Published in final edited form as:

J Neurol Sci. 2009 January 15; 276(1-2): 115–117. doi:10.1016/j.jns.2008.09.012.

Reliability of TMS Motor Evoked Potentials in Quadriceps of Subjects with Chronic Hemiparesis after Stroke

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Abstract

Transcranial magnetic stimulation (TMS) non-invasively measures excitability of central motor pathways in humans and is used to characterize neuroplasticity after stroke. Using TMS to index lower extremity neuroplasticity after gait rehabilitation requires test-retest reliability. This study assesses the reliability of TMS-derived variables measured at bilateral quadriceps of chronic hemiparetic stroke survivors. Results support using measures of both paretic and nonparetic motor threshold, MEP latencies; and nonparetic MEP amplitudes. Implications for longitudinal research are discussed.

Keywords

TMS; Lower extremity; stroke; reliability; quadriceps; paretic

Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive technique used to assess corticospinal excitability and plasticity of the central nervous system (CNS) [1]. TMS has been used to measure CNS adaptation and its relationship to changes in neural control and function, primarily focusing on hand muscles in healthy subjects and patients with stroke [2]. For example, reliability of TMS measures has been reported for finger extensor motor evoked potentials (MEPs) in stroke patients [3]. To date no studies have assessed the reliability of TMS to the lower extremities (LE) of stroke patients, where the motor homunculus is deeper and less accessible. This is a critical need if TMS is to be useful in determining neurophysiological mechanisms underlying training-induced rehabilitation of hemiparetic gait, such as seen in

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aerobic treadmill training in chronic stroke [4]. There is limited understanding of how training-induced neuroplasticity in the CNS contributes to improvement in control of lower extremities and gait function. The current study addresses the reliability of TMS MEPs at the paretic (P) and nonparetic (NP) quadriceps muscles of chronic stroke patients, to help define its potential for indexing neuroplasticity after locomotor re-training or other interventions. We hypothesized that MEP motor thresholds, amplitudes and latencies in the paretic (P) and nonparetic (NP) leg muscles will be reproducible in two consecutive TMS tests administered at least one week apart.

Materials and Methods

As part of an ongoing study of short-term CNS excitability responses, 23 patients (age: 68.4 ± 8.1 years, mean and SD, 12 male, 11 female; 15 left hemiparesis and 8 right hemiparesis; 6 cortical, 9 subcortical, 8 brainstem) who suffered a first stroke 57.6 months (median) before inclusion were screened for eligibility in an aerobic treadmill training program, as previously described [4]. Inclusion criteria were age 40–80 years, residual lower extremity hemiparesis, ability to walk 3 minutes ≥ 0.13 m/s on a treadmill with handrail-support, and no history of seizures, metal implants, or pacemaker.

Subjects sat in a cushioned reclining chair with legs supported and knees flexed at 45° . The legs were strapped into padded cuffs connected to force transducers, to provide online feedback of activation effort. Surface electromyography (EMG) electrodes (Ag-AgCl) were placed bilaterally on *vastus lateralis* (VL) and *vastus medialis* (VM), in close-spaced arrangement (2 cm). Electrode locations were referenced to anatomical landmarks to enable duplication of placements for subsequent testing. Amplified (1000x) EMG was sampled at 4 kHz and filtered (10–1000 Hz). The head was stabilized in a cushioned support to standardize position and minimize extraneous movements.

TMS was delivered by a Magstim 200, with a double-cone coil (maximum power 1.4 T) to the motor cortices for bilateral VL and VM muscles. All stimulations were facilitated by pre-activation of the target quadriceps and standardized according to the knee extensor force required to offset the weight of the leg against gravity. Onscreen feedback of the force output was provided to maintain a standardized activation level (~10–15% MVIC). To locate contralateral stimulation sites for the quadriceps of each leg, the coil was moved in 1 cm orthogonal increments relative to the vertex until maximal MEP responses were detected on each side. The location on each hemisphere was marked, referenced by vertex-centered coordinates, and recorded. Motor threshold (MT) expressed as %-stimulator power was determined for each hemisphere by observing MEPs with $> 50 \mu\text{V}$ peak-to-peak amplitude in ≥ 5 of 10 responses [1]. Suprathreshold TMS was applied at 120% MT while subjects maintained the required activation. A total of 10 stimulations were collected at approximately 8 sec. intervals and averaged for analysis.

Subjects returned 7–10 days later, and the paretic and nonparetic quadriceps were retested using the same protocols. Tests were conducted at the same time each day to limit the potential for differences in fatigue and arousal states to affect TMS parameters. Outcome variables included, MT (%-stimulator power), latency (ms) as time from stimulation to MEP onset defined by $\geq 3\text{SD}$ above background EMG level, and peak-to-peak MEP amplitudes (mV) for each muscle. Intra-class correlations were performed on all variables for which values were obtained on both days to assess test-retest reliability, and paired t-tests were conducted to compare means between days ($\alpha = 0.05$).

