Brief Report

Absence of a Transcranial Magnetic Stimulation–Induced Lower Limb Corticomotor Response Does Not Affect Walking Speed in Chronic Stroke Survivors

Anjali Sivaramakrishnan, PT, MS; Sangeetha Madhavan, PT, PhD

Background and Purpose—Transcranial magnetic stimulation is used to measure the functional integrity of the corticomotor system via motor evoked potentials (MEPs) in stroke. The association between corticomotor mechanisms and walking recovery is still not completely understood. This study determined the association between transcranial magnetic stimulation–induced MEPs and walking outcomes and examined the contribution of the contralesional hemisphere to walking recovery.

Methods—Contralateral and ipsilateral transcranial magnetic stimulation responses from the contralesional and ipsilesional hemispheres were collected from 61 chronic stroke survivors. Clinical assessments included gait speeds, 6-minute walk distance, Timed Up and Go test, Fugl Meyer lower extremity scale, and strength measurements.

Results—Stroke participants were classified based on the presence (MEP+ [n=28]) or absence (MEP− [n=33]) of MEPs in the paretic tibialis anterior and rectus femoris muscles. A between-group analyses showed no significant differences for any gait variable. MEP+ group showed significantly higher Fugl Meyer lower extremity and ankle dorsiflexor strength. Ipsilateral conductivity was not significantly different between groups. Finally, in the MEP+ group, MEP parameters did not predict gait recovery.

Conclusions—Our study investigated the association between walking outcomes and neurophysiological parameters of lower limb function in a large cohort of stroke survivors. We did not find an associations between transcranial magnetic stimulation–induced tibialis anterior and rectus femoris MEPs and walking speeds. Further work is required to develop more comprehensive models in stroke for predicting walking recovery. **(*Stroke*. 2018;49:00-00. DOI: 10.1161/STROKEAHA.118.021718.)**

Key Words: cerebrovascular disorders ■ evoked potentials, motor ■ stroke ■ transcranial magnetic stimulation ■ walking speed

Regaining the ability to walk independently is an important functional goal for stroke survivors. Gait speed is an important determinant of walking recovery, and descending corticomotor control is a significant contributor to gait recovery poststroke[1] Several studies have shown that the presence or absence of a transcranial magnetic stimulation (TMS)–induced motor evoked potential (MEP) is related to upper limb functional recovery in acute and chronic stroke.[2] For the lower limb (LL), few studies suggest that absent MEP responses may be associated with greater walking difficulty.[3,4] However, the relationship of the MEP to gait speed and other measures of LL function still needs to be elucidated. In addition, there remains a large gap in our understanding of the adaptive or maladaptive nature of the contralesional hemisphere and its contribution to walking recovery. Few LL stroke studies have shown that greater ipsilateral drive from the contralesional hemisphere is associated with greater LL impairment and reduced performance in a skilled motor task.[5,6] Whether this increased ipsilateral drive also affects walking speed is still unknown.

Identification of MEP as a neurophysiological biomarker for walking recovery has the potential to effectively tailor neuromodulation-related treatments and other therapies. In this study, our primary aim was to determine whether LL functional corticospinal tract integrity, determined by the presence or absence of tibialis anterior (TA) and rectus femoris (RF) MEPs, was associated with gait speeds in chronic stroke. We also examined the relationship between ipsilateral connectivity

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from the contralesional M1 to the paretic LL muscles and its association to walking recovery.

Methods

Deidentified data that support the findings of this study will be available on reasonable request from the corresponding author (S.M.) after the completion of the ongoing randomized controlled trial. Please see online-only Data Supplement for detailed methodology. Briefly, subjects with a first-ever mono-hemispheric stroke >6 months since onset, residual hemiparetic gait deficits (abnormal gait pattern or 10-m walk time exceeding age-related time by 2 seconds), and ability to walk without an ankle orthotic for 5 minutes at self-paced speed were included in this study.[7] Subjects with contraindications to TMS, brain stem or cerebellar lesions, presence of cognitive and cardiorespiratory impairments were excluded. A written informed consent was obtained from everyone, and the study was approved by the institutional review board.

A physical therapist assessed gait speed using the 10-meter walk test (2 trials each of self-selected and fast speed), endurance with the 6-minute walk test, dynamic balance using the Timed Up and Go test, LL impairment with the Fugl Meyer lower extremity scale, and muscle strength using maximum voluntary contractions.

