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Automated-Parameterization of the Motor Evoked Potential and Cortical Silent Period Induced by Transcranial Magnetic Stimulation

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Abstract

Objective—To standardize the characterization of motor evoked potential (MEP) and cortical silent period (CSP) recordings elicited with transcranial magnetic stimulation (TMS).

Methods—A computer-based, automated-parameterization program (APP) was developed and tested which provides a comprehensive set of electromyography (EMG) magnitude and temporal measures. The APP was tested using MEP, CSP, and isolated CSP (iCSP) TMS stimulus-response data from a healthy adult population (N = 13).

Results—The APP had the highest internal reliability (Cronbach's $\alpha = .98$) for CSP offset time compared with two prominent automated methods. The immediate post-CSP EMG recovery level was 49% higher than the pre-TMS EMG level. MEP size (peak amplitude, mean amplitude, peak-to-peak amplitude, and area) correlated higher with effective E-field (E_{eff}) than other intensity measures ($r \approx 0.5$ vs. $r \approx 0.3$) suggesting that E_{eff} is better suited for standardizing MEP stimulus-response relationships.

Conclusions—The APP successfully characterized individual and mean epochs containing MEP, CSP, and iCSP responses. The APP provided common signal and temporal measures consistent with previous studies and novel additional parameters. Significance: With the use of the APP modeling method and the E_{eff} , a standard approach for the analysis and reporting of MEP-CSP complex and iCSP measurements is achievable.

Keywords

Transcranial magnetic stimulation; Motor evoked potential; Cortical silent period; Automated Parameterization; Effective electrical-field

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INTRODUCTION

Transcranial magnetic stimulation (TMS) applied to the hand area of the primary motor cortex ($M1_{hand}$) elicits a motor evoked potential (MEP) followed by a post excitatory interruption of voluntary activity in targeted muscles, termed the cortical silent period (CSP). Together they form the MEP-CSP complex and are utilized to investigate cortical excitability and inhibition. A well established method for evaluating cortical excitability and inhibition is the generation of MEP and CSP stimulus response curves (Kimiskidis, et al. 2005, Werhahn, et al. 2007). Stimulus response curves for MEP and CSP represent the input-output functions for the motor cortex and potentially quantify neuronal dysfunction, disease progression, and drug treatment responsiveness in various neurological disorders. A variety of calculation techniques and criteria exist to define stimulus variables and response measures in TMS motor response experiments, emphasizing the need for standardization.

The stimulus variable for MEP and CSP stimulus response experiments is TMS intensity. Resting motor threshold (rMT) and machine output percentage are the most common expressions of TMS intensity (Borojerd, et al. 2001, Devanne, et al. 1997, Hess, et al. 1987, Kimiskidis, et al. 2005, Werhahn, et al. 2007). Measures of rMT attempt to normalize for individual differences in cortical excitability at rest. Effective electrical-field (E_{eff}) has also been proposed as a measure for stimulus intensity. E_{eff} corrects for the depth of the target neuronal population and their orientation to the induced E-field (Fox, et al. 2004).

MEP “size” is a common excitatory response measure in stimulus response experiments utilized to estimate cortical excitability (Werhahn, et al. 2007), and can be defined as the MEP peak-to-peak amplitude or MEP area in the target muscle (Devanne, et al. 1997). MEP area is normally calculated from mean rectified epochs by integrating the entire MEP response (Devanne, et al. 1997, Trompetto, et al. 2001). MEP onset and offset times are needed to define the response duration and are often determined by visual inspection. In addition to its subjectivity, MEP offset time determination by visual inspection is difficult at high TMS intensities where the MEP is confounded by additional descending volleys (Di Lazzaro, et al. 1998). Similarly, individuals with neurological disease often have diffuse, polyphasic MEP configurations which may be difficult to characterize with visual and automated methods (Tataroglu, et al. 2003, van der Salm, et al. 2008). The mean amplitude throughout the MEP can also be used as a MEP response size measure. Variations in the determination of MEP duration can affect the calculation of MEP area and mean amplitude.

The most common inhibitory response measure used for a CSP stimulus response curve is duration (Kimiskidis, et al. 2006, Trompetto, et al. 2001, Werhahn, et al. 1995). CSP duration is defined as the difference between CSP onset and offset times. However, methods for determining CSP onset and offset times are variable between investigators. The following times have been used to define CSP onset: (a) onset of TMS, (b) TMS artifact appearance, (c) MEP onset, (d) MEP offset, and (e) when electromyography (EMG) drops below the volitional pre-TMS EMG level. Additionally, the following times have been used as CSP offset: (a) the first return of any volitional EMG, (b) the absolute return of EMG to the pre-TMS level, and (c) when EMG no longer significantly differs from pre-TMS EMG level. Collectively, these CSP temporal measures account for 15 possible methods for calculating CSP duration.

The lack of a standardized method for characterizing the MEP-CSP complex confounds the comparisons of cortical excitability and inhibition across different studies. An automated objective method is needed to better characterize the MEP-CSP complex and provide common response measures. Furthermore, in order to form reliable conclusions about cortical excitability and inhibition from the MEP-CSP stimulus response curves, the relationship between the stimulus variables and response measures should be assessed.

Four groups have developed automated methods for the determination of CSP duration (Daskalakis, et al. 2003, Garvey, et al. 2001, King, et al. 2006, Nilsson, et al. 1997). In general, these methods compare CSP related EMG to the pre-TMS EMG signal to determine CSP offset and/or onset times. However, the possibility exists that the recovery of volitional EMG might differ from pre-TMS EMG in such a manner as to confound the use of the pre-TMS EMG as a reference level. If the immediate post-CSP EMG level recovers to a level lower than the pre-TMS EMG level, then the calculation of CSP offset time would be indeterminate. In contrast, investigators have reported a period of facilitation following the CSP where the volitional EMG recovers to a higher level compared to pre-TMS EMG (Calancie, et al. 1987, Holmgren, et al. 1990, Mills 1988, Wassermann, et al. 1993). In this case, the measured CSP offset time may be shortened and not reflect the duration of the CSP. Special cases may also occur when EMG is seen to “breakthrough” the CSP valley, termed a late excitatory potential (LEP). The LEP and pre-TMS EMG could be of similar amplitudes as to cause the automated methods to mark the LEP as the end of the CSP. Furthermore, multiple LEPs break the CSP into multiple valleys and recoveries (Holmgren, et al. 1990) which might be difficult for the automated methods to quantify. In all these scenarios, information about the pre-TMS, LEP, and post-CSP EMG levels and times would be lost by not modeling and assessing them independently. The CSP modeling method described in this study was developed to adapt to all levels of recovery and is particularly useful in cases where LEPs and/or multiple CSPs are present.

