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Pulse width dependence of motor threshold and input–output curve characterized with controllable pulse parameter transcranial magnetic stimulation

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Abstract

Objective—To demonstrate the use of a novel controllable pulse parameter TMS (cTMS) device to characterize human corticospinal tract physiology.

Methods—Motor threshold and input-output (IO) curve of right first dorsal interosseus were determined in 26 and 12 healthy volunteers, respectively, at pulse widths of 30, 60, and 120 μ s using a custom-built cTMS device. Strength–duration curve rheobase and time constant were estimated from the motor thresholds. IO slope was estimated from sigmoid functions fitted to the IO data.

Results—All procedures were well tolerated with no seizures or other serious adverse events. Increasing pulse width decreased the motor threshold and increased the pulse energy and IO slope. The average strength–duration curve time constant is estimated to be 196 μ s, 95% CI [181 μ s, 210 μ s]. IO slope is inversely correlated with motor threshold both across and within pulse width. A simple quantitative model explains these dependencies.

Conclusions—Our strength–duration time constant estimate compares well to published values and may be more accurate given increased sample size and enhanced methodology. Multiplying the IO slope by the motor threshold may provide a sensitive measure of individual differences in corticospinal tract physiology.

Significance—Pulse parameter control offered by cTMS provides enhanced flexibility that can contribute novel insights in TMS studies.

Keywords

transcranial magnetic stimulation; pulse width; motor threshold; strength–duration curve; time constant; rheobase; input–output curve; slope

Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive technique for probing and modulating brain function. For example, it is widely used for assessing excitability changes in the human motor system in health and disease with measures including motor threshold and input–output (IO) curve (also known as recruitment or stimulus–response curve) (Boroojerdi et al., 2001; Devanne et al., 1997; Groppa et al., 2012; Pitcher et al., 2003). These measures quantify the relationship between the TMS pulse amplitude and the motor evoked potential (MEP) strength. The MEP strength also depends on other pulse parameters such as the pulse width. This dependence may provide additional information about the properties of the stimulated neural populations, but it has not been fully explored.

Briefer TMS pulses are associated with higher motor threshold but lower energy (Barker et al., 1991; Kammer et al., 2011; Rothkegel et al., 2010). The dependence of motor threshold on the pulse width is typically described by a strength–duration curve that is parameterized by rheobase and time constant (or, alternatively, chronaxie) (Geddes, 2004; Geddes and Bourland, 1985; Lopicque, 1907). Barker et al. (1991) estimated the strength–duration time constant for both cortical and peripheral magnetic stimulation to be about 150 μ s. No TMS study has estimated strength–duration rheobase.

The strength–duration curve parameters could be useful in characterizing the physiology of the stimulated neurons. For example, studies with electrical stimulation of peripheral nerves have shown significant changes in the strength–duration rheobase and/or time constant in various neurodegenerative disorders (Farrar et al., 2011; Lin et al., 2011; Moldovan et al., 2012). The peripheral strength–duration rheobase and time constant are also affected by therapeutic interventions (Lin et al., 2011) and could therefore serve as putative biomarkers of therapeutic action to screen novel interventions.

Compared to the motor threshold, the IO curve provides more extensive information about the relationship between the stimulus strength and the MEP size, but the effect of the TMS pulse width on the IO curve characteristics is relatively unexplored. Rothkegel et al. (2010) observed that the IO curve is invariant at two different (but closely spaced) pulse widths if normalized to the individual motor threshold. Since the motor threshold varies with pulse width, this result suggests that the IO curve characteristics change with pulse width as well, but this hypothesis was not tested directly. Indeed, measurements of the IO curve with peripheral electric stimulation of the ulnar and median nerves show steeper slopes for long versus short pulse durations (Boerio et al., 2008). However, the mechanism of IO slope dependence on pulse width or motor threshold has not been explained.

Thus, characterizing the effect of stimulus pulse width on cortical excitability measures could provide novel information about the underlying physiology as well as biomarkers for brain based disorders and therapeutic interventions. Conventional TMS devices, however, generate only damped cosine electric field pulses with non-existent or very limited pulse width selection (Peterchev et al., 2008a; Peterchev et al., 2011a). Consequently, the few studies of the effect of TMS pulse width used either a modified TMS device with mechanically reconfigurable capacitor bank (Barker et al., 1991), a conventional device with two closely spaced pulse widths (Rothkegel et al., 2010), or two different devices connected

to the same coil (Kammer et al., 2011). The technical limitations of these approaches impede wider exploration of the role of pulse width in TMS applications.

