014; Temesi et al., 2017)—whereas the reliability of motor evoked torque was similar between 120% and 140% AMT. Hence, motor evoked torque can be evaluated at lower TMS intensities than MEP_{EMG}, which is again known to improve participant's comfort during testing. There are also some potential limitations when using TMS-induced motor evoked torque responses. Because motor evoked torque is a composite measure, unless combined with MEP_{EMG}, the exact contribution of each of the quadriceps muscles to the observed changes in corticospinal excitability cannot be quantified. Further, the motor evoked torque could be affected by the antagonistic responses due to the poor spatial resolution of TMS; thus, making this approach only suitable for active TMS (i.e., during background contraction of the targeted muscle group) and not for resting TMS evaluation.

There are some limitations to this study. We tested only a small group of young, healthy participants, as this is a commonly studied population in TMS research and because we wanted to minimize the confounding effects of aging and injury. As a result, it is unclear if the results are generalizable to a broad population (e.g., individuals with neurological or orthopedic injuries), although preliminary experiments in individuals with anterior cruciate ligament reconstruction support our conclusion (Krishnan et al., 2019). Additionally, we note that the results are only a reflection of repeatability for the quadriceps muscle group and may not translate equivalently when measuring corticospinal excitability of other muscle groups (Menon et al., 2018). While we do not foresee a reason for deviation from our current study findings in other muscles, further testing is warranted to determine the extent of applicability of these findings to other muscles. Finally, we did not evaluate the reliability of the MEP_{EMG} normalized to M-wave, as we wanted to minimize participant discomfort due to electrical stimulation of the femoral nerve (Place et al., 2010; Wellauer et al., 2015) and assumed that this approach would yield good reliability based on outcomes of prior studies (Cronin et al., 2015; Zellers et al., 2019). Hence, it is not clear from this study if the reliability of motor evoked torque normalized to the resting twitch torque of the quadriceps muscle is superior to reliability of MEP_{EMG} normalized to M-wave. However, given that the reliability scores were generally good even for raw motor evoked torque responses and were about 0.9 when normalized to the resting twitch torque, we believe that the reliability of motor evoked torque may be at least comparable to MEP_{EMG} normalized to M-wave.

CONCLUSION

This study was performed to test the reliability of TMS-induced motor evoked torque and EMG responses (MEP_{EMG}), as well as to identify the best normalization procedure to obtain consistent MEPs across testing sessions. We found that the motor evoked torque obtained during an active contraction of the quadriceps muscle provides reliable estimates of corticospinal excitability of the quadriceps muscle and may offer comparable abilities to MEP_{EMG} in an investigative setting. Specifically, the use of TMS-evoked resting twitch torque to normalize motor evoked torque appears to be extremely reliable and could serve as an acceptable substitution for conventional M-wave normalized MEP_{EMG}. The use of peak MEP obtained from the recruitment curve to normalize MEPs are not recommended due to poor reliability. The results also emphasize the importance of testing MEPs at higher TMS intensities as MEPs obtained at near motor threshold intensities were less reliable. Future studies evaluating the reliability of motor evoked torque across different muscle groups and patient populations could further extend our understanding of the applicability of TMS-induced torque responses to quantify corticospinal excitability after an injury or an intervention.

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HIGHLIGHTS

- TMS-induced raw torque showed good to excellent reliability at ≥110% AMT
- Reliability of TMS-induced torque normalized to resting twitch torque was excellent
- Motor evoked torque was more reliable than MEP_{EMG} for all normalization methods
- MEPs normalized to peak MEP amplitude showed the least reliability
- In general, the reliability of MEPs improved with higher TMS intensities

