Agreement Between Investigators Using Paired-Pulse Transcranial Magnetic Stimulation to Assess Quadriceps Intracortical Excitability

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Context: Transcranial magnetic stimulation (TMS) may provide important information regarding the corticospinal mechanisms that may contribute to neuromuscular activation impairments. Paired-pulse TMS testing is a reliable method for measuring intracortical facilitation and inhibition; however, little evidence exists regarding agreement of these measures in the quadriceps. Objective: To determine the between-sessions and interrater agreement of intracortical excitability (short- and long-interval intracortical inhibition [SICI, LICI] and intracortical facilitation [ICF]) in the dominant-limb quadriceps. Design: Reliability study. Setting: Research laboratory. Participants: 13 healthy volunteers (n = 6 women; age 24.7 ± 2.1 y, height 1.7 ± 0.1 m, mass 77.1 ± 17.4 kg). Intervention: Participants completed 2 TMS sessions separated by 1 wk. Main Outcome Measures: Two investigators measured quadriceps SICI, LICI, and ICF at rest and actively (5% of maximal voluntary isometric contraction). All participants were seated in a dynamometer with the knee flexed to 90°. Intracortical-excitability paradigm and investigator order were randomized. Bland-Altman analyses were used to establish agreement. Results: Agreement was stronger between sessions within a single investigator than between investigators and for active than resting measures. Agreement was strongest for resting SICI and active ICF and LICI between sessions for each investigator. Conclusions: Quadriceps intracortical excitability may be measured longitudinally by a single investigator, although active muscle contraction should be elicited during testing.

Keywords: TMS, knee, knee extensors, quadriceps

Transcranial magnetic stimulation (TMS) may be useful in elucidating potential contributors to neuromuscular activation deficits by determining corticospinal excitability to the musculature.1 Paired-pulse TMS (ppTMS) represents specific TMS testing paradigms and is beneficial in understanding neuromuscular mechanisms related to intracortical-pathway involvement. Short- and long-interval intracortical inhibition (SICI and LICI, respectively) and intracortical facilitation (ICF) are commonly used ppTMS paradigms.1 SICI and LICI may be influenced by the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), while ICF may target excitatory N-methyl-D-aspartate (NMDA) or glutamate-mediated pathways.2 While TMS indicates general corticospinal excitability, knowledge of the specific intracortical pathways involved in muscle dysfunction provided through ppTMS may allow for the development of targeted interventions to improve neuromuscular activation.

TMS has been used extensively in the upper extremity, primarily under resting conditions, while the number of lower-extremity-focused and active TMS studies is growing. Therefore, establishing TMS reliability in the lower-extremity musculature and determining which testing condition (resting or active) is more reproducible is imperative. Previous investigators have established acceptable reliability for measuring the amplitude of quadriceps motor-evoked potential (MEP).3 Similarly, Luc et al4 reported strong intersession reliability of active motor-threshold determination for the quadriceps and fibularis longus. However, no evidence of lower-extremity ppTMS agreement is available. ppTMS testing can advance our understanding of intracortical excitability and inform rehabilitation strategies to improve neuromuscular activation. This is important in the quadriceps, which are vital to daily activity and are impaired after knee-joint injury. To advance our understanding of quadriceps dysfunction, establishing agreement of ppTMS measures is a necessary step. Therefore, this investigation sought to determine the intrarater and interrater agreement of SICI, LICI, and ICF ppTMS paradigms for quadriceps intracortical-excitability testing.
Methods

Thirteen healthy volunteers (n = 6 women; age 24.7 ± 2.1 y, height 1.7 ± 0.1 m, mass 77.1 ± 17.4 kg) participated. Participants were screened for safety, had a body-mass index (BMI) ≤35 kg/m², reported no concussion or lower-extremity orthopedic injury in the previous 6 months, and had no history of lower-extremity surgery. All participants consented. The university institutional review board approved this study.

Participants completed 2 sessions separated by 1 week. Testing order (paradigm [SICI, ICF, LICI] and investigator [1 vs 2]) were randomized before the first session and maintained between sessions for each participant. Resting assessments were performed before active trials. The quadriceps on the dominant limb, that with which the participant would kick a ball, was tested.

Participants were seated with the hip and knee flexed to 85° and 90°, respectively, on an isokinetic dynamometer (Biodex System III Pro, Biodex Medical Systems, Shirley, NY). For resting trials, participants sat quietly with their arms folded across their chests. During active testing conditions, participants crossed their arms over their chests and isometrically contracted the limb to 5% of their maximal voluntary isometric contraction (MVIC), maintaining this contraction while the stimulus was delivered. To determine MVIC, participants performed a series of submaximal warm-up contractions followed by 3 contractions at 100% effort with 1 minute of rest between repetitions. The average of the 3 trials quantified MVIC. Participants were provided visual feedback of their real-time torque output displayed on a computer screen in front of them.

MEPs were obtained using a Magstim BiStim² (Jali Medical, Inc, Waltham, MA) and associated double-cone coil. Electromyography data were obtained by placing two 10-mm pregelled, Ag/AgCl electrodes (EL503, BIOPAC Systems, Inc, Goleta, CA) over the muscle belly of the distal vastus medialis. Investigator 2 placed all electromyography electrodes. Data were collected using an MP150 data-acquisition system and associated EMG100C devices and BIOPAC AcqKnowledge 4.0 software.