To address these limitations of TMS technology we developed a controllable pulse parameter TMS (cTMS) device that induces efficient near-rectangular electric field pulses with parameters, including pulse width, that are adjustable over a wide continuous range (Huang et al., 2009; Peterchev, 2011; Peterchev et al., 2008a; Peterchev et al., 2011a; Goetz et al., 2012b). The expanded pulse width control of the cTMS device enables rapid switching among a wide range of pulse widths, allowing simultaneous, interleaved acquisition of the motor thresholds and IO curves for different pulse width conditions. The wide range and interleaving of pulse widths could potentially permit higher estimation accuracy for pulse-width-dependent measures.

In this paper we present data from the first study of cTMS in humans. We characterize the pulse width dependence of the resting motor threshold and the pulse energy at threshold, and estimate the strength–duration curve time constant and rheobase. We also explore the effect of pulse width on the IO curve. We introduce a simple quantitative model that explains the dependence of the IO curve slope on the pulse width and the individual motor threshold. Finally, we propose the IO slope $\times$ motor threshold product as a potentially sensitive measure of individual differences in corticospinal tract physiology.

Methods

Subjects

The New York State Psychiatric Institute/Columbia University Investigational Review Board approved this study. Volunteers between the ages of 18–50 were recruited and after giving written informed consent underwent medical and psychiatric screening using standardized interviews and medical and neurological examination. Subjects were screened to exclude history of any Axis I psychiatric disorders including substance abuse or dependence as determined by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-NP). Subjects were screened by a physician for history of neurological disease or seizure risk factors, including medications known to lower seizure threshold. Subjects were also screened with urine toxicology tests and, for women of childbearing capacity, urine pregnancy tests.

Two subjects (22 and 23 year old females, 1 left-handed) had very high motor thresholds that were above the device output limit for one or more of the three stimulus pulse widths. Therefore, the participation of these two subjects in the study was terminated. The remaining 26 subjects completed the motor threshold portion of the study (18 female, age range = 19–49 years, mean $\pm$ SD = 28 ± 7 years, 2 left-handed). In a subgroup of 12 subjects, we also measured IO curves (7 female, age range = 19–49 years, mean $\pm$ SD = 30 ± 8 years, 2 left-handed).

Transcranial magnetic stimulation session

The study reported in this paper was part of a larger study conducted in a single session. To evaluate potential side effects of cTMS, before and after the complete TMS session subjects were given a side effects checklist and a computerized five-item visual analog scale characterizing mood (sadness, nervousness, happiness, anger, tiredness). The subject was seated in a chair, and the subject's head was supported by a head rest and stabilized between the TMS coil and a padded bracket countering the coil pressure. The TMS session consisted of motor threshold determination, IO curve measurement, and single-pulse stimulation of the dorsolateral prefrontal cortex (data to be reported in separate paper), always administered in that order.

Transcranial magnetic stimulation device

The study used a custom built cTMS device that generates monophasic pulses with independent control of the pulse amplitude and pulse width (Peterchev et al., 2008a). The energy storage capacitance was $C = 777 \mu\text{F}$. The cTMS device was connected to a commercial 70 mm figure-8 coil with inductance $L = 16.35 \mu\text{H}$ (P/N 9925-00, Magstim Co., Spring Gardens, Whitland, Carmarthenshire, UK) (The Magstim Company Ltd, 2003). The device was controlled with an NI PCI-7831R control/acquisition board running a custom LabVIEW program (National Instruments, Austin, TX).

As in conventional TMS devices, the cTMS pulse amplitude is controlled by adjusting the energy-storage capacitor voltage, V_C , since the electric field pulse amplitude is directly proportional to the capacitor voltage. The maximum capacitor voltage was 1,984 V, corresponding to maximum pulse amplitude. For reference, the maximum capacitor voltage, corresponding to maximum output, is approximately 1,650 V and 2,800 V for the Magstim Rapid and Magstim 200, respectively (Jalinous, 2002; Peterchev et al., 2008a). The electric field pulse amplitude is reported as percent of the maximum amplitude (% MA). The delivered pulse amplitude error was less than 1.8% MA (SD = 0.26% MA).

The pulse width and interpulse timing were controlled with the digital control board with accuracy of $0.1 \mu\text{s}$ (Peterchev et al., 2011a). We explored three pulse widths, $t_p = 30, 60,$ and $120 \mu\text{s}$, illustrated in Fig. 1. The pulse width was defined as the duration of the initial electric field phase, equal to the magnetic field rise time. Longer pulse widths were not explored since the discharge of the stimulator capacitor resulted in a cosine decay of the electric field intensity so that pulses longer than about $120 \mu\text{s}$ did not contribute additional neural membrane depolarization (Peterchev et al., 2008a).