Results

The reliability in TMS outcomes differed across measures and legs (Table 1). MT measures demonstrated highest reproducibility with ICC r-values of 0.97 on NP and P quadriceps. The ICCs for the NP and P latencies ranged between 0.65 – 0.79, approaching the criterion for strong reliability ($r \geq 0.80$). MEP amplitudes from both NP muscles were reliable ($r > 0.83$), but the P-side values were not (P-VM, $r = 0.54$; P-VL, $r = 0.21$). Paired t-tests comparing means of all variables between sessions showed no differences, while comparisons between sides showed greater threshold levels, longer latencies, and reduced amplitudes on P vs. NP sides on both days, ($p \leq 0.01$)

Discussion

This study assessed the reliability of TMS-induced MEP measures in quadriceps muscles of chronic hemiparetic stroke survivors. A consistent finding was higher MTs, longer latencies and lower amplitudes in P vs. NP sides. We observed good reliability in MTs bilaterally and in nonparetic MEP amplitudes. Moderate reliability was found in MEP latencies bilaterally, but there was poor reliability in P-side amplitudes. These results suggest that caution must be exercised when interpreting TMS amplitudes on the P-side leg, while MT and latencies are more reliable.

Our findings confirm a recent cross-sectional report of higher MT, delayed latency and reduced amplitude in TMS MEPs of P-leg [5], similar to TMS responses reported in the hemiparetic upper extremity [6]. However, the reason for reliable latency but unreliable P-leg MEP amplitudes is unclear. Functional MRI studies of paretic knee movement reveal greater heterogeneity in brain activation patterns, compared to NP-side and healthy controls [7]. This could increase variance of the ipsilesional TMS response leading to reduced reliability of P-side amplitudes, while subcortical and descending white matter tracts governing latency response are more invariant and yield consistent central motor conduction times.

Reliability may be improved by referencing P-side MEP amplitudes to peripheral M-waves at each test time. However, maximal peripheral stimulation of the femoral nerve poses excessive patient burden and has not been reliable. An alternative approach that may improve reliability of MEP amplitudes at the leg is to quantify excitability changes on a given day before and after a standardized short-term training bout. We found that after short-term bouts of treadmill walking (≤ 20 -min.), hemiparetic stroke patients with 6-months treadmill training increased P-side MEP amplitudes to the VM, whereas untrained patients did not [5]. Detection of rapid alterations in MEP amplitude after short-term exercise suggests such a protocol may be useful for gauging long-term CNS excitability changes in the hemiparetic leg. This approach needs further study to establish validity and reliability.

It should be noted that after baseline TMS on the first visit the subjects participated in 10–20 minutes of either treadmill walking or stretching, followed by a second round of TMS. Because the baseline retest occurred at least 7 days after this exposure, we assume that any short-term alterations in CNS excitability were not maintained. This is supported by other reports that interventions require weeks or months to induce persistent neurophysiological adaptations [7].

Future studies are needed to better define appropriate methods for using this noninvasive tool in neurorehabilitation, particularly with respect to surmounting the low reliability of paretic MEP amplitudes. Current studies are investigating whether long-term training will alter short-term exercise excitability responses observed at baseline.

Acknowledgements

Grant support: National Institutes of Health, NIA (P60AG 12583) University of Maryland Claude D. Pepper Older Americans Independence Center; the Department of Veterans Affairs and Veterans Affairs Medical Center Baltimore Geriatrics Research, Education and Clinical Center (GRECC), and Rehabilitation Research & Development Exercise and Robotics Center of Excellence (B3390K); NINDS 1RO1 NS 24282-08; the France-Merrick Foundation, the Johns Hopkins GCRC (NCRR #MO1-00052) and the Eleanor Naylor Dana Charitable Trust

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Table 1

Test-retest results from TMS to paretic and nonparetic quadriceps.

	Test 1 Mean (SE)	Test 2 Mean (SE)	ICC r-value	Paired t-test p-value
Thresholds (% power)				
P (n = 22)	53.7 (2.6)	54.8 (2.7)	0.978	0.164
NP (n = 23)	45.7 (2.4)	45.3 (2.3)	0.975	0.642
MEP Latencies (ms)				
P-VM (n = 20)	32.40 (0.92)	31.87 (0.94)	0.789	0.505
P-VL (n = 19)	32.16 (1.28)	32.63 (1.12)	0.689	0.696
NP-VM (n = 22)	27.48 (0.44)	27.95 (0.76)	0.645	0.468
NP-VL (n = 23)	26.87 (0.70)	27.40 (0.85)	0.791	0.427
MEP Amplitudes (mV)				
P-VM (n = 20)	0.483 (0.063)	0.563 (0.098)	0.537	0.401
P-VL (n = 19)	0.295 (0.047)	0.344 (0.052)	0.205	0.509
NP-VM (n = 22)	1.004 (0.189)	0.803 (0.129)	0.831	0.108
NP-VL (n = 23)	0.599 (0.075)	0.659 (0.079)	0.874	0.255