A grid drawn on a Lycra swim cap was centered on each participant’s head using a cloth tape measure as previously described. The optimal stimulating point was determined as the area that produced the largest, most consistent MEPs after providing a minimum of 2 stimuli to a variety of positions on the grid. All subsequent testing was performed over the optimal stimulating point. Motor threshold was assessed using a single pulse stimulus and determined as the minimum stimulator intensity that yielded 4/8 MEPs with peak-to-peak amplitudes greater than 50 μV (resting) or 100 μV (active). Only investigator 1 determined what the optimal stimulating point and motor threshold were.

All ppTMS paradigms (SICI, ICF, and LICI) were completed by both investigators. Eight repetitions of each measure were performed and normalized to MEP amplitudes obtained at 120% of resting or active motor threshold by investigator 1. Data were averaged within each participant and paradigm. A third, blinded investigator analyzed all data.

Bland-Altman plots determined agreement between and within investigators for ppTMS data. Bland-Altman plots graphed the data as the average of 2 measures obtained (x-axis) against the difference between the 2 measures (y-axis). Statistical analyses were performed using SPSS (IBM, Armonk, NY) and Matlab (Mathworks, Inc, Natick, MA).

Results

Resting data were not available for 3 participants due to an inability to locate the quadriceps optimal stimulating point.

Short-Interval Intracortical Inhibition

Resting SICI demonstrated strong intersession agreement for both investigators (Figure 1). Interrater agreement for resting SICI was variable, with session 1 yielding poor agreement and session 2 yielding strong interrater agreement (Figure 1).

Active SICI demonstrated moderate agreement between sessions for both investigators, with narrow upper and lower bounds and data clustering (Figure 1). Comparing active SICI data between investigators yielded poor agreement for both sessions (Figure 1).

Intracortical Facilitation

Resting ICF demonstrated poor intersession agreement for both investigators, with wide limits of agreement and poorly clustered data (Figure 2). Poor interrater agreement was demonstrated during session 1 (Figure 2). However, session 2 yielded moderate agreement for resting ICF (Figure 2).

Active ICF demonstrated strong intersession agreement for both investigators with narrow limits of agreement and tight clustering of data (Figure 2). For both sessions, there was moderate interrater agreement (Figure 2).

Long-Interval Intracortical Inhibition

Resting LICI demonstrated poor intersession agreement for both investigators (Figure 3). Between investigators for session 1, there was poor agreement (Figure 3). Session 2 yielded poor agreement between investigators with poor data clustering and several data points outside the limits of agreement (Figure 3).

Active LICI demonstrated moderate to strong intersession agreement for both investigators, with clustering of the data and few data points outside the limits of agreement (Figure 3). Interrater agreement for session 1 was poor (Figure 3). For session 2, data demonstrated strong agreement between investigators (Figure 3).
Discussion

Quadriceps ppTMS demonstrates variable agreement between and within sessions. Generally, agreement is stronger within than between investigators, suggesting that a single investigator may collect data longitudinally, especially when active muscle contractions are used.

ppTMS reliability has been examined previously for the first dorsal interosseous muscle. Boroojerdi et al. assessed active SICI and ICF, reporting better interrater reliability for ICF than SICI. Our active ppTMS findings agree with these previous results. However, our interrater agreement for resting ppTMS measures was no better for ICF than SICI. Ngomo et al. observed that SICI of the first dorsal interosseous muscle was reliable under resting but not active conditions. We observed that both resting and active SICI measures were agreeable between sessions, although our agreement was greater for resting SICI. Reliability of TMS outcomes may differ between muscles, making comparisons with studies on upper-extremity musculature difficult.

Intersession agreement was moderate to strong except for resting ICF and LICI. Previous researchers have reported substantial variability in active ppTMS measures between sessions. The poor reliability may be due to high interindividual variability. The number of MEPs obtained per paradigm may also influence variability. We collected 8 recordings of each measure. Bastani and Jaberzadeh reported that data obtained from 10 or 15 recordings were more reliable than those obtained from 5 recordings between sessions. Thus, while 8 stimuli may be sufficient for most ppTMS measures, we may have observed better intersession agreement with more recordings.

Poor agreement may be attributable to differences in coil placement between sessions. The optimal stimulating point during session 1 was noted; however, to account for differences in swim-cap placement and to decrease the chances of stimulating different brain regions between sessions, the location of the optimal stimulating point was reestablished during session 2. The optimal stimulating point shifted no more than 1 cm in any direction between sessions. Motor threshold and measurement amplitudes were not different between sessions; thus, we believe that coil placement did not negatively influence our outcomes. In addition, agreement could have been affected by changes in the participant’s mental state, as well as medication or caffeine. To minimize these effects, participants were tested at the same time of day and asked to refrain from medication and caffeine use.

Figure 1 — Resting and active short-interval intracortical inhibition (SICI) data for both investigators and sessions. Dashed lines represent upper and lower limits of agreement. Solid line represents mean difference.
Figure 2 — Resting and active intracortical facilitation (ICF) data for both investigators and sessions. Dashed lines represent upper and lower limits of agreement. Solid line represents mean difference.
Figure 3 — Resting and active long-interval intracortical inhibition (LICI) data for both investigators and sessions. Dashed lines represent upper and lower limits of agreement. Solid line represents mean difference.
before testing. Participants were further instructed to keep all activities (e.g., exercise) consistent between sessions.

**Conclusions**

ppTMS is valuable in elucidating the causes of persistent muscle dysfunction. Our data demonstrate that the strongest agreement between sessions is achieved when a single investigator obtains active quadriceps ppTMS measures.

**References**