Electromyography

Motor evoked potentials (MEPs) were recorded using electromyography (EMG) of the right first dorsal interosseous muscle. EMG was measured using a bioamplifier (BIOAMP-4, SA Instrumentation Co., San Diego, CA) with a gain of 1,000 and bandwidth of 30–1,000 Hz, and digitized at a rate of 4,000 Hz using the NI PCI-7831R board and custom LabVIEW programs. The recorded data were processed in MATLAB including baseline subtraction to remove any amplifier offset and filtering with a 3-point median and a 4th order low-pass Butterworth filter with cutoff frequency of 1,000 Hz. The MEP peak-to-peak amplitude, V_{MEP} , was determined as the difference between the maximum and minimum values of the processed EMG waveform occurring between 20 ms and 60 ms after the TMS stimulus.

Transcranial magnetic stimulation targeting

The TMS coil was positioned by finding the optimal spot over the left motor cortex eliciting the largest MEP via a systematic search strategy. The coil was oriented at a 45° angle from the median plane and tangential to the skull beneath the center of the coil. The initial phase of the induced electric field pulse (positive phase in Fig. 1) had posterior–anterior direction. This electric field direction results, on average, in the lowest motor threshold (Balslev et al., 2007; Brasil-Neto et al., 1992; Di Lazzaro et al., 2004; Kammer et al., 2001; Niehaus et al., 2000). The coil was held by hand during the optimal spot search and was subsequently fixed in a coil holder during the motor threshold and IO curve data acquisition. The coil position was monitored throughout the TMS session with a Brainsight computerized frameless stereotaxic system (Rogue Research Inc., Montreal, Canada) and adjusted if necessary to compensate for movements of the subject's head relative to the coil.

Motor threshold

The motor threshold was defined as the lowest pulse amplitude that produced MEPs with $V_{MEP} \geq 50 \mu V$ on at least 5 out of 10 trials (Rossini et al., 1994). The motor threshold was determined simultaneously for three pulse widths (30, 60, and 120 μs) using an automated procedure that randomly interleaved stimuli at each of the pulse widths with randomized interstimulus interval of 6–8 s to curb carry-over, entrainment, and expectancy effects.

The pulse energy delivered to the TMS coil at motor threshold quantifies the neural stimulation efficiency associated with the pulse shape and width, and the specific device hardware implementation. The pulse energy, U , was calculated by

$$U = \frac{1}{2} L I_{Lpk}^2 \quad (1)$$

where I_{Lpk} is the peak coil current. The coil current waveforms were measured offline with a Rogowski current probe (CWT30B, Powertek, Holbrook, NY, USA).

Strength–duration curve model

The set of pulse amplitudes at motor threshold for the three pulse widths represents a strength–duration curve. The curvature of the strength–duration function depends on the TMS pulse shape and the membrane dynamics of the neurons directly depolarized by the TMS electric field (Rattay et al., 2012). To parameterize the strength–duration curve, the neural membrane can be approximated as a low-pass filter with time constant τ_m (Barker et al., 1991; Corthout et al., 2001; Lapicque, 1907). The neural membrane depolarization is then proportional to $V_c(\tau_m, t_p)$, where

$$r(\tau_m, t_p) = \max_t ((w * h)(t)) \quad (2)$$

is a depolarization factor computed from the convolution of the normalized electric field pulse waveform $w(t_p, t)$ (illustrated in Fig. 1) and the impulse response of a first-order low-pass filter with time constant τ_m

$$h(\tau_m, t) = \frac{1}{\tau_m} e^{-t/\tau_m} u(t) \quad (3)$$

where $u(t)$ is the Heaviside step function. An MEP is generated when the depolarization strength $V_c(\tau_m, t_p)$ reaches a threshold $V_{th\infty}$. Therefore, the motor threshold as a function of pulse width can be modeled as

$$V'_{th}(t_p) = \frac{V_{th\infty}}{r(\tau_m, t_p)}. \quad (4)$$

Equation (4) is the strength–duration curve model. Parameter $V_{th\infty}$ is called rheobase and can be interpreted as the motor threshold for pulses that are very long compared to the membrane time constant, resulting in $r \rightarrow 1$.

To estimate parameters $V_{th\infty}$ and τ_m , the empirical motor threshold data comprising a set of $V_{th}(t_p)$ for each subject was fitted to the parametric model in equation (4) by minimizing the sum of $(V'_{th}(t_p)/V_{th}(t_p) - 1)^2$ using the trust region reflective algorithm in MATLAB (version

R2011b, The MathWorks, Inc., Natick, MA, USA). Using the ratio of modeled to measured motor threshold in the least squares fitting equalizes sensitivity to the estimated parameters across pulse widths.

