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Characterizing the corticomotor connectivity of the bilateral ankle muscles during rest and isometric contraction in healthy adults

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ABSTRACT

The investigation of the corticomotor connectivity (CMC) to leg muscles is an emerging research area, and establishing reliability of measures is critical. This study examined the measurement reliability and the differences between bilateral soleus (SOL) and tibialis anterior (TA) CMC in 21 neurologically intact adults. Using single pulse transcranial magnetic stimulation (TMS), each muscle's CMC was assessed twice (7 ± 2 days apart) during rest and active conditions. CMC was quantified using a standardized battery of eight measures (4/condition): motor threshold during resting (RMT), motor evoked potential amplitude and latency (raw and normalized to height) in both conditions, contralateral silent period (CSP) during active. Using two reliability metrics (intraclass correlation coefficient and coefficient of variation of method error; good reliability: ≥0.75 and ≤15, respectively) and repeated-measures ANOVA, we investigated the reliability and Muscle X Body Side interaction. For both muscles, RMT, resting raw and normalized latencies, and active raw latency demonstrated good reliability, while CSP had good reliability only for TA. Amplitude did not demonstrate good reliability for both muscles. SOL CMC was significantly different from TA CMC for all measures but CSP; body side had no significant effect. Therefore, only certain measures may reliably quantify SOL and TA CMC while different CMC (except CSP) between SOL and TA suggests dissimilar corticospinal drive to each muscle regardless of the side.

1. Introduction

The functional state of the neural connection between the motor cortex and a target muscle, corticomotor connectivity (CMC), can be assessed using transcranial magnetic stimulation (TMS) (Hallett, 2007). While most of the literature to date has focused mainly on CMC of the upper extremity muscles, a growing number of studies have gradually begun investigating the CMC of lower extremity muscles, including the soleus (SOL) and tibialis anterior (TA). Given the functional importance of SOL and TA in functional walking, several studies have investigated those muscles' CMC either before, during, or after various tasks (Capaday et al., 1999, Mouthon et al., 2015, Obata et al., 2009) in various cohorts (Kumpulainen et al., 2015, Palmer et al., 2017, Thomas and Gorassini, 2005). However, despite the increased interest in examining SOL and TA CMC in different tasks and patient populations, gaps still exist regarding the CMC of these two ankle joint muscles in neurologically intact adults.

A thorough reliability analysis is required for both SOL and TA CMC during both rest (i.e., target muscle is not contracted) or active contraction (i.e., target muscle is actively contracted at a percentage of maximum isometric voluntary contraction, MVIC). The reliability (intra-rater, inter-rater, and test-retest) of these measures in neurologically intact adults has been inconsistently examined in the past decade, partly due to the variation in methodology and laboratory set-up. These studies have demonstrated that some SOL (Gray et al., 2017, Lewis et al., 2014) and TA (Cacchio et al., 2009, Chung and Mak, 2015, Forster et al., 2014, Forster et al., 2012, Souron et al., 2016, Tallent et al., 2012, van Hedel et al., 2007) CMC measures can be reliably assessed in healthy adults, including resting and active motor thresholds, amplitude and latency of the motor evoked potential (MEP), and

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cortical silent period (CSP). Despite the valuable information that these studies have provided to the field, several methodological considerations make compilation of the reliability data difficult. A need exists for a comprehensive reliability examination using a standardized methodology.

Inconsistencies in lower extremity reliability TMS studies include the following: (1) each of the reliability studies only investigated one muscle, either SOL or TA; therefore, the reliability assessment of one muscle was independently conducted from the other; and (2) the TMS-related methodological parameters, such as type of coil (e.g., circular coil, figure-of-eight coil, and double cone coil), stimulator type (e.g., monophasic, biphasic), use of neuronavigation software, muscle state (e.g., either rest or active), level of muscle state during active contraction (e.g., 10, 10–20, 30–80% MVIC), and CMC measures of interest varied widely across studies. This substantial variability of testing parameters is of critical concern in the interpretation of reliability data (Beaulieu et al., 2017a), given their possible effects on the quantified CMC and the reproducibility of methods and results (Baker, 2016).

As the methodology for lower extremity TMS testing has evolved, it has become clear that upper extremity reliability findings cannot be simply extrapolated to the lower extremity. Compared to CMC hand muscle assessment, measuring the CMC of a distal leg muscle involves increased complexity due to the anatomical properties of the leg motor areas. These areas are located adjacent to the interhemispheric fissure at approximately 3–4 cm below the scalp surface, (Alkadhi et al., 2002, Conti et al., 2014, Terao and Ugawa, 2002) while the axons of the corticospinal neurons are oriented perpendicular to the medial cortical surface. In addition, these areas are relatively small and are less segregated than the hand muscle areas (Conti et al., 2014, Saisanen et al., 2010). Therefore, precise activation of leg motor areas requires cautious selection of stimulation parameters (e.g., type of coil, finding the optimal hotspot of each muscle separately, use of neuronavigation) that may influence the measured CMC of a muscle (Ridding and Ziemann, 2010).