For TMS, a double cone coil with a posterior-anterior current orientation was used to determine corticomotor excitability for the TA and RF muscles. For contralateral responses, the coil was placed over the hemisphere contralateral to the muscle, and for ipsilateral responses, the coil was placed ipsilateral to the muscle (Figure). TMS-induced responses were collected from the paretic TA and paretic RF and the nonparetic TA and nonparetic RF. MEP area were considered as the primary outcome of corticomotor excitability. To determine the relative magnitude of ipsilateral contributions, we calculated a physiological index of corticomotor excitability for the paretic TA and nonparetic TA.[6]

We classified our participants into MEP+ (present) and MEP– (absent) groups based on the presence of MEPs from the ipsilesional hemisphere for both the contralateral paretic TA and paretic RF. Between-group comparisons were performed for all clinical and neurophysiological parameters. For the MEP+ group, multiple regression models were used to investigate relationships between MEP parameters, maximum voluntary contractions (paretic TA and paretic RF), Fugl Meyer lower extremity, age, time since stroke, and gait speeds.

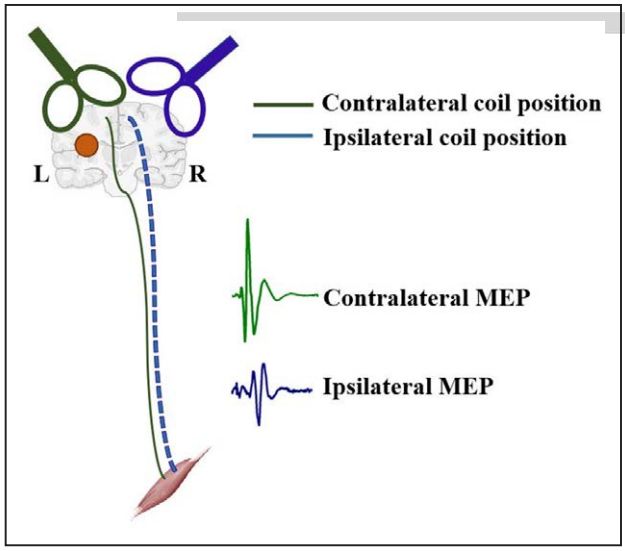

Figure. Schematic showing an example of a contralateral motor evoked potential (MEP; green) and an ipsilateral MEP (blue). Ideally, when the transcranial magnetic stimulation coil is positioned contralateral to the target muscle, the MEP is larger (green) and when placed ipsilateral to the target muscle, the MEP (blue) is smaller. Ipsilateral conductivity is assumed when the ipsilateral MEP slope is higher than the contralateral MEP slope, suggestive of a lower index of corticomotor excitability (ICE).

Results

Data from 61 participants (age range, 41–76 years) were analyzed (Table I in the online-only Data Supplement). MEPs were elicitable from the paretic TA and paretic RF in 28 participants. There were no significant differences between the MEP+ and MEP– groups for self-selected and fast walking speeds (Figure I in the online-only Data Supplement), 6-minute walk test, or Timed Up and Go test. The Fugl Meyer lower extremity and paretic TA maximum voluntary contractions values were significantly higher in the MEP+ group (Table 1). The MEP– group showed significantly higher active motor threshold and lower contralateral recruitment curve slopes for the nonparetic TA and nonparetic RF compared with the MEP+ group. No significant differences were noted for the index of corticomotor excitability values between the MEP+ and MEP– groups (Table 2). For the MEP+ group, the multiple regression models were unable to significantly predict self-selected or fast gait speeds (Table II in the online-only Data Supplement).

Discussion

Our results showed that the presence or absence of a LL MEP from the ipsilesional hemisphere does not affect gait outcomes in chronic stroke. These findings may imply that functional corticospinal tract integrity may not be a useful biomarker for explaining walking recovery in chronic stroke survivors. Even though TMS has been shown to reliably predict upper limb motor recovery in acute and subacute stroke,[8,9] its role

Table 1. Comparison of Clinical Parameters in Both Groups

	MEP+ (n=28)	MEP– (n=33)	95% CI Lower	Upper	*P* Value
Gait speed, m/s					
Self-selected	0.74 (0.2)	0.74 (0.2)	–0.1	0.11	0.97
Fast velocity	0.99 (0.3)	0.97 (0.3)	–0.1	0.14	0.87
TUG, s*	15.8 (6)	15.01 (5)			0.65
6MWD, m	278.66 (94.08)	285.4 (86.1)	–38	54.5	0.72
FMLE (paretic)	24.14 (3.34)	18.7 (3.8)	–7.2	–3.4	<0.001†
MVC					
NPTA	0.19 (0.09)	0.15 (0.07)	–0.08	0.002	0.06
PTA*	0.09 (0.05)	0.05 (0.03)			0.004†
NPRF	0.08 (0.06)	0.08 (0.05)	–0.03	0.02	0.7
PRF	0.04 (0.02)	0.03 (0.01)	–0.08	0.002	0.18

Values are means (SDs). 6MWD indicates 6-minute walk distance; FMLE, Fugl Meyer lower extremity scale; MEP, motor evoked potentials; MVC, maximum voluntary contraction; NPRF, nonparetic rectus femoris; NPTA, nonparetic tibialis anterior; PRF, paretic rectus femoris; PTA, paretic tibialis anterior; and TUG, Timed Up and Go test.