Additionally, prior methods for automating measurements of CSP duration have not attempted to automate characterization of the MEP. Nilsson et al., Garvey et al., and Daskalakis et al. also did not attempt to measure CSP onset time. A “true” CSP onset time can only be determined from a silent period without a preceding MEP, termed an “isolated silent period” by Cantello et al. (1992). In MEP-CSP complexes, the excitatory potentials contributing to MEP can mask the initial inhibition of volitional EMG at the beginning of the silent period. Cantello et al. were able to detect isolated cortical silent periods (iCSP) in 7 of 12 subjects at low TMS intensities. Their average reported iCSP onset time was 57 ms from the TMS pulse with an average duration of 37 ms. King et al. (2006) also reported iCSPs during low intensity TMS. They did not report the iCSP onset time other than to state that their method could determine latency. Furthermore, King et al. did not describe the use of their method at higher TMS intensities.

A computer-based, automated-parameterization program (APP) was developed to standardize and quantify the characterization of MEP, CSP, and iCSP recordings through modeling. The intent was to have a high success rate in modeling both individual and mean epochs containing MEP, CSP, and iCSP stimulus responses. The APP’s internal consistency (reliability) was compared to the Nilsson and Garvey methods for calculation of CSP duration (Garvey, et al. 2001, Nilsson, et al. 1997). Also, the E_{eff} was tested as a novel correlate to MEP and CSP responses.

METHODS

Subjects

Fourteen healthy right-handed adults (7 males; mean age 34.9, range: 21–48) participated in this study. One subject’s data was excluded due to lack of responsiveness with increasing TMS intensity, possibly due to head movement leading to stimulation of the wrong area. Prior to enrollment in this study, each volunteer was screened to exclude history of neurologic and/or psychiatric illness. Likewise, volunteers who had a history of neurologically active drug use were not enrolled in this study. Those volunteers whom passed the history screens underwent neurologic and mini mental state (Folstein, et al. 1975) examination prior to continuing in the study. Furthermore, anatomical magnetic resonance images were used to screen for cortical abnormalities prior to TMS. Hand dominance was determined using the Edinburg Inventory

(Oldfield 1971). This study was approved by the University of Texas Health Science Center at San Antonio Institutional Review Board and informed consent was obtained from all participants.

Anatomical and Functional Imaging of M1_{hand}

Magnetic resonance imaging (MRI) was done using a Siemens 3T Trio scanner with a high-resolution 8-channel head coil. T1-weighted anatomical MRIs were acquired with a retrospective motion-corrected protocol using high-resolution (isotropic 800 μ m), high GM-WM (~25%) contrast (Kochunov, et al. 2006). Additionally, sixteen contiguous functional MRI slices were acquired in a transverse plane using a T2*-weighted gradient-echo echo-planar-imaging (EPI) sequence with slice thickness of 5 mm. The in-plane resolution for the images was 2 $\times$ 2 mm². Participants performed alternating abduction and adduction of the left index finger for a total of 6 minutes in a block design, performing this activity for 30 s and resting for 30 s.

Functional MRI data was analyzed using FSL, a comprehensive library of functional and structural brain image analysis tools (Image Analysis Group, FMRIB, Oxford, UK), and a statistical parametric image contrasting the motor task with rest was created. TMS target-site (M1_{hand}) determination was based upon co-registered anatomical and functional MRIs (Lancaster, et al. 2004).

Maximum Voluntary Contraction Task

The participants performed an isometric contraction of their left first dorsal interosseous (FDI) muscle to a constant force equal to 25% of their maximum voluntary contraction (MVC) level. Each participant's force was measured as they abducted their first finger against a strain gauge (SML-10, Interface, www.interfaceforce.com). Interface's 9840 intelligent indicator was used to pass the force data to a computer monitor to provide constant visual feedback of the target MVC level.

EMG Recordings

Surface EMG for the left FDI muscle was monitored with a single pre-amplified double differential MA-411 electrode (Motion Lab Systems, Baton Rouge, LA) placed over the muscle belly. The electrode was connected to a Neuroscan SynAmps 32 channel head box and amplifier with a CMRR of 108 dB (Neuroscan, El Paso, Texas). A third Ag/AgCl disc (1 cm dia.) electrode was used as a skin ground placed on the left ulnar styloid process. EMG was band-pass filtered from 10Hz to 500Hz with a 500 $\times$ gain prior to sampling (2.5 kHz). The force and EMG data were time locked and recorded simultaneously with "Scan 4.3" acquisition software (Neuroscan, El Paso, Texas).

TMS and E_{eff}

This study used the image-guided, robotically-positioned TMS system, which integrates the cortical column cosine (C³) theory for stimulation planning, with TMS coil positioning and holding capabilities of a robotic system (Lancaster, et al. 2004). Coil pose based on the C³ aiming model (Fox et al., 2004) was determined. This orientation scheme assumes that the greatest stimulation efficiency occurs if the TMS coil's induced E-field (y-axis) is parallel to cortical columns. Multiple target sites within the cortical area of activation were created from the co-registered anatomical and functional images. EMG feedback from the left FDI was used to assess each target site. The site chosen as the final target site was the one which elicited the best MEP response at the lowest rMT.

The effective E-Field (E_{eff}) is calculated as a function of the TMS machine output (MO):

$$EF_{\text{eff}}(\text{MO}) = EF_{\text{surf}}(\text{MO}) * dM1 * \cos(\Phi) \quad (1)$$

E_{surf} represents the primary E-Field (V/m) at the coil's surface (at the scalp). The E_{surf} at various machine output levels for the Cadwell B-Shaped coil was calculated recently (Salinas, et al. 2007). The C³ planning tool reports the coordinates for the cortical region being stimulated and a depth correction factor (dM1) that accounts for the decrease in the induced E-field with distance. Likewise, the C³ planning tool provides an orientation correction factor (Φ) based on the angle between the induced E-Field and the direction to the cortical columns, which are assumed to be directed normal to the cortical surface.

A water-cooled, B-Shaped TMS coil (Cadwell, Inc, Kennewick, Washington) was used in this study. Each subject's rMT was determined using a standardized method and defined as the minimum stimulus intensity that produced a MEP greater than 100 μ V in 50% of trials during complete muscle relaxation (Rossini, et al. 1994).

Stimulus Response Profiling

MEP, CSP, and iCSP responses were elicited for ten single pulses of TMS delivered to M1_{hand} using 5–7 second inter-stimulus intervals. A 600 ms epoch of EMG from the left FDI was recorded for each TMS pulse starting 100 ms before TMS and ending 500 ms afterward. Individual epochs were rectified then time-lock averaged to produce a mean rectified epoch for 10–15 intensities. The machine output was set initially to 100% rMT and randomly ramped up or down in 5% increments. The lowest intensity delivered was the one that produced a CSP with no visible MEP (e.g. an iCSP). The highest intensity delivered was the maximum TMS machine output.

