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Characterization of stimulus response curves obtained with transcranial magnetic stimulation from bilateral tibialis anterior muscles post stroke

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Abstract

Background: Stimulus response curves (SR curves), measured using transcranial magnetic stimulation (TMS) induced motor evoked potentials (MEP), yield important information regarding corticomotor connectivity. Limited understanding of SR curve analyses techniques for leg muscles after stroke may limit the utility of TMS data for walking recovery.

Objective: To compare linear and non-linear curve fitting for MEP responses from the non-paretic and paretic tibialis anterior (TA) muscles.

Methods: Accuracy of fit was measured using coefficient of determination (R^2). Similarities of the fit were compared using slopes and area under the curve (AUC).

Results: The non-linear function demonstrated higher R^2 and slopes. The AUC was not significantly different between the two analyses approaches. The non-linear non-paretic SR slopes and paretic AUC had significant associations with walking speed.

Conclusion: Our results highlight the differences between non-linear and linear approaches to best fit the SR curves from bilateral TA muscles in stroke survivors. Although the linear function can appropriately fit the SR curve of the paretic and non-paretic TA, the non-linear function estimated a higher slope. We found the AUC to be a more robust measure that was not affected by the type of curve-fitting approach and only the AUC of the paretic TA showed significant association with walking speeds. A better understanding of SR curve fitting approaches for the TA muscles in individuals with chronic stroke allows for their optimal use in interpretation of TMS data and literature.

Keywords

Stroke; Stimulus response curve; Boltzmann fit; Linear regression; Area under recruitment curve; Lower limb

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Declaration of Competing Interest

None of the authors have potential conflicts of interest to be disclosed.

1. Introduction

Transcranial magnetic stimulation (TMS) has now been used for more than three decades to understand corticomotor excitability of muscle motor representations [1-3]. Motor evoked potentials (MEP) elicited with TMS have been utilized as the primary outcome measure to quantify functional integrity of descending corticomotor pathways [4]. As the MEP size typically increases with stimulation intensity, studies attempt to quantify the neurophysiology of the target motor representation using stimulus-response (SR) curves. In healthy brains, when MEP amplitude or area is plotted across the corresponding TMS intensity during rest or tonic background activity, a sigmoid shaped SR curves is seen. Devanne et al. (1997) was the first to introduce the use of a 3-parameter non-linear Boltzmann function to represent TMS-induced SR curves [5]. Carroll et al. (2001) later used a variation of this function by modifying the slope function in the equation to represent a larger increase in MEP response [6]. The non-linear function is contingent on a maximum MEP value (MEP_{max}). The MEP_{max} is the MEP elicited at the highest maximum stimulator intensity (MSO) or when saturation of MEP occurs [6]. The non-linear Boltzman function can be optimally applied to conditions where a MEP_{max} is possible. This best applies to situations where a tolerable maximum MSO can be administered such as with the figure-of-eight coil or when saturation of MEPs occur at a lower MSO. These conditions are characteristic of upper limb muscles, healthy muscles or individuals with low TMS motor thresholds.

Experiments investigating the leg muscles in healthy and stroke brains use the conservative linear function analyses for SR curves [5,7-13]. Lower limb TMS studies use the double cone coil, which provides diffuse but deeper penetrating currents given its angled shape, to stimulate the leg areas which are deep within the interhemispheric fissure [14-18]. As the contact surface area of the double cone coil is larger than the figure-of-eight coil, intensities above 80% MSO are typically not well tolerated by participants resulting in inability to obtain MEP_{max} or sometimes even accurately estimate motor threshold. This results in insufficient measurements necessary to perform non-linear analyses. Massie et al. (2013) demonstrated that the linear function for the hand muscles in individuals with chronic stroke accurately captures the rising slope for SR curve and may in fact have an advantage over the non-linear function as it uses less complex mathematical functions and overcomes some of the challenges seen in a Boltzmann fit such as identifying the correct slope parameter [19]. However, no study has attempted to compare the linear and non-linear data analyses processes for leg muscles and to validate the use of the linear function for experiments that are unable to elicit a MEP_{max} .