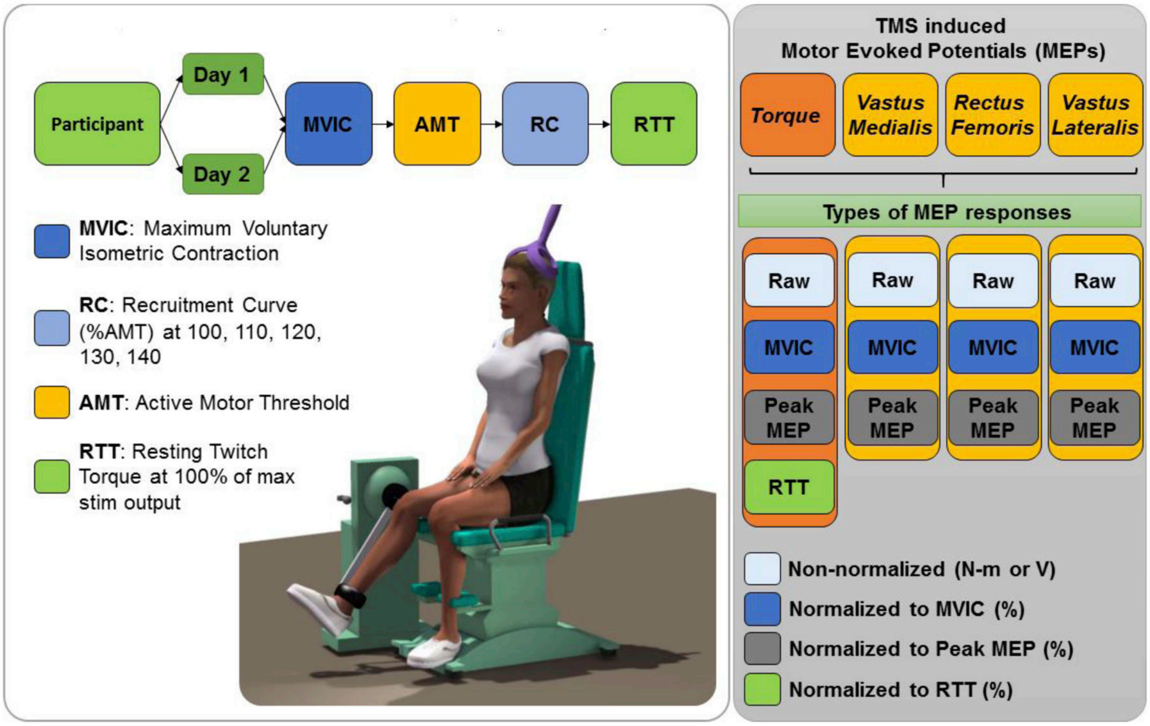

Figure 1.

Schematic of the (a) experimental setup, (b) experimental protocol, and (c) normalization methods used for assessment across both test days. *Abbreviations*: MVIC, maximal voluntary isometric contraction; AMT, Active motor threshold; RC, recruitment curve; RTT, TMS-evoked peripheral resting twitch torque.