Automated-Parameterization Program

The Automated-Parameterization Program (APP) was written in Mathcad 14 (Parametric Technology Corporation). Two versions of the APP were implemented that report response parameters from either MEP-CSP complexes or iCSPs. The APP can fit and characterize both individual and mean epochs of MEP-CSP complexes and iCSPs. A display of the epoch being fit is provided for visual inspection. All epochs were visually inspected for averaging, motion, and electrical artifacts prior to fitting.

MEP

The initial portion of the MEP-CSP complex is marked by a MEP that rises well above the background pre-TMS EMG (Figure 1). The APP determines MEP onset and offset times using an inflection point searching algorithm which adapts to the MEP amplitude. The MEP onset time was defined as the inflection point on the leading edge of MEP. Similarly, MEP offset time was defined as the inflection point on the trailing edge of MEP. MEP duration (ms) is the difference in MEP onset and offset times. The MEP mean amplitude (mV) is the average MEP voltage level within this range. The MEP area (mV-ms) was calculated as the product of MEP mean amplitude and duration. Also reported are the time of the maximum peak voltage (MEP peak time) and the value at this peak (MEP peak amplitude).

CSP

The recovery portion of the MEP-CSP complex has a characteristic sigmoid-shaped curve that reflects the EMG transition from the loss of volitional activity in the CSP valley to its immediate post recovery level. This transition from the valley and into recovery can be easily modeled using a logistic population growth equation:

$$\text{EMG}(t; \text{VL}, \text{RL}, T_{1/2R}, \text{TC}_{\text{rec}}) = \text{VL} + \frac{\text{RL} - \text{VL}}{1 + e^{-\frac{(t - T_{1/2R})}{\text{TC}_{\text{rec}}}}} \quad (2)$$

In this equation, the model CSP curve is a function of time (t) and has four parameters (Figure 2): CSP valley level (VL), recovery time constant (TC_{rec}), recovery level (RL), and the time at half EMG recovery ($T_{1/2R}$). The CSP offset time was defined as $T_{1/2R}$ from Equation 2, which is the time when EMG recovers to 50% of the post-CSP recovery level.

Isolated CSP

The initial portion of an iCSP has a sigmoid-shaped curve reflecting the transition from the pre-CSP volitional EMG level to the CSP valley level. This transition into the CSP valley can be easily modeled using a logistic population decay equation:

$$\text{EMG}(t; \text{VL}, \text{PL}, T_{1/2D}, \text{TC}_{\text{dec}}) = \text{PL} - \frac{\text{PL} - \text{VL}}{1 + e^{-\frac{(t - T_{1/2D})}{\text{TC}_{\text{dec}}}}} \quad (3)$$

In this equation, the model population decay curve is a function of time (t) and has four parameters (Figure 3): pre-CSP EMG level (PL), decay time constant (TC_{dec}), CSP valley level (VL), and time at half EMG loss ($T_{1/2D}$). The CSP onset time is determined from modeled iCSPs and defined as $T_{1/2D}$ from Equation 3. Similar to other CSP modeling, the recovery portion of an iCSP is modeled using Equation 2. The iCSP duration is the difference between the iCSP onset and offset times.

Optimizing Equation Parameters

Equations 2 and 3 require the initialization of four parameters for fitting. The APP estimates initial values for the four parameters and two times that mark the beginning and end of the fit (Table 1). The APP then generates a best fit model by iteratively adjusting the parameters to minimize the least-square error between the fitted functions and the CSP data using the “Minerr” function in Mathcad. Goodness of fit is assessed using a Pearson product correlation between model and raw CSP data points.

LEPs and Multiple CSPs

From visual inspections, individual epochs with LEPs and/or multiple CSPs were identified and fit using an interactive mode in the APP. In this mode, the user adjusts the time window to model each CSP and/or LEP individually. The display of the epoch and time window is updated graphically as the user changes the initial and terminal fit times.

Adaptive, Fixed, and Epoch Fitting

The APP was used to model both individual and mean epochs of MEP-CSP complexes and iCSPs. The MEP-CSP complex’s terminal end, which includes the return of volitional EMG, was modeled using two different fit strategies that differ only by the time point used to end the fit. The adaptive fitting strategy requires that the fitted curve have an equal number of data points on either side of $T_{1/2R}$. The fixed fitting strategy used a fixed ending time point 200 ms after $T_{1/2R}$.

CSP vs. Stimulation Intensity

CSP response, assessed using model parameters, was calculated at different TMS intensities. First, response measures were grouped into lower and higher halves of stimulation intensities in each subject. Differences in the stimulus intensities delivered between individuals were handled by pairing intensities by rank. In the case of an odd number of intensities, the median intensity was omitted. The model parameters for these two groupings were compared using paired t-tests with a total of 78 pairings.

Second, a comparison was made by selecting a typical low and high stimulation intensity for each subject. The low and high intensities that all subjects received within the narrowest range were 84% (5.8 SD) and 151% (2.7 SD) rMT. The model parameters for these two intensities were compared using paired t-tests with a total of 13 pairings.

Comparison of CSP Methods

Nilsson et al. (1997) and Garvey et al. (2001) methods were used to determine CSP offset times in the data sets. Specifically, these methods were tested against the APP using ten individual epochs obtained at 100% rMT in each subject.

Nilsson's method uses a running serial student's t-test comparing EMG within the CSP to the pre-TMS EMG level to determine CSP offset time. Nilsson et al. (1997) defined CSP offset time as the time when EMG was no longer significantly different from pre-TMS EMG. For testing the Nilsson method, the pre-TMS EMG level was calculated as the average voltage in a 36 ms window centered at 58 ms prior to TMS. CSP offset time was defined as the median time point of an 8 ms window from which the window's mean voltage was not significantly different from the pre-TMS EMG at $t < 1.96$ ($p > 0.05$).

Garvey's method uses the mean consecutive difference (MCD) and pre-TMS EMG level to delineate lower variation limits to determine CSP onset and offset times. For testing the Garvey method, the pre-TMS EMG level was calculated as the average voltage in a 90 ms window from 10 – 100 ms prior to TMS. CSP offset time was defined as the time point in which the voltage exceeded the lower limit threshold as calculated using the MCD. Following Garvey's guidelines, three lower limit thresholds were determined: 1) pre-TMS EMG level – 2.66MCD, 2) pre-TMS EMG level – 2.22MCD, and 3) pre-TMS EMG level – 1.77MCD.