In this study, our primary objective was to compare linear and non-linear curve fitting approaches for MEP responses obtained from the non-paretic and paretic tibialis anterior (TA) muscle in persons with stroke. We chose to study the TA muscle as it plays a significant role in ankle dorsiflexion during walking and standing balance [20,21]. Also, MEPs from the TA are more easily elicited than other leg muscles, and the reliability of TMS related measures for the TA in stroke has been reported previously [22,23]. To compare the linear and non-linear SR curves, we first quantified accuracy of fit using

coefficient of determination (R^2). Next, similarities of the fit were compared using estimated slopes as well as area under the curve (AUC) measures.

Our second objective for this study was to determine which SR curve parameter can best relate to clinical outcomes. Specifically, we estimated if the linear and non-linear slopes and AUC (which are all considered to reflect the strength of corticomotor projections) are related to gait speed and lower limb impairment. SR slopes and AUC has shown to have a positive relationship with hand motor recovery [24-26]. Conflicting results exist for the relationship between descending drive to the TA and walking outcomes; in addition, the relationship of AUC of the TA SR curve with clinical outcomes has not been previously studied [8,27-31]. Understanding the characterization of the SR curves in stroke will enable future studies to select the best analyses technique that is suitable for the tibialis anterior muscle representation in chronic stroke survivors.

2. Methods

In this retrospective study, baseline TMS and clinical measures that were collected as a part of a larger ongoing randomized control conducted in the Brain Plasticity Laboratory [Clinical trial registration: NCT03492229] at the University of Illinois at Chicago were included. This ongoing study explores the effects of neuromodulation for gait recovery in chronic stroke survivors. Broader inclusion criteria for the RCT included subjects with a first-ever mono-hemispheric stroke, greater than six months since occurrence of stroke, residual hemiparetic gait deficits (abnormal gait pattern or 10-m walk time, exceeding age-related time by 2 s), and ability to walk without an ankle orthotic for 5 min at self-paced speed. Subjects with contraindications to TMS, brain stem or cerebellar lesions, presence of cognitive and cardiorespiratory impairments were excluded. From the cohort who were enrolled in this RCT, we selectively recruited participants with a visible MEP in the electromyographic (EMG) recording of their paretic TA after TMS stimulation. Twenty-eight participants matched these criteria and were included in the data analyses processes (Table 1).

2.1. Clinical outcomes

Gait speed was assessed using the 10-meter walk test at each participant's self-selected and fastest speed. An average of two trials were used to represent gait speed. Lower limb sensorimotor recovery, assessed using lower limb Fugl Meyer scale (FMLE), included the motor assessment of the paretic and non-paretic legs.

2.2. Transcranial magnetic stimulation (TMS)

Participants were seated comfortably in a chair with knees flexed to 90 degrees. Their foot was placed on a custom built manipulandum which consisted of a wooden board with a cushioned metal clamp applied on the dorsum of the foot to limit motion. EMG activity was collected using surface Ag/AgCl electrodes placed over the paretic and non-paretic TA muscle belly and the reference electrode over the spinous process of C7 vertebra. Spike2 software (Cambridge Electronic design, Cambridge, UK) was used for all EMG data collection and to automate the TMS trigger and record the trigger pulses. EMG data were