*Results for the TUG and PTA variables are from Mann-Whitney *U* tests, and 95% CI are not reported for these variables.

†*P* value indicates statistical significance.

Table 2. Comparison of Neurophysiological Parameters in Both Groups

	MEP+ (n=28)	MEP− (n=33)	*P* Value
Active motor threshold (% MSO)			
$NPTA_{contra}$	41.67 (9.3)	50.39 (8.7)	<0.001*
$NPRF_{contra}$	45.1 (10.1)	52.73 (9.7)	0.007*
PTA_{contra}	52.1 (10.2)	N/A	
PRF_{contra}	56.14 (12.2)	N/A	
RC slope			
$NPTA_{contra}$	0.072 (0.004)	0.041(0.003)	0.005*
$NPRF_{contra}$	0.076 (0.005)	0.069 (0.009)	0.04*
PTA_{contra}	0.043 (0.003)	N/A	
PRF_{contra}	0.038 (0.004)	N/A	
Index of corticomotor excitability (ICE)			
NPTA	0.23	0.24	0.68
PTA	0.02	−0.07	0.3

Values are means (SDs). ICE indicates index of corticomotor excitability; MEP, motor evoked potentials; MSO, maximum stimulator output; N/A, not applicable; $NPRF_{contra}$, nonparetic rectus femoris; $NPTA_{contra}$, nonparetic tibialis anterior; PRF_{contra}, paretic rectus femoris; PTA_{contra}, paretic tibialis anterior; and RC, recruitment curve.

**P* value indicates statistical significance.

in the explanation of walking recovery in chronic stroke may be more complex. Our findings concur with studies that did not show an association between LL MEPs and independent ambulation.[10–12] Cho et al[10] reported that chronic stroke survivors without TA MEPs and reduced corticospinal tract integrity could walk independently, and Smith et al[11] reported that even in the acute-subacute stages, presence of a MEP was not predictive of independent ambulation. Our finding that participants with MEPs demonstrate lesser motor impairment (higher Fugl Meyer lower extremity scores) is in line with other studies that prospectively evaluated MEPs from the acute to chronic stages and showed that the presence of a MEP was associated with better clinical recovery.[3,4,13,14]

A plausible explanation for the absence of differences in gait speeds in stroke survivors with and without MEPs could be the possible recruitment of redundant pathways, such as the reticulospinal tract, in those without MEPs,[15] or it could be a reflection of motor compensation, such as increased swing amplitudes on the nonparetic side.

We did not find any differences in ipsilateral activity from the contralesional hemisphere between groups. These results suggest that in chronic stroke survivors, the contralesional hemisphere may not be upregulated in those with reduced ipsilesional drive or it is possible that TMS may not be sensitive to capture ipsilateral activity in the LL M1. Interestingly, the contralesional hemisphere in the MEP− group showed reduced corticomotor excitability. This may be clinically relevant because these individuals may benefit from facilitatory bihemispheric noninvasive brain stimulation compared with suppression of the contralesional hemisphere which is standard for neuromodulation for upper limb recovery.

Our study is limited by the lack of gait kinematic and kinetic measures and quantification of MEPs for other LL muscles, such as plantar flexors, which may provide further explanation of our results. The proximity of the LL motor cortices may have accounted for inadvertent stimulation of both hemispheres during TMS, thus confounding some of our TMS measures. Finally, our participants were community ambulators who walked with higher speeds, thus limiting the generalizability of our findings.

Conclusions

The results of this study suggest that the absence of a TMS-induced MEP of the TA and RF does not affect gait speed in chronic stroke survivors. Our study is the first to investigate the association between different gait outcomes and neurophysiological parameters for both the TA and RF muscles and quantify ipsilateral connectivity to the paretic TA in a large cohort of stroke survivors. Future research with a larger, heterogeneous sample and comprehensive predictive models is warranted to identify the factors influencing gait recovery.

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Disclosures

None.