A repeated (two-way mixed) measure ANOVA of CSP offsets was performed using the ten individual epochs obtained at 100% rMT in each subject. This was done for each method (i.e. the APP, Nilsson, and Garvey). A Cronbach's alpha coefficient was calculated for each method and used as a measure of internal consistency (i.e. reliability) (Cronbach 1951). A two-way mixed effects ANOVA model was used to calculate the intraclass correlation coefficient (ICC) between the three methods (Shrout and Fleiss 1979). These comparisons and calculations were completed using SPSS Statistics 17.0 (www.spss.com).

Correlation of Stimulus Variables and Response Measures

Three groups of response measures were correlated with three measures of stimulation intensity to determine which estimate of TMS stimulation intensity was best suited for normalizing MEP and CSP response measures. The three groups of response measures were: (a) MEP size, (b) MEP times, and (c) CSP times. The three stimulus intensity estimates used were: (a) rMT, (b) E_{surf} , and (c) E_{eff} . The three response measures came from modeled mean epochs in all subjects and across all intensities.

RESULTS

Stimulus Response Data

Approximately 10% of the EMG waveforms were excluded following visual inspection due to the presence of various artifacts in the MEP-CSP complexes. A total of 168 mean epochs and 1715 individual epochs were available for modeling from the 13 subjects. iCSPs were seen in 12 of the 13 subjects at low intensities, accounting for 15 mean epochs and 62 individual epochs. The APP successfully modeled over 93% of all data. The total number MEPs, CSPs, and ISPs that were modeled and successfully fitted are shown in Table 2.

Adaptive, Fixed, and Epoch Fitting

The adaptive fitting strategy successfully modeled mean epochs in all 15 iCSPs compared with 11 for the fixed strategy. The adaptive strategy also had a higher fit correlation than the fixed strategy for the recovery portion of iCSPs and CSPs, Pearson correlation coefficient of .83 compared to .78 (Table 2). Similar success rates were seen for fitting of mean CSP epochs. Based on these findings the adaptive strategy was selected as the preferred method of fitting and used for all further analyses.

Individual vs. Mean Epochs

The MEP times and sizes did not significantly differ between values derived from the mean of individual epochs or from mean epochs (Table 3). In a t-test comparison, paired by intensity and subject, differences in all MEP temporal measures for mean or individual epochs remained non-significant. In contrast, the MEP area and mean amplitude were significantly lower ($p < 0.01$) in mean vs. individual epochs.

In the mean and individual epochs, the post-CSP recovery EMG level was higher than the pre-TMS EMG level, 49% for mean and 61% for individual ($p < 0.01$) (Table 4). Clearly, the recovery level for individual epochs was higher than the recovery level of mean epochs (Table 4). The recovery level of mean epochs was still 28% above the pre-TMS EMG level ($p < 0.01$) when evaluated using the 200 ms fixed fitting strategy.

The recovery time constant in mean epochs of iCSPs and CSPs were significantly longer than those in individual epochs. The recovery time constants were significantly longer ($p < 0.01$) than the decay time constants for both mean and individual epochs. The recovery and decay time constants tested solely from the iCSPs were not significantly different. The iCSP onset times in both mean (36.1 ms, 0.8 SEM) and individual epochs (36.4 ms, 0.5 SEM) were similar (Table 4).

LEPs and Multiple CSPs

LEPs were only seen in 3 subjects and spanned a range of intensities (98 – 179 % rMT). Only 35 epochs (2%) contained a LEP and multiple LEPs were not observed. The initial and terminal portions of the LEP were modeled using the logistic population growth and decay equations, respectively. All 35 LEPs were successfully modeled and had an onset latency range of 88.6 – 233.6 ms with durations between 6.5 – 36.3 ms. Generally, the second CSP had a much shorter duration (19.6 – 69.1 ms) compared to the first CSP (88.6 – 233.6 ms). EMG during the second CSP valley was less suppressed and was an average of 3 times larger than the first CSP valley level. The LEP EMG level ranged from 4.3% and 57.5 % lower than pre-TMS EMG. The post-CSP recovery level was between 10.1 and 360.9 % higher than the LEP EMG level and between 13.9 and 247.1% higher than pre-TMS EMG.

Comparison of CSP Methods

All automated methods were able to determine CSP offset times in over 89% of the epochs (Table 5). The Nilsson method reported a CSP offset time for every epoch in all subjects; the APP did this for 8–10 epochs per subject, and the Garvey method in 7–10 epochs per subject. Only the results using the lowest limit (1.77MCD) from the Garvey method are reported as it had the greatest number of successful calculations. The Garvey method could not calculate CSP offset times in any of the ten epochs of Subject 8. In general, the APP reported later CSP offset times than those determined by the Garvey or Nilsson methods.

The APP had the highest internal reliability (Cronbach's $\alpha = 0.99$) followed by Nilsson (0.94) and Garvey (0.85). The associated repeated measure ANOVAs show no significant differences within each method's calculated CSP offset times ($n = 130$, $F < 2.0$, $p > 0.04$). The ANOVA between methods used to determine the ICC indicated that each method calculated unique sets of CSP offset times from the same data ($n = 130$, $F > 3.2$, $p < 0.001$). The APP had the highest ICC with Nilsson's method (0.83) and lowest ICC with Garvey's method (0.52). The ICC between the Nilsson and Garvey methods was of 0.56.

The CSP offset times calculated by Nilsson and Garvey methods corresponded to $79.4 \pm 26.3\%$ and $80.1 \pm 16.1\%$ of the pre-TMS EMG level. The APP was designed to adapt to the recovery levels and report offsets at a consistent fraction of recovery independent of pre-TMS EMG levels. While the CSP offset time for APP was at 50% of the immediate post EMG recovery level, the Nilsson method reported offsets that were slightly lower at $48.8 \pm 31.1\%$ of the post-CSP recovery level. Similarly, Garvey's method calculated offsets that were much lower at $38.1 \pm 27.9\%$ of the post-CSP recovery level.

CSP vs. Stimulation Intensity

Varying stimulation intensities led to a varying CSP offset times (Table 6), ranging from 47.1 and 347.7 ms. However, high intensities did not cause significant differences in the valley level. The recovery level increased and the recovery time constant was longer at higher intensities, but neither was statistically significant.

Correlation of Stimulus and Response Variables

In general, MEP temporal measures (onset, peak time, offset, and duration) remained stable with increasing stimulus intensity (Table 7A), especially for intensity gauged using E_{eff} . MEP offset time and duration had large positive correlations with rMT and E_{surf} , and both were significantly correlated with rMT.