The estimation of parameters $V_{th\infty}$ and τ_m was carried out in two ways. The first approach estimated the two parameters for each subject independent of the data for the other subjects. With this approach 2 parameters were estimated from the 3 motor threshold data points per subject. The second approach aimed to reduce the number of estimated parameters in order to avoid potentially overfitting the data. We reasoned that among healthy subjects the strength–duration time constant, which depends on the neural membrane properties and the local electric field distribution, would vary less than the rheobase, which depends on macroscopic anatomical factors such as head size and coil-to-cortex distance. Therefore, the second model assumed that the time constant is identical for all subjects while the rheobase has an individual value. Barker et al. (1991) used a conceptually similar pair of approaches to estimate the strength–duration time constant that either matched a common time constant to the averaged threshold data or, alternatively, calculated a potentially noisier individual time constant estimate.

Input–output curves

IO curves were measured for each of the three pulse widths. The range for the IO curve acquisition for each pulse width was informed by the corresponding motor threshold. We sampled 3–6 amplitudes below the motor threshold, reaching the lower IO saturation region. Above the motor threshold, we sampled the IO curve to the maximum amplitude allowable by the device output limit or by the subject's discomfort. The transition region between the lower and upper IO saturation levels was sampled with a step of 2% MA, whereas the saturation regions were sampled more sparsely with 4–8% MA steps. Across all subjects and pulse width conditions, the minimum and maximum number of distinct pulse amplitudes were 8 and 24, respectively. The MEP measurement was repeated 5 times for each pair of pulse width and amplitude. The pulse width and amplitude conditions were randomized on a trial by trial basis to avoid order effects (Möller et al., 2009). The IO data were log-transformed to normalize the MEP amplitude distribution (Nielsen, 1996a, b; Pasqualetti and Ferreri, 2011). Thus we analyzed the quantity

$$y = \log_{10}(V_{MEP}) \quad (5)$$

where V_{MEP} is the peak-to-peak MEP amplitude and the logarithm base is arbitrarily chosen to be 10.

For each PW, the IO curve of the log-transformed MEP amplitudes was fitted to a cumulative Gaussian sigmoid curve (Groppa et al., 2012)

$$y = y_l + \frac{y_h - y_l}{2} \left(1 + \operatorname{erf} \left(\frac{V_c - V_0}{s\sqrt{2}} \right) \right) \quad (6)$$

where y_l and y_h are respectively the lower and upper saturation levels, V_c is the TMS pulse amplitude, $\operatorname{erf}(\cdot)$ is the Gauss error function, V_0 is the midpoint of the slope (Gaussian mean), and s is the slope spread (Gaussian standard deviation). Within subject, y_l and y_h were fixed for all pulse widths. The lower saturation limit, y_l , was derived from the rms value of the EMG signal noise level before the TMS pulse delivery. The maximum output level, y_h , was estimated from the $t_p = 60 \mu s$ data, since we obtained more saturation data at that pulse width than at $t_p = 30$ or $120 \mu s$ and since the MEP saturation level appears to be

independent of pulse width (Rothkegel et al., 2010). The maximum slope of the sigmoid curve in (6), occurring at $V_C = V_0$, is

$$m = \frac{y_h - y_l}{s \sqrt{2\pi}}. \quad (7)$$

Other sigmoid functions such as Boltzmann or Hill-type functions could be used to model the IO curve as well (Devanne et al., 1997; Goetz and Peterchev, 2012; Möller et al., 2009).

Statistical analysis

Outcome variables were log-transformed to improve the distribution normality and variance equality across pulse width conditions. The log-transformed variables were analyzed with regressions or mixed models. Subject was treated as a random effect in the mixed model analysis. Significant mixed model results were followed up with post hoc Tukey HSD tests for differences between specific pulse width conditions. The statistical analysis and data plotting were carried out in JMP 10 (SAS Institute Inc., Cary, NC, USA) and MATLAB R2011b.

In one of the subjects (40 year old right-handed female), we could not estimate the IO curve parameters for pulse width of 30 μ s since the motor threshold was very high and close to the TMS device voltage limit, thus precluding adequate sampling of the IO curve. For this subject, the slope for 30 μ s pulse width was treated as missing data in the mixed model analysis and was omitted from the regression analysis.

Results

Safety and tolerability

All procedures were well tolerated with no seizures or other serious adverse events. Of the 28 subjects who received TMS, 3 reported headache, 2 reported scalp pain, 1 reported neck pain, and 1 reported sore shoulders after the TMS session that were not present before the session. The subjects rated these side effects as mild and possibly or probably related to the TMS session. One subject reported mild dizziness possibly related to TMS after completion of the motor threshold determination but prior to IO curve measurement, and the session was stopped. The subject felt better after resting briefly and reported no subsequent side effects, but at the investigators' discretion did not continue with the study. Twenty-four of the participating subjects completed the mood visual analog scales before and after the TMS session. The only significant change in the mood ratings was increase in tiredness (paired Student's t-test with Bonferroni correction for multiple comparisons, $t = 3.41$, $df = 23$, $p = .012$). The range and frequency of side effects in this cTMS study do not exceed those reported with conventional TMS (Rossi et al., 