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SUPPLEMENTAL MATERIAL

Absence of a TMS-induced lower limb corticomotor response does not affect walking speed in chronic stroke survivors

Supplemental Methods

Study design

This is a retrospective study, where TMS and clinical measurements were collected from a larger ongoing randomized controlled trial (RCT) examining the effects of cortical priming for gait recovery (clinical trial registration: NCT03492229).

Electromyography (EMG)

Participants were seated comfortably in a chair with knees flexed to 90 degrees. EMG data were collected bilaterally from the tibialis anterior (TA) and rectus femoris (RF) muscles. Surface Ag/AgCl electrodes were placed over the muscle belly of the TA and RF muscles, and the reference electrode was placed over the spinous process of the seventh cervical vertebra. EMG data were sampled at 2000 Hz, amplified (1000X) and band pass filtered (10-500 Hz) with a Delsys EMG system (Bagnoli 8, MA USA). The EMG data collection was performed using Spike2 software (Cambridge Electronic design, Cambridge). Maximum voluntary contraction (MVC) of the TA and RF muscles were obtained in three five-second trials and the mean electromyography activity over a five-second window was computed as the MVC. Participants were instructed to 'pull up their foot as hard as possible' for the TA muscle, and 'kick out their leg as hard as possible' for the RF muscle against maximal resistance. Visual feedback was provided by a large screen in which participants could see the muscle activation.

TMS

The hotspots for the TA and RF muscles were established according to techniques that we have established previously.[1, 2] Participants were instructed to maintain a tonic contraction of the TA or RF representing approximately 10% MVC We considered the active motor threshold (AMT) as the stimulus intensity resulting in identifiable MEPs of at least 0.4 mV peak to peak in 50% of eight trials each from the contralateral TA/RF muscle. MEPs were considered absent when no responses were observed even after stimulating the ipsilesional hemisphere at 90-100% the maximum stimulator output (MSO). For those without MEPs on the paretic side, coil location of the contralesional hemisphere was mirrored. Recruitment curves were recorded from two positions: contralateral and ipsilateral to the muscle.[1] Recruitment curves (RC) curves were measured using intensities ranging from 80-140% AMT (seven intensities, six stimuli at each intensity). Only one muscle was active at a time, and we obtained 42 MEPs for each muscle at each coil position. For all participants, contralateral recruitment curves for the non-paretic and paretic TA and RF was recorded. For participants with ipsilesional MEPs, we also recorded ipsilateral responses to the paretic and non-paretic TA. For participants without paretic MEPs, only ipsilateral responses to the paretic TA were recorded. This was based on the assumption that absence of contralateral activity from the ipsilesional hemisphere will also confirm absence of ipsilateral activity from the ipsilesional hemisphere. Due to the low spatial resolution of the double cone coil and proximity of the lower limb motor cortices, it is likely that the ipsilateral responses are a combination of descending volleys from both hemispheres, with a preferential activation of the hemisphere on which the coil is placed. Hence, ipsilateral activity was estimated as a ratio relative to contralateral activity (see ICE below) Stimulation intensities for AMT ranged from 40–75% maximum stimulator output (MSO) for the paretic leg, and 35–60% MSO for the non-paretic leg.

Data Analyses

Spike 2 was used to analyze all TMS data. For MVC analyses, we used a custom algorithm for rectification and calculation of the average root mean square of the TA and RF EMG signal. Our previous work has showed that motoneuron activity resulting from weak TMS-induced descending volleys can be effectively captured by calculating the rectified area of EMG within a specified time window.[1] A MEP window was established for each muscle by finding the onset and offset latencies of MEPs. The average MEP area was plotted against the corresponding stimulus intensity (expressed as % AMT), and the recruitment curve was plotted using a conservative linear fit. The slope of the linear function was calculated for estimating the corticomotor excitability for each hemisphere. The following variables were calculated: $NPTA_{contra}$ slopes and $NPRF_{contra}$ from the contralesional M1; PTA_{contra} and PRF_{contra} slopes from the ipsilesional M1; $NPTA_{ipsi,}$ slopes for the non-paretic TA from ipsilesional M1; and PTA_{ipsi} slopes for the paretic TA from contralesional M1. The $NPTA_{ipsi}$ and PTA_{ipsi} were only estimated to calculate the ICE ratios. For the regression model, the dependent variables were self-selected gait speed (model 1) and fast gait speed (model 2).