The time-locked averages of un-rectified epochs were used to create mean un-rectified epochs for MEP peak-to-peak amplitude. Unlike temporal measures, all MEP size measures (peak amplitude, mean amplitude, peak-to-peak amplitude, and area) correlated significantly with all three TMS intensity measures (Table 7B). This correlation was lowest for rMT and highest for E_{eff} .

iCSP onset and offset times were relatively stable with increasing stimulation intensity (Table 7C). A non-significant shortening of the iCSP onset time with increasing stimulation intensity was observed relative to rMT. Conversely, a non-significant lengthening was observed relative to E_{eff} . A non-significant lengthening of the iCSP offset time was seen with increasing stimulation intensity and had the highest correlation relative to rMT. CSP offset times had the highest correlation with all estimates of TMS stimulation intensity; however, it correlated best with rMT, and even machine output (equivalent to E_{surf}) showed a higher correlation than E_{eff} . A small significant correlation was measured between MEP durations and CSP offset times ($r = 0.26$, $p < 0.001$).

DISCUSSION

Image-Guided, Robotically-Positioned TMS System

The use of anatomical and functional MRI has improved the accuracy of identifying the target sites and the precision of TMS coil positioning (Krings, et al. 2001, Sparing, et al. 2008). Imaging combined with the robotic arm allows for quick and accurate repositioning of the TMS coil between and within sessions as well as holding in place during sessions. Furthermore, imaging provides the depth of M1 and orientation of the cortical columns. Most clinical studies do not need calculate the induced E-field via the C^3 model. A correction for the depth of the targeted site is however recommended. However, modeling can be done without an MRI, and the recommended stimulus intensity would then be machine output (which directly relates to E_{surf}) or rMT.

Automated-Parameterization Program

The APP accepts a variety of data files and must contain the fields of time and EMG voltages. In standard mode, the APP models a single epoch in approximately 30 s on a PC (3.4 GHz Pentium 4, 2.0 GB RAM) running Microsoft Windows XP. Time needed for visual inspection of data within the APP can vary with the user's experience at analyzing MEP, CSP, LEP, and iCSP waveforms. In batch mode, the graphics are bypassed and 20 waveforms (either individual or mean epochs) run in 30 s. The limit can be increased to run a higher number of epochs. As an example, the 168 mean epochs from the 13 subjects took the APP about two hours to run including visual inspection of every fit. All parameters can be exported and formatted for analysis through the built-in Microsoft Excel module or into another statistical package. The short time requirement to model large data sets supports the practical use of the APP in both research and clinical environments. The APP is being developed to run "live" as data is captured.

The logistic population decay and growth equations in the APP were chosen because they allow for the saturation of an effect by a fixed number of neurons. In particular, EMG growth and decay is limited by the number of neurons in the target population that can be recruited or inhibited. The logistic population decay and growth equations can model the maximum and minimum EMG levels (i.e. pre-TMS EMG, CSP valley, and post-TMS EMG) and the transitions between them using time constants. The Boltzman equation (Press et al. 1986 and Devanne et al. 1997) was considered since it matched the characteristic sigmoid-shape of the CSP in rectified EMG. For modeling using the Boltzman equation, the EMG response amplitude is a function of TMS intensity. Time could be substituted for TMS intensity in this equation, and if this is done, the denominators of the Boltzman and logistic population decay and growth equations would be near identical. However, the Boltzman equation uses only the post-transition EMG response as a fit parameter, while the logistic population decay and growth equations include both the pre- and post-transition levels as fit parameters. The logistic population decay and growth equations readily fit the natural trends of the CSP and provide essential parameters for its characterization.

Individual vs. Mean Epochs

The logistic population decay and growth equations successfully modeled the response of compound motor action potentials during the CSP as a function of time. As such these equations approximate the mean epoch that would result from time-lock averaging a large number of identical individual epochs with low SNR. The goodness of fit improved for mean epochs with improved SNR (Table 2). However, modeling provided with the APP lessens the requirement for the analysis of mean epochs as it can be used to approximate the mean epoch from an individual epoch. Furthermore, modeling of multiple individual epochs provides a means to assess variability within a trial.

In general, mean modeled epochs were similar to individual modeled epochs, but were susceptible to averaging effects secondary to within trial variability. Variability between individual epochs led to reduce EMG amplitude and smoothing of CSP decay and recovery slopes in mean epochs. These averaging effects led to lowering of MEP area, MEP mean amplitude, and the post-CSP recovery level. Smoothing of the recovery slope from averaging of individual epochs resulted in the lengthening of recovery time constant in mean epochs. Fortunately, the APP can be used to model individual epochs to avoid the averaging effects seen in mean epochs.

Analysis of the decay and recovery time constants in individual epochs revealed a longer transition of EMG during recovery than during the initiation of the CSP for both individual and mean epochs. However, the difference between recovery and decay time constants was less in individual epochs (Table 4). The rapid decay of volitional activity into the CSP valley suggests a coherent action of the inhibitory elements that contribute to the beginning of the CSP. This seems to agree with similar coherent TMS-induced activation of the neuronal elements at the MEP onset and peak times. In contrast, the volitional recovery slope appears to be shallower and less coherent than the decay. This would be expected as the volitional recovery should be independent of the TMS-induced coherence.

Post-CSP Recovery Level

Both mean and individual epochs showed a significantly higher immediate post-CSP recovery level compared to the pre-TMS EMG level. The fixed and adaptive time fit strategy both measured an increase of immediate (30–100 ms) post-CSP EMG above the pre-TMS level. This so-called “rebound” has been noted by investigators as a period of facilitation secondary to an increase in single motor unit firing probabilities of similar durations (50 – 150 ms) (Calancie, et al. 1987, Holmgren, et al. 1990, Mills 1988, Wassermann, et al. 1993).

The physiologic process which governs the post-CSP recovery level rebound is not well understood. A motor reaction to the TMS sound has been reported to contribute additional activity during post-CSP recovery (Cantello, et al. 1992). This reaction has been described as a “startle” response to TMS that can be seen in active and resting muscles (Calancie, et al. 1987, Holmgren, et al. 1990). This explanation is not supported by this study’s data or TMS auditory reaction time experiments. Pascual-Leone and his colleagues (1992) found that the earliest EMG reaction to the TMS sound occurred at 87.7 ms at maximum stimulator output. This reaction time was later (154.8 ms) in sub-threshold trials (Pascual-Leone, et al. 1992). These data suggest that the EMG motor reaction for high intensity stimulations would occur early in the CSP rather following the recovery at 200-plus ms (Table 6B). Also, the EMG reaction for sub-threshold trails would occur well beyond the CSP recovery time at around 80 ms. Finally, our study did not demonstrate a significant difference in the recovery level for sub- and supra-threshold intensities (Table 6B).