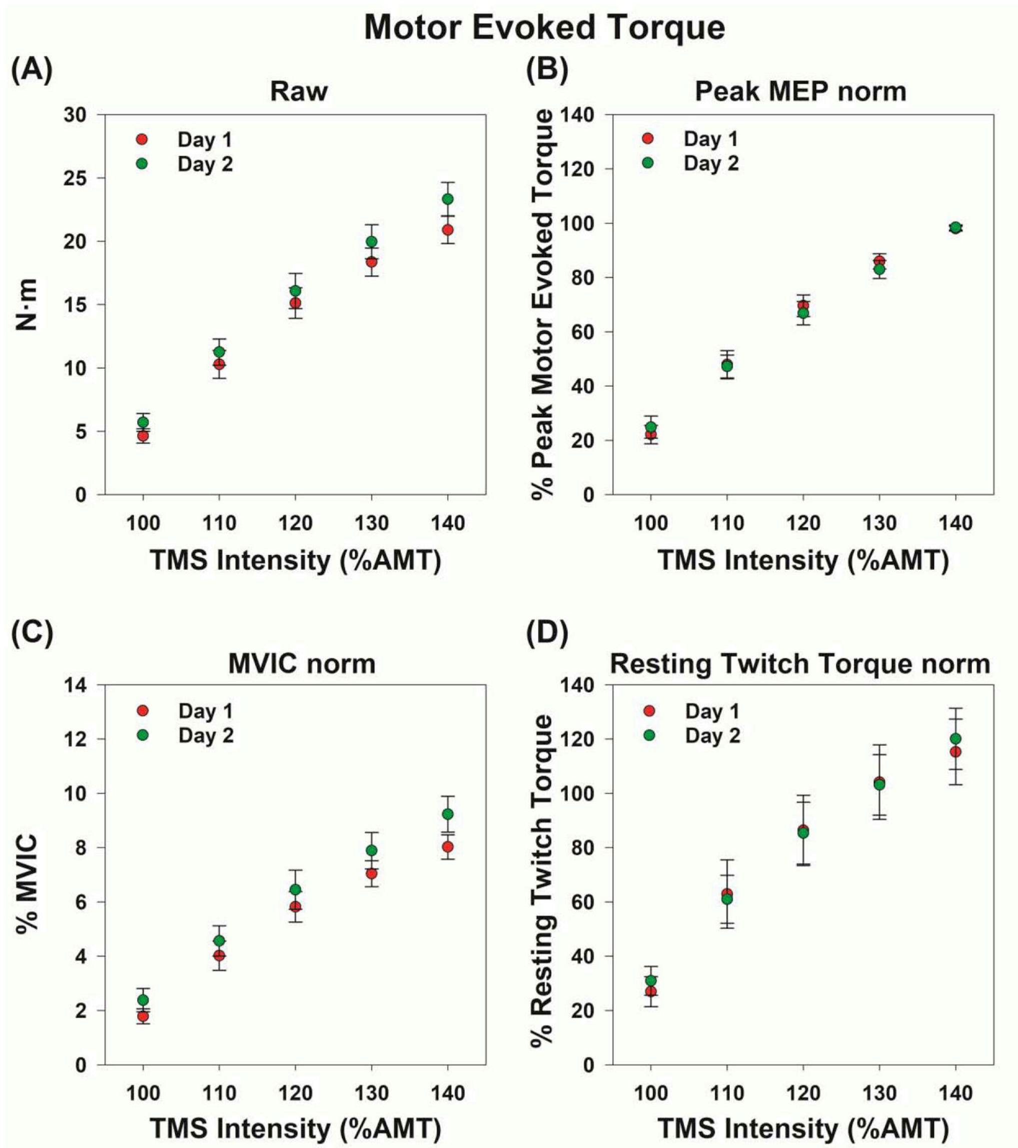

Figure 2.

Plots showing the mean motor evoked torque at each TMS intensity for the four different normalization techniques across the two testing sessions: (A) raw MEP with no normalization, (B) MEP normalized to the peak MEP amplitude elicited between 100% −140% of AMT, (C) MEP normalized to the peak torque values obtained during maximum voluntary isometric contraction (MVIC), and (D) MEP normalized to the TMS-evoked peripheral resting twitch torque (RTT) elicited at 100% of maximum stimulator output with the TMS coil placed directly over the quadriceps muscle. Error bars represent standard error of the mean.