sampled at 2000 Hz, amplified *1000 and band pass filtered (10–500 Hz) with a Delsys EMG system (Bagnoli 8, MA USA). Maximum voluntary contraction (MVC) of each TA muscle was obtained with the ankle at neutral position restricted by the tightened clamp. We ensured that no movement of the foot was possible when performing MVCs and during voluntary contractions. Single pulse TMS was delivered using a 110 cm double cone coil in a posterior-anterior direction using a single-pulse monophasic stimulator (Magstim, Dyfed, Wales, and UK) during 10% MVC of the TA. A background activation of 10% MVC ensured a weak tonic activation increasing the probability of eliciting a MEP and reducing MEP variability without inducing fatigue [32]. All the participants included in this study were able to maintain 10% MVC with sufficient rest in between blocks of stimuli. The ‘hotspot’ for the lower limb M1 was determined as the location that produced consistent and maximum MEPs in the contralateral TA muscle at the lowest stimulator intensity [33]. This spot was marked relative to the vertex on a tight-fitting cap to maintain consistency in coil positioning across the session. Active motor threshold (AMT) was defined as the maximum stimulator output (MSO) resulting in identifiable MEPs of at least 0.4 mV peak to peak in 50% of successive trials from the active contralateral muscle [8,9,33]. TMS intensities were randomly assigned within the range of 80–140% AMT with a 10% increment and blocks of six MEPs were recorded at each intensity. SR curves were obtained for each muscle separately (80–140% active threshold, 7 intensities, 6 stimuli at each intensity).

2.3. Data analyses

The SR curve was built using the averaged peak to peak MEP amplitude value at each TMS intensity and plotted across % MSO for each participant. Curve fitting was done using MATLAB. Linear fit was performed using the formula for the 1st order polynomial equation. The non-linear fit (Fig. 1) was done using three-parameter sigmoid function which is as shown below:

$$\text{MEP}(s) = \frac{\text{MEP}_{\max}}{1 + e^{m(S50 - s)}}$$

Where $\text{MEP}_{\max}$ is the maximum MEP amplitude estimated by the function; S50, is the stimulus intensity at which the MEP amplitude is 50% of the maximal MEP amplitude, m , the slope parameter of the function; s , stimulation intensities.

Non-linear curve fitting was performed using a modified Boltzmann equation reported by Carroll et al. (2001) and is similar to the logistic function described by Devanne et al. (1997) [5,6]. Carroll et al. used a slope parameter ‘ m ’ which is an inverse of the Boltzmann slope parameter ‘ k ’ proposed by Devanne et al. The slope parameter ‘ m ’ is a general measure of steepness that represents the rate of increase in the magnitude of response relative to the maximum MEP size with increasing stimulus intensity. The fitting procedures were done in MATLAB using Levenberg-Marquardt in a least squares curve fitting algorithm with the maximum number of function evaluations and iterations up to 500 [5,6,19,24]. The coefficient of determination (R^2) was exported from the goodness of fit evaluation using the curve fitting function of MATLAB.

After accuracy of fit was confirmed, SR slope and area under the curve (AUC) were compared between the two functions. The SR slope indicates the maximal rate of increase in MEP amplitude with stimulus intensity and is constrained to occur at S50 between the two inflection points. Higher the value of SR slope, greater is the strength of corticomotor projections. It is given by the formula:

$$\frac{m \times \text{MEP}_{\text{max}}}{4}$$

The AUC represents the summation of total corticomotor output over the range of TMS intensities used in the experiment [24,26]. Larger values of AUC indicate greater corticomotor output. AUC is calculated as a sum of squares in MATLAB using a trapezoidal formula constrained within the boundary of MEP amplitude and stimulus intensities. For AUC after the non-linear fit, trapezoidal formula was applied for estimated MEP amplitudes derived from the Boltzmann equation (Fig. 2).

2.4. Statistical analyses

Statistical analyses were performed using SPSS (IBM SPSS statistics 25). We performed the Shapiro-Wilk tests to confirm normal distributions and parametric/non-parametric analyses were conducted accordingly. All measures, except for AUC and clinical measures, were not normally distributed. Friedman's two-way analysis of variance by ranks with pairwise comparisons was performed to examine differences in R^2 , slopes, and AUC with the type of fit (linear vs non-linear) and side (paretic vs non-paretic) as the main factors. The Pearson correlation coefficient was used to examine the relationship between AUC (linear and non-linear) of paretic TA and clinical measures (gait speeds and FMLE). The Spearman rank correlation was used to study the rest of the TMS measures which were not normally distributed vs. clinical measures. Cohen's d was computed using G*Power 3.0.10. to calculate effect sizes. Effect size greater than 0.8 was considered to be high, between 0.5-0.79 moderate and less than 0.5 as low.