The perception of the CSP contraction pause has also been suggested to cause the rebound of additional effort during post-CSP recovery (Säisänen, et al. 2008). The perception of the contraction pause infers the conscious knowledge of the mechanical unloading of muscle spindles and golgi tendon organs following the silence of EMG. Subjects did not report knowledge of the contraction cessation caused by the CSP. However, neither an involuntary nor voluntary reaction to the contraction pause would likely arrive at a time early enough to influence the level of EMG recovery, especially in short duration CSPs (Mathis, et al. 1999). Proprioceptive input following a muscle twitch is claimed to play no major role in the CSP (Inghilleri, et al. 1993). If the stretch reflex was evoked by a TMS induced muscle twitch, it might be observed as a breakthrough of the EMG within the CSP, similar to the LEP. This breakthrough would have a fixed latency secondary to stable CSP onset and conduction times in individuals. Breakthroughs at fixed time were not observed. Furthermore, the post-CSP

rebound was also seen in iCSPs where no MEP was present. This argues against the activation of muscle spindles as the mechanism for the rebound (Holmgren, et al. 1990).

The immediate increase in post-CSP EMG could be the result of long-lasting excitatory and inhibitory processes competing for dominance in active muscle (Holmgren, et al. 1990). The binding of the inhibitory neuro-transmitter GABA at the GABA_B receptor site is thought to contribute to the CSP and disrupt volitional activity (Irlbacher 2006, McDonnell, et al. 2006, Werhahn, et al. 1999, Ziemann 2004). During volitional activity an efferent copy of the motor program is sent to cortical centers downstream which act as comparison centers (Kelso 1982). In this scenario, the CSP registers as a mismatch to the efferent copy of the volitional target level. Pre-motor areas would compensate for the loss in volitional activity by increasing cortical drive that release additional excitatory neuro-transmitters at M1. A resulting surge in excitatory activity would occur upon the clearance of GABA_B. In contrast, the same efferent copy mismatch could result in a decrease in GABA_B release causing a surge of excitatory potentials. In either case, the return of the volitional activity to pre-TMS levels occurred at latest, 200 ms post-CSP. If this were the mechanism, it indicates that the total time course for downstream comparison centers to reset volitional activity to the target level in the midst of inhibitory competitors.

LEPs and Multiple CSPs

A LEP with small amplitude and/or duration may be averaged out when fitting to the model equations. Similarly, small motion and electrical artifacts are suppressed within the CSP. However, the user of the APP may determine that a breakthrough signal within the CSP is a LEP and can run the APP in an interactive mode.

An LEP was observed in only 2% of the individual epochs. Data containing LEPs were excluded from the formal MEP, CSP, and iCSP analyses. LEP modeled parameters were comparable with results of studies which focused on LEPs (Holmgren, et al. 1990, Wilson, et al. 1995). LEP onset latencies (88.6 – 233.6 ms) determined from modeled data were similar to the ranges (50 – 114 ms) seen by Holmgren et al. and Wilson et al.

Comparison of CSP Methods

Together the repeated measure ANOVAs and Cronbach's alphas are indicators of the methods' internal consistency (reliability). CSP offset times from ten individual epochs per subject at the same TMS intensity were used as measures in the test-retest analysis. Test-retest analysis between TMS sessions (i.e. over days) would require the repositioning of the TMS coil and surface EMG potentially adding to the total methodological error. Furthermore, test-retest analysis between TMS sessions would not isolate the reliability of the APP. Variability in the subject's task performance could affect the APP reliability; even in this single-session, repeated measure design. However, all methods (the APP, Nilsson, and Garvey) had a high internal reliability (Cronbach's Alpha > 0.85) with the highest reliability measured for the APP (0.99). These data indicate that subjects' task performance and this study's method for eliciting the CSP is very reliable.

By definition, $T_{1/2R}$ is the time when EMG recovers to 50% of the immediate post-CSP recovery level. The CSP offset time determined at $T_{1/2R}$ from the APP had the least variability among all methods (Table 5). $T_{1/2R}$ is independent of the recovery slope, which can vary with averaging or at various intensities, making it a robust landmark for the end of the silent period. This landmark time point readily adapts to varying post-CSP recovery levels and does not depend on pre-TMS EMG levels.

Daskalakis, et al. (2003), Garvey, et al. (2001), King, et al. (2006), and Nilsson et al. (1997) calculated CSP offset times using the pre-TMS EMG. In this study, post-CSP EMG recovered to a broad range of pre-TMS EMG levels spanning from below to above pre-TMS levels. If post-CSP EMG did not recover to pre-TMS levels CSP offset times for the Nilsson or Garvey methods were indeterminate. In other cases, CSP offset times using the Nilsson and Garvey methods appeared to be from signal artifacts within the CSP leading to a shortened offset times. As a result, average CSP offset times were longer than those from either the Nilsson or Garvey methods (Table 5). The APP modeling method was robust against these problem cases, and correlated best ($ICC = 0.83$) with Nilsson's method. Due to their definitions of CSP onset and offset times, each method reports a different CSP duration. Nilsson defined the CSP onset time as the time point where the EMG fell two standard deviations below the mean pre-TMS EMG. Garvey defined CSP onset time as the first of 5 consecutive time points that fell below a pre-TMS EMG limit. However, true CSP (iCSP) onset time can only be seen without the presence of an MEP. In this modeling study, the mean iCSP onset time occurred at 36.1 ms post TMS, approximately 14.5 ms (0.3 ms SEM) after the average MEP onset time and before the average MEP offset time. As such, the iCSP onset time is the earliest onset latency that can be measured. CSP duration calculated using iCSP onset time is believed to be more physiologically appropriate than duration by other methods.

CSP vs. Intensity

CSP offset time was the only silent period measure that was significantly influenced by TMS intensity (Table 6). Its increase is well documented in the literature (Säisänen, et al. 2008, Werhahn, et al. 2007). The recovery time constant lengthened at higher intensities, but the difference was not statistically significant. This lengthening may be due to a decrease in the coherence of the volitional recovery with increasing intensity for individual epochs. A decrease in coherence would decrease the recovery slope and increase the recovery time constant, but should have minimal effect on the CSP offset time measured at $T_{1/2R}$.

Correlation of Stimulus and Response Variables

We found, in agreement with other studies (Devanne, et al. 1997, Lavoie, et al. 1995), that both MEP peak-to-peak amplitude and area are highly correlated with TMS intensity. MEP area correlated higher with all estimates of TMS intensity than MEP peak-to-peak amplitude. However, no significant difference was seen between the correlations of MEP area and peak-to-peak amplitude with E_{eff} . This result indicates that stimulus intensity corrected for depth of targeted neurons and orientation of the E-field is more directly related to MEP responses than the more traditional methods.