Given that each muscle has a different function and action for ankle mechanics, it is unclear whether CMC differs between these two muscles, as well as between the two legs (i.e., body side). The SOL and TA likely have a similar number of corticomotoneuronal connections, but the strength of these connections is weaker in SOL than in TA (Bawa et al., 2002). Weak responses of SOL to TMS might potentially be related to the contribution from other descending pathways (e.g., corticorubrospinal, corticoreticulospinal, etc.) to SOL activation (Nielsen and Petersen, 1995). Also, the different functional role that each muscle plays may explain this discrepancy in the strength of the measured CMC. Both muscles influence ankle motion during upright postural tasks and walking (Winter, 1991, Winter, 1995), but they differ in their primary function and action. SOL is an antigravity muscle designed to generate high force with small excursion of the muscle (Lieber and Friden, 2000), especially when the foot is in contact with the ground and sensory feedback is present (e.g., stance phase of walking and upright standing posture). In contrast, TA is less important for high force production and more functional for long muscle excursions (Lieber and Friden, 2000), especially when sensory feedback is minimum (e.g., swing phase of walking). Therefore, activation of SOL may not rely on the corticospinal tract to the same degree as TA given that other subdivisions of the nervous system may contribute to its activation (e.g. spinal modulation of sensory feedback). Moreover, given that leg dominance is not as robust as arm dominance and leg muscles are bilaterally active during upright static and dynamic motor tasks, it is crucial to assess whether the CMC of each muscle differs between legs. If the SOL or TA CMC differs between legs, this would indicate either stronger unilateral connectivity (i.e., indirect neurophysiological proxy of footedness) or a neurological insult along the neuromotor axis of the target muscle.

Therefore, the primary aim of this exploratory investigation was two-fold. First, we aimed to determine the intra-rater test-retest reliability, which was assessed using two measures (intraclass correlation coefficient – ICC, coefficient of variation of method error – CV_{ME}), for a comprehensive set of commonly reported SOL and TA CMC measures. Second, we aimed to determine if CMC differs between muscles (SOL and TA) and body side (left and right lower extremities). We completed this study in a group of neurologically intact adults using a battery of CMC measures calculated by automated methods, MRI-guided TMS leg-specific methodology, and two independent reliability metrics to maximize the experimental and data analysis rigor. By addressing these aims, we designed this experiment to provide the field with the first comprehensive battery of CMC assessment measures for SOL and TA, allowing for bilateral quantification of CMC properties and between-muscle or between-limb comparisons.

2. Materials and methods

2.1. Participants

Twenty-one right-leg dominant neurologically intact adults (gender: 8 women; mean ± SD, age: 42 ± 11 years, height: 174.2 ± 11.7 cm, body mass: 74.9 ± 16.7 kg) participated in this study. We excluded individuals who had any history of brain injury or pre-existing neurological disorder, and/or contraindications to TMS (Rossi et al., 2009). All participants completed MRI (Shellock and Spinazzi, 2008) and TMS (Rossi et al., 2011) screening questionnaires to ensure safety and eligibility for MRI and TMS testing. Written informed consent was obtained from all participants prior to the experimental procedures, which were approved by the Medical University of South Carolina Institutional Review Board and adhered to the Declaration of Helsinki.

2.2. Experimental organization

Fig. 1 presents the experimental flow. Participants attended two experimental sessions (7 ± 2 days apart). Both sessions occurred at similar time of the day to eliminate any influence of diurnal variation on neural excitability (Castaingts et al., 2004). Given the potential effect of caffeine (Cerqueira et al., 2006) and alcohol (Conte et al., 2008) on CMC, we instructed participants to avoid consuming either substance for at least 3 hours prior to experimental procedures.

2.3. Structural MRI and neuronavigation system

To ensure accurate and precise positioning of the coil throughout the CMC testing and across visits, we used Brainsight™ (v2.2) neuronavigation system (Rogue Research Inc.; Montreal, Quebec, Canada) with the structural brain MRI of each participant. Before the first experimental session, participants attended a single structural MRI (magnetization-prepared rapid gradient-echo sequence) session (~ 30 min) (Fig. 1A), and then shortly after, a Brainsight™ file for each participant was created (Fig. 1B).

2.4. EMG recording

Following standard skin preparation and surface EMG (sEMG) electrode placement procedures (Hermens et al. (1999)), sEMG electrodes (Motion Lab Systems; Baton Rouge, LN, USA) were attached over SOL (i.e., 2/3 of the line between the lateral femoral condyle to the lateral malleolus) and TA (i.e., 1/3 of the line between the tip of the fibula and the tip of the medial malleolus) bilaterally while a ground reference electrode (Natus Medical Incorporated; San Carlos, CA, USA) was placed on the patella. The signals were filtered (anti-alias filter of 1000 Hz), amplified (×2000) (Motion Lab Systems MA-300 system; Baton Rouge, LN, USA), sampled at 5 kHz (Cambridge Electronic Design Micro 1401-3; Cambridge, UK), and stored for offline analysis (Signal v5.11 and Spike2 v7.12, Cambridge Electronic Design; Cambridge, UK).