3. Results

The summary of data is available in Tables 2 and 3. The mean R^2 values for linear and non-linear function analyses was greater than 0.75. The R^2 values were significantly different across fit and side ($\chi^2(3) = 26.014$, $p = 0.0001$). Pairwise comparisons revealed that the R^2 for the non-linear function was significantly higher than the linear function for both the non-paretic TA ($t = -1.107$, $p = 0.008$, $d = 0.99$) and paretic TA ($t = -1.250$, $p = 0.002$, $d = 0.51$). The R^2 for the non-paretic TA was greater than the paretic TA for the non-linear analyses ($t = -1.571$, $p = 0.0001$, $d = 0.83$).

Similarly, slopes were significantly different across fit and side [$\chi^2(3) = 56.357$, $p = 0.0001$]. The slope of the non-linear function was significantly higher than linear function for the non-paretic ($t = -1.107$, $p = 0.008$, $d = 1.37$) and paretic TA ($t = -1.536$, $p = 0.0001$, $d = 0.25$). The slope for the non-paretic TA was greater than the paretic TA for the non-linear ($t = 1.036$, $p = 0.016$, $d = 0.25$) and linear ($t = 1.464$, $p = 0.0001$, $d = 0.82$) analyses. The AUC showed only a main effect of side ($\chi^2(3) = 32.014$, $p = 0.0001$). AUC of non-paretic

TA was significantly higher than the AUC of the paretic TA after non-linear ($t = 1.179$, $p = 0.004$, $d = 1.15$) and linear ($t = 1.536$, $p = 0.0001$, $d = 1.14$) analyses.

The slope of non-paretic TA after non-linear fit was significantly but poorly associated with self-selected speed ($r_s(27) = -0.380$, $p = 0.046$, $d = 0.55$). The AUC of paretic TA with non-linear fit was significantly and moderately associated with self-selected speed ($r_s = 0.389$, $n = 29$, $p = 0.041$, $d = 0.62$). The AUC of the paretic TA with the linear fit was significantly and moderately associated with self-selected speed ($r_s = 0.400$, $n = 29$, $p = 0.035$, $d = 0.63$) and fastest speed ($r_s = 0.375$, $n = 29$, $p = 0.050$, $d = 0.61$). No other significant correlations were noted.

4. Discussion

This study aimed to compare two analyses approaches to characterize TMS-generated SR curves for the bilateral TA muscles post stroke. We sought to answer if the conservative linear function typically used to fit SR curves in TMS-based leg muscle studies was comparable to the non-linear Boltzmann fit used in upper limb or healthy TMS studies. Our data confirm that both curve fitting techniques can appropriately fit the SR curves for the paretic and non-paretic TA muscles. The accuracy of fit was moderate to excellent, and greater than 75% variability was explained by the curve fitting procedures done using the linear and non-linear approach for both muscles. We also noted that the non-linear function explained a greater variability of the data compared to the linear analyses for both muscles. As expected, accuracy of fit was higher for the non-paretic TA than the paretic TA with both approaches.

Our purpose in this study was to understand the type of curve fitting procedure that best characterizes the SR curve elicited from leg muscles using TMS. Although the human motor system typically responds with a sigmoidal output, the technical challenges associated with using double cone coil for the leg motor representations precludes this assumption that is commonly applied to upper limb studies [14-18]. The deeper location of the lower limb M1 representation necessitates the use of the double-cone coil which is more penetrating than the figure-of-eight, flat or batwing coils. In our research experience, more than 90% of participants do not tolerate intensities above 75% MSO with the double cone coil, which makes it difficult to elicit a MEP maximum for leg muscles. Also, persons with stroke typically have high motor thresholds close to 50% MSO which limits the number of tolerable stimulations delivered to elicit the saturation of responses required to appropriately fit the non-linear function [2,34].