While rMT remains a common measure of cortical excitability and a means to normalize TMS intensity across subjects, it is subject to variability. Tissue volume conduction differences under surface EMG electrodes can affect the amplitudes of the muscle responses between subjects. Thus, using a universal MEP amplitude (50 or 100 μV) may not be the best method for determining the rMT. Also, EMG of the target muscle is the only measure used to ensure a resting state. EMG of the target muscle cannot reflect mental anticipation and/or contractions of neighboring muscle which may alter the MEP response. Furthermore, rMT may not be consistent longitudinally. The rMT can vary by time of day and level of alertness. E_{eff} strictly confines the estimate of stimulation "dose" to cortical elements that are congruent with the induced E-Field at cortical depths that do not change within an individual. Additionally, E_{eff} does not have a cortical excitability component and thus is not influenced by variability in excitability between and within subjects.

The higher correlation between CSP offset time and rMT rather than E_{eff} could be explained by the nature of rMT. The rMT can account for depth but not cortical column orientation, so

both target neurons as well as cortical inhibitory ones are assumed to receive similar stimulus intensities. Thus, a higher correlation with rMT might be expected with CSP offset time if inhibition arises from activations in a larger volume surrounding the target neurons. Even machine output (or E_{surf}) correlated higher with CSP offset time than E_{eff} (Table 7), and machine output is neither depth nor orientation corrected

The current consensus is that stimulus response graphs for CSP duration use either machine output or the CSP threshold to normalize the TMS intensity axis (Wolters, Ziemann & Benecke, 2008). In healthy normal subjects, the inhibitory elements contributing to the CSP are recruited at lower machine output settings than the excitatory elements (Werhahn et al., 2007). The findings support the use of the machine output and rMT as an estimate for TMS intensity in healthy, non-medicated individuals. Yet, the thresholds for the MEP and CSP can be influenced by drug-use and/or disease (Ziemann, 2004; Chen, 2008) and may influence the use of these thresholds in the construct of MEP and CSP stimulus response curves. E_{eff} is unaffected by drug-use and/or disease in individuals making it the stimulus measure of choice for stimulus response studies of both MEP and CSP in this population. It must be emphasized that E_{eff} is a calculation of the effective E-field, not a change in machine settings. The calculation is based on machine output as well as orientation and depth of targeted cortical columns. Machine output is directly related to the E-field at the scalp (E_{surf} in Table 7). Orientation and scalp positioning similar to that used in this study can be approximated by iterative movement and rotation of the TMS coil to find the maximum EMG response for the target muscle. However, depth which varied from 18.6 mm to 32.8 mm accounts for a wide range of variability in E-field at the target site (21.6% to 37.8% of E_{surf}). This is a bit more complex but information regarding drop off of E-field with depth has been published for many TMS coils (Salinas, et al., 2008) or can be obtained from the coil manufacturer. It is recommended that users attempt to obtain at least an anatomical MRI to determine depth.

Limitations

This modeling study was part of a motor learning study targeting the non-dominant hand and motor cortex. While the stimuli and responses reported here are for the non-dominant motor cortex, this should not affect the use of the proposed models.

In pilot work, response measures were seen to be highly dependant on the task. Visual feedback of muscle force was provided in order to increase the consistency of subject's performance. Subjects practiced and were instructed to maintain the same level of force while all 10 stimuli were administered. TMS induced movement of the target hand and/or limb could cause a break in subject's task performance. Likewise, muscle supplementation during the task could result in achievement of the target force with variable effort from the target muscle. A post-hoc analysis was performed and both the force and the associated FDI muscle EMG returned to target levels prior to the next stimulation.

Subjects were not required to perform at various levels of MVC. At this time, it is not known how CSP duration and the immediate post-CSP recovery will be affected by changing levels of MVC. Yet, a large number of studies (Haug, et al. 1992, Inghilleri, et al. 1993, Roick, et al. 1993, Säisänen, et al. 2008, Taylor, et al. 1997, Wu, et al. 2002) indicated that CSP duration is independent of the level of muscle activation.

Finally, emphasis should be placed on the fact that this study was performed with healthy, non-medicated volunteers. It is unclear how these modeling techniques will work with MEP, CSP and iCSP data from individuals with disease and/or using medication.

Conclusion

The proposed models provided a means to automate and more fully characterize MEP, CSP, and iCSP responses. This was done with a high modeling success rate (over 93%) for both individual and mean epochs. The APP modeling method had the highest internal consistency (reliability) for determining CSP_{off} times when compared to the Nilsson and Garvey methods. The E_{eff} was the best stimulus measure for MEP responses, and will be robust against conditions that affect rMT such as medications. The measurement precision from the models within the APP supports their use in other fields, such as with normal kinesiological measures of EMG for electrophysiologic characterization of movement.

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List of Abbreviations

APP, Automated-Parameterization Program; C³, Cortical Column Cosine; CSP, Cortical Silent Period; E_{eff}, Effective Electrical Field; iCSP, Isolated Cortical Silent Period; LEP, Late Excitatory Potential; MEP, Motor Evoked Potential; rMT, Resting Motor Threshold.

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Figure 1.
The MEP-CSP complex in a mean rectified epoch shown with regions of interests.

Figure 2.

A graph showing the fitted logistic population growth curve (solid line) to the CSP valley level, recovery slope, and recovery level for a mean rectified epoch (dotted line).

Figure 3.

A graph showing the fitted logistic population decay curve (solid line) to the pre-CSP EMG, decay slope, and CSP valley of an individual rectified epoch with an iCSP (dotted line). Also shown is the fitted logistic population growth curve to the CSP valley level, recovery slope, and recovery level.

Table 1

Initial values used to seed the (A) logistic growth equation and (B) logistic decay equation.

	Parameters	Initial Values
A.	Fit Start	Leading time point of 8 ms running window from 30–120 ms with lowest mean voltage
	TC _{rec}	2 ms
	VL	Minimum voltage in the fit range
	RL	Average voltage from Fit Start to last data point; Reinitialized to average voltage from T _{1/2R} to last data point once T _{1/2R} initialized
	T _{1/2R}	first time point after Fit Start where EMG exceeds the first initial value of RL
	Fit Stop	Equal to T _{1/2R} plus time difference between the start of fit and T _{1/2R}
B.	Fit Start	6 ms after TMS stimulation
	Fit Stop	Trailing time point of 8 ms running window from 30–120 ms with lowest mean voltage
	TC _{dec}	2 ms
	VL	Minimum voltage in the fit range
	PL	Average voltage in Fit Range; Reinitialized to average voltage from Fit Start to T _{1/2D} once T _{1/2D} initialized
	T _{1/2D}	First time point after Fit Start where EMG falls below the first initial value of RL

Table 2
The number of mean and individual epochs modeled using the APP. Also shown are the number of successful model fits and the corresponding Pearson correlation coefficients.