ICE

To determine a relative measure of ipsilateral conductivity, we estimated the magnitude of ipsilateral response compared to the contralateral responses (see ICE below).[1]

$$ICE = \frac{Contralateral\ slope - Ipsilateral\ slope}{Contalateral\ slope + Ipsilateral\ slope}$$

Values for ICE range from -1 to 1, where positive values indicate greater contralateral responses, and negative values indicate greater ipsilateral responses.[1]

Supplemental Results

Table I. Participant characteristics

		MEP+ (n = 28)	MEP– (n = 33)
Age (y)		59.89 (10.2)	58.2 (8.1)
Sex (females, n)		8	9
Affected hemisphere (right, n)		13	17
Ethnicity, n			
	White	5	10
	African American	18	16
	Asian	2	4
	Hispanic/Latino	2	2
	Other	1	1
Stroke type*			
	Ischemic (n)	14	23
	Hemorrhagic (n)	8	6
Time since stroke (y)		5.3 (4.2)	6.47 (5.96)
Paretic FMLE		24.14 (3.34)	18.7 (3.80)
Self-selected gait speed (m/s)		0.74 (0.21)	0.74 (0.23)
Use of assistive device (n)		2	0

Values are means (standard deviations). Abbreviations: FMLE, Fugl Meyer Lower Extremity Scale.*Data for type of stroke was not available for 10 participants.

Table II. Results from the regression models for the MEP+ group

Predictor		ß	95% CI		P value
			Lower	Upper	
Model 1 – Self-selected gait speed					
Age		-0.3	-0.01	0.003	0.16
Time since stroke		-0.09	-0.02	0.01	0.63
FMLE		0.2	-0.01	0.04	0.24
MVC	PTA	0.4	-0.2	3.5	0.07
	PRF	0.03	-4.3	5.1	0.86
RC slope	$NPTA_{contra}$	0.004	-1909.5	1945.8	0.98
	$NPRF_{contra}$	0.1	-1821.6	2733.4	0.67
	PTA_{contra}	-0.1	-4155.4	2307.2	0.55
	PRF_{contra}	0.06	-2100.1	2786.7	0.77
Model 2 – Fast gait speed					
Age		-0.3	-0.02	0.002	0.08
Time since stroke		-0.23	-0.04	0.013	0.24
FMLE		0.25	-0.01	0.06	0.19
MVC	PTA	0.28	-0.9	4.01	0.2
	PRF	0.11	-4.6	7.7	0.61
RC slope	$NPTA_{contra}$	-0.09	-3071.8	1944.8	0.64
	$NPRF_{contra}$	-0.03	-3180.9	2746.2	0.88
	PTA_{contra}	-0.07	-4943.2	3466.09	0.71
	PRF_{contra}	0.17	-2015.9	4344.05	0.45

Abbreviations: FMLE, Fugl Meyer Lower Extremity; MVC, Maximum Voluntary Contraction; RC, Recruitment Curve; $NPTA_{contra}$, Non-paretic tibialis anterior; PTA_{contra}, Paretic tibialis anterior; $NPRF_{contra}$, Non-paretic rectus femoris; PRF_{contra}, Paretic rectus femoris.

Figure. I

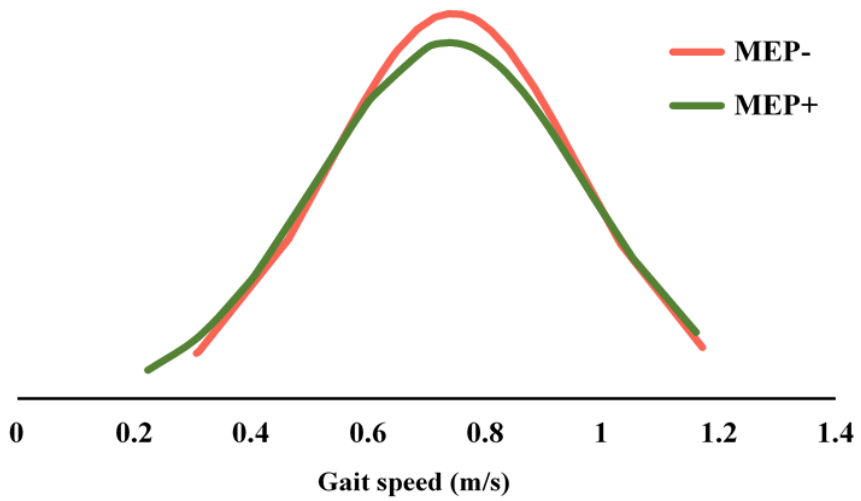

Fig. I. Normal distribution curves for self-selected gait speeds for the MEP+ (green) and MEP- (red) groups. Each data point is computed with the probability mass function for establishing a Gaussian fit. Note the lack of difference between the two groups.

Supplemental References

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