The strength of the functional corticospinal tract is typically assessed using the slope of the SR curve in TMS studies [4]. It reflects the ability of corticospinal neurons to respond to a specific input stimulus. In our study, we found that the non-paretic TA demonstrated higher slopes than the paretic TA, confirming the imbalance in corticomotor excitability typically seen in a stroke brain [2,35]. We noted that the non-linear function estimated a higher slope than the linear function for all muscles. In contrast to the R^2 and slopes, the AUC was not significantly different between the two analyses approaches for the same muscles but as expected we found higher values for the non-paretic TA than the paretic TA. The non-linear

non-paretic TA slope was negatively associated with self-selected walking speed and both the linear and non-linear AUC for the paretic TA was positively associated with self-selected walking speed.

Our results confirm the findings that have been observed in upper limb TMS studies. Massie et al. (2012) also noted greater accuracy and slope values for the non-linear approach compared to the linear fitting [19]. This is not surprising as the peak slope estimated by the Boltzmann equation occurs at the point of maximal steepness, which is influenced by the two inflection points in the curve and not by the end points of the SR curves [6]. The slope calculated by the linear function represents the best fit line that includes all data points in the given SR curve and is likely influenced by the minimum and maximum data points.

We further explored the utility of the SR curves by exploring the association between SR slopes and gait related clinical measures. The linear slopes were not significantly associated with any clinical measures, in line with our previous study [8]. The non-linear slopes were also not associated with clinical outcomes except for the non-paretic TA which was negatively associated with gait speed. This negative association may reflect the theory of interhemispheric imbalance where increased excitability of the non-lesioned hemisphere is associated with increased interference with function [35]. The absence of a correlation between the slope and clinical measures maybe because the SR curve slope does not represent all neural mechanisms that may contribute to walking, (i.e.) input from other descending pathways such as the reticulospinal tract, or compensatory movements involved in walking that are not being assessed with TMS in this study.

The AUC parameter reflects the sum of corticospinal output from all TMS intensities. The AUC has been used in upper limb studies but has not been reported for leg muscles [24,26]. The AUCs were similar for the linear and non-linear functions; perhaps because the estimated MEP amplitudes used in the non-linear function were not different from actual MEP amplitudes in the linear function. Unlike the peak slope, which is constrained to occur at the maximal steepness and is mainly influenced with distribution of inflection points, AUC appears to be a more robust measure as there was no significant difference based on the type of fit. In addition, the AUCs for both the linear and non-linear functions were moderately associated with walking speeds, suggesting that this maybe a more practical measurement to consider in future studies interested in understanding the relationship between walking recovery and corticomotor excitability.

The results of this study should be interpreted with the following caveats. We intentionally chose participants with MEPs to fully understand SR curves. These participants were moderate to high functioning individuals and our results may not apply to those with more severe impairment with minimal activation of the TA. Although upper limb MEP parameters have not been reported to be influenced by gender, we should note that we had a greater representation of males in this study warranting caution with interpretation of results with respect to females [36]. Lastly, we report results only from the tibialis anterior muscles and these findings may not be generalized to other leg muscles.

In conclusion, we report that the linear function can accurately describe the nature of the TMS generated SR curve; however, it should be understood to be a more conservative approach. The non-linear function provides a better representation and estimates a higher slope. The AUC parameter was not influenced differently by the type of approach and can be considered a more robust parameter to describe the SR curve. We also found the AUC to be better associated with walking speeds when the other SR parameters did not. These results highlight the different approaches to best fit the SR curves from the lower limb M1 and identify the parameters that maybe best utilized describe lower limb corticomotor excitability. A better understanding of SR curve fitting approaches for the paretic and non-paretic TA muscles in individuals with chronic stroke allows for their optimal use in interpretation of TMS data and literature.

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Abbreviations:

TMS	transcranial magnetic stimulation
SR curves	stimulus response curves
SR slope	stimulus response slope
AUC	area under recruitment curve
MEP	motor evoked potentials
MEP_{max}	highest MEP amplitude
%MSO	machine stimulated output

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Fig. 1.