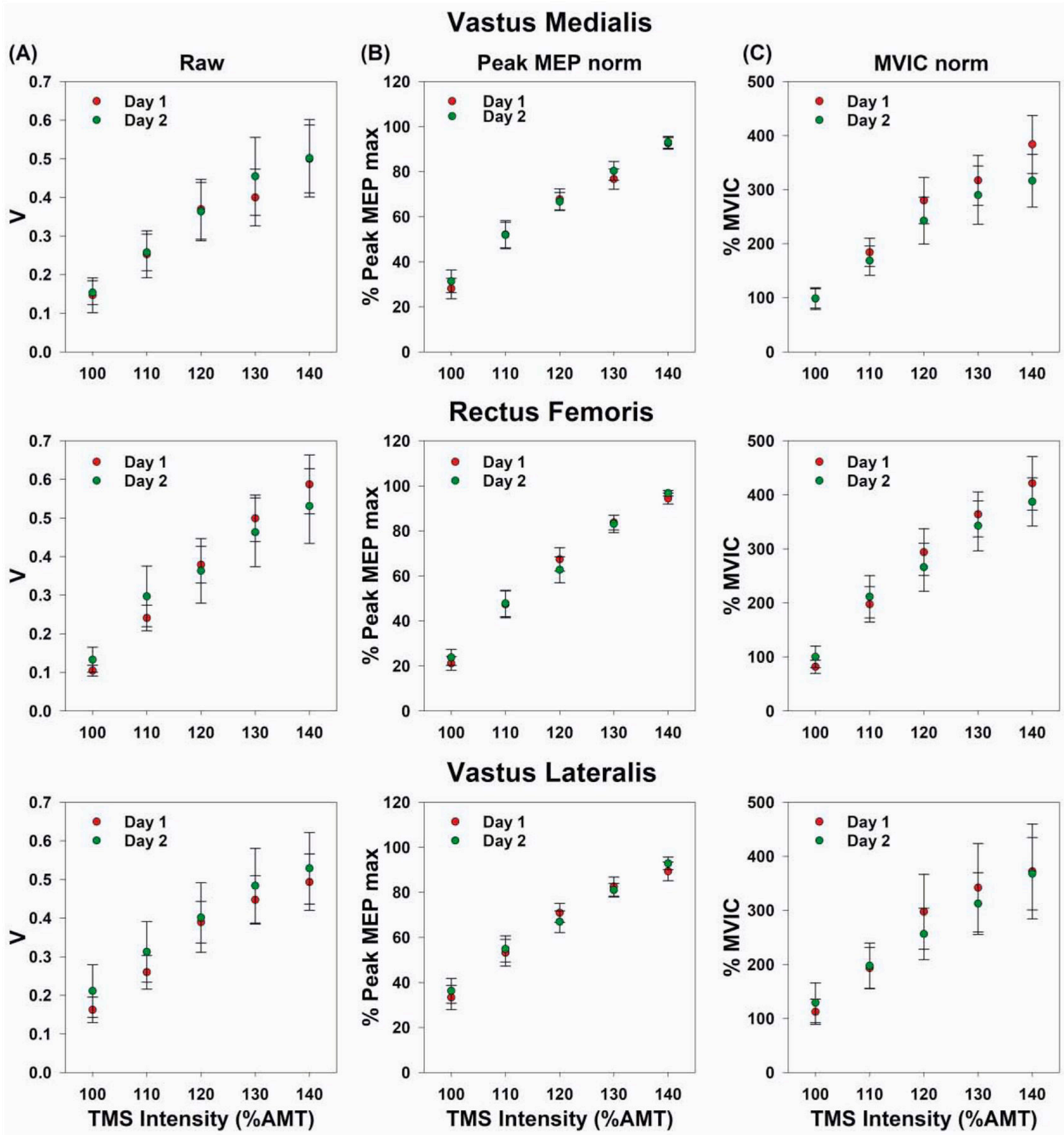

Figure 3.

Plots showing the mean motor evoked potential (MEP) of the *vastus medialis* (MEP_{VM}), *rectus femoris* (MEP_{RF}), and *vastus lateralis* (MEP_{VM}) muscles at each TMS intensity for the three different normalization techniques across the two testing sessions: (A) raw MEP with no normalization, (B) MEP normalized to the peak MEP amplitude elicited between 100%−140% of AMT, and (C) MEP normalized to the peak values obtained during maximum voluntary isometric contraction (MVIC). Error bars represent standard error of the mean.

Table 1.

Between-session reliability scores [ICC (3, 1)] for TMS-induced motor evoked torque and EMG (MEP_{EMG}) responses across different TMS intensities.

Normalization	Variable	100 (%AMT)	110 (%AMT)	120 (%AMT)	130 (%AMT)	140 (%AMT)
Raw	Torque	.43	.69	.82	.83	.79
	VM	.66	.32	.38	.42	.42
	RF	.11	.36	.32	.59	.82
	VL	.26	.29	.63	.42	.64
Peak MEP	Torque	.20	.26	.34	.28	−.05
	VM	.20	.46	.41	.16	.17
	RF	.16	.28	.31	.23	−.04
	VL	.25	.29	.22	−.15	−.16
MVIC	Torque	.37	.70	.79	.75	.65
	VM	.64	.29	.44	.60	.63
	RF	.37	.62	.57	.65	.83
	VL	.07	.09	.41	.46	.76
RTT	Torque	.57	.80	.90	.90	.90

Abbreviations: VM (*vastus medialis*), RF (*rectus femoris*), VL (*vastus lateralis*), MEP (motor evoked potential), MVIC (maximum voluntary isometric contraction), RTT (TMS-evoked peripheral resting twitch torque). Shaded numbers indicate ICC scores that are ≥ 0.60 (i.e., indicating good reliability).