Fit Strategy	MEP # (Success #)	CSP # (Success #)	iCSP # (Success #)	iCSP Decay Corr. (SEM)	iCSP/CSP Recovery Corr. (SEM)
Mean Epochs [Adapt]	159 (154)	153 (145)	15 (15)	0.76 (0.02)	0.83 (0.01)
Mean Epochs [Fixed]	159 (154)	153 (150)	15 (11)	0.76 (0.02)	0.78 (0.01)
Indiv. Epochs [Adapt]	1527 (1486)	1595 (1536)	62 (58)	0.70 (0.01)	0.63 (0.01)

(SEM) denotes the standard error of the mean for the given measures.

Table 3
MEP measurements from mean (n = 154) and individual (n = 1486) epochs.

	Onset Time (ms)	Peak Time (ms)	Offset Time (ms)	Duration (ms)	Mean Amp. (mV)	Area (mV·ms)
Mean Epochs	22.1 (0.2)	29.0 (0.2)	42.5 (0.4)	20.4 (0.4)	0.657 (0.034)	12.835 (0.628)
Indiv. Epochs	22.4 (0.1)	29.2 (0.1)	42.5 (0.1)	20.1 (0.1)	0.694 (0.012)	13.128 (0.208)

Values in () denote the standard error of the mean for the given measures.

Model parameters and measurements from mean epochs with CSP (n = 145) and iCSP (n = 15) compared to individual epochs with CSP (n = 1536) and iCSP (n = 58).

	Pre-TMS Level (mV)	Valley Level "VL" (mV)	*Recovery Level "RL" (mV)	CSP Offset Time (ms)	iCSP TC _{dec} (ms)	*iCSP/CSP TC _{rec} (ms)	iCSP Onset Time (ms)	iCSP Offset Time (ms)
Mean Epochs	0.065 (0.003)	0.008 (0.000)	0.097 (0.005) _–	179.5 _– (5.5)	0.8 (0.2)	4.3 (0.4) _–	36.1 _– (0.8)	74.4 _– (2.9)
Indiv. Epochs	0.067 (0.001)	0.007 (0.000)	0.108 (0.003) _–	181.6 _– (1.6)	0.7 (0.1)	2.0 (0.1) _–	36.4 _– (0.5)	78.3 _– (2.4)

Values in () denote the standard error of the mean for the given measures. Significance differences determined from un-paired t-tests.

* indicates p < 0.01

Table 5

Comparison of mean CSP Offset Time (ms) with standard deviations (SD) for each subject at 100% rMT using three automated methods.

Methods	APP			Nilsson			Garvey		
	T _{1/2R}			P > 0.05			1.77 MCD		
Subject	Success	Mean	SD	Success	Mean	SD	Success	Mean	SD
1	10	203.5	8.9	10	176.4	39.0	10	101.8	13.6
2	10	141.2	28.6	10	133.6	32.5	10	126.0	33.2
3	9	165.8	14.3	10	155.8	10.5	10	149.8	6.4
4	8	107.1	17.7	10	106.5	16.4	10	102.2	5.0
5	10	193.2	20.3	10	165.3	33.8	7	153.5	38.8
6	10	197.6	8.0	10	187.8	13.5	9	171.1	15.2
7	8	95.2	6.2	10	88.5	5.7	10	88.0	5.0
8	10	196.0	8.8	10	150.9	56.5	0	n/a	n.a
9	10	108.8	18.2	10	92.7	14.7	10	102.6	13.7
10	9	215.7	18.7	10	203.2	25.2	10	134.4	49.2
11	9	151.4	30.2	10	152.0	28.6	10	147.5	25.6
12	9	95.4	9.0	10	90.6	9.6	10	89.6	7.5
13	10	203.2	20.5	10	197.4	19.1	10	145.8	39.6
Mean	9.4	159.5	16.1	10.0	146.2	23.5	8.9	126.0	21.1
SD	0.8	45.6	7.8	0.0	40.9	14.4	2.8	28.2	15.6

CSP model parameters at low and high TMS intensities in the mean epochs. **(A)** The mean values for the lower half of the intensities were paired (n = 78) against the higher half in each subject. **(B)** The values at the intensity closest to 84% rMT were paired (n = 13) against the intensity closest to 151% rMT in each subject.

Table 6

Intensities	Valley Level (mV)	Recovery Level (mV)	* CSP _{off} (ms)	TC _{rec} (ms)
A.	Lower 1/2	0.009 (0.001)	128.4 (6.2)	3.6 (0.4)
	Higher 1/2	0.007 (0.001)	231.1 (4.3)	5.0 (0.6)
B.	84% rMT	0.008 (0.002)	77.5 (6.4)	2.2 (0.9)
	151% rMT	0.007 (0.001)	225.8 (9.5)	4.9 (1.0)

Values in () denote the standard error of the mean for the given measures.

* indicates p < 0.01

Table 7

Correlation of three response measures A–C with three stimulus intensity measures. (A) MEP timing, (B) MEP size, and (C) CSP timing.

	Response Measures	Stimulation Intensity Measures		
		rMT	E _{surf} (V/m)	E _{eff} (V/m)
A.	MEP Onset Time	0.05 ₋	-0.10 ₋	-0.01 ₋
	MEP Peak Time	0.00 ₋	-0.06 ₋	0.06
	MEP Offset Time	0.26 [*]	0.22 ₋	0.10
	MEP Duration	0.25 [*]	0.28 [*]	0.11
B.	MEP Peak Amp.	0.33 [*]	0.35 [*]	0.45 [*]
	MEP Mean Amp.	0.28 [*]	0.31 [*]	0.46 [*]
	MEP Peak-to-Peak	0.24 [*]	0.35 [*]	0.50 [*]
	MEP Area	0.37 [*]	0.43 [*]	0.52 [*]
C.	iCSP Onset Time	-0.24 ₋	-0.24 ₋	0.33 [*]
	iCSP Offset Time	0.35 ₋	0.26 ₋	0.13 [*]
	CSP Offset Time	0.85 [*]	0.80 [*]	0.76 [*]

Significant of correlation determined from the probable difference from the Null (Pearson Correlation coefficient, $r = 0$). MEP: $n = 154$, CSP: $n = 145$; iCSP: $n = 15$

* indicates $p < 0.01$