Parameters used in the Boltzmann equation.

Schematic representation of the maximum motor evoked potential (MEP_{max}) and half of MEP_{max} (S50) estimated from Boltzmann function are shown. The peak slope is depicted as line passing through the point of maximal steepness which occurs at S50.

Fig. 2.

Linear and non-linear curve fitting for one representative participant.

Stimulus response (SR) curves for the non-paretic tibialis anterior (Fig. 2A) and paretic tibialis anterior (Fig. 2B) muscles are shown. Motor evoked potential (MEP) amplitude is plotted as a function of maximum stimulator output (MSO). The characteristics of the linear function are shown in *blue* and the non-linear function in *red*. Note that the MEPs used in the non-linear function analyses are slightly different from the MEPs collected during the experiment as these were estimated values from Boltzmann equation. For the paretic TA, only 4 stimulus intensities were collected as the participant had a high threshold and could not tolerate intensities above 75%. Overlapping area under curve (AUC) is shown in *purple*.

Table 1

Participant demographics.

Characteristics	
No. of Participants:	28
Gender (Male/female):	20/8
Age (years):	60 $\pm$ 10
Time since stroke (years):	5 $\pm$ 4
Side of affected hemisphere (Right/Left):	14/14
Type of stroke	
Ischemic:	15
Hemorrhagic:	9
Unknown:	4
FMLE (Motor)	
Paretic side:	24.3 $\pm$ 3.2
Non-paretic side:	29.3 $\pm$ 2.3
Walking speeds (m/s)	
Self-selected:	0.8 $\pm$ 0.2
Fastest speed:	1.0 $\pm$ 0.3

All values are mean $\pm$ standard deviation.

Abbreviations: FMLE, Fugl-Meyer assessment of lower extremity.

Table 2

Linear and non-linear characteristics of stimulus response curves.

MEASURES	Non-linear		Linear	
	Non-paretic	Paretic	Non-paretic	Paretic
R ²	0.937 (0.061) ^{##}	0.883 (0.165) [*]	0.866 (0.088)	0.788 (0.202)
SR Slope	0.077 (0.086) ^{##}	0.051 (0.112) [*]	0.028 (0.016) [#]	0.009 (0.007)
AUC	9.60 (4.47) [#]	5.12 (2.36)	9.49 (4.45) [#]	5.16 (2.39)

All values are shown as mean (standard deviation).

^{*} significantly different from linear;

Abbreviations: R², coefficient of determination; SR, stimulus response; AUC, area under recruitment curve.

[#] significantly different from paretic of the same fit. p < 0.05.

Table 3

Correlation between stimulus response curve parameters and clinical measures.

TMS Parameters	Non-Paretic TA		Paretic TA		Gait Measures	
	Non-Linear r (p)	Linear r (p)	Non-Linear r (p)	Linear r (p)		
SR Slope	-0.380 (0.046)*	-0.054 (0.788)	0.248 (0.203)	0.342 (0.075)	Self-selected speed	
	-0.348 (0.070)	0.010 (0.958)	0.187 (0.342)	0.341 (0.076)	Fastest Speed	
	-0.115 (0.559)	0.175 (0.373)	0.209 (0.286)	0.061 (0.760)	FMLE	
AUC	0.221 (0.258)	0.210 (0.283)	0.413 (0.029)*	0.423 (0.025)*	Self-selected speed	
	0.187 (0.340)	0.179 (0.362)	0.354 (0.065)	0.375 (0.050)*	Fastest Speed	
	0.361 (0.059)	0.370 (0.052)	0.076 (0.702)	0.097 (0.624)	FMLE	

Abbreviations: r, Pearson's or Spearman's correlation coefficient; p, probability value; SR, stimulus response; AUC, area under recruitment curve; FMLE, Fugl-Meyer assessment of lower extremity.

*
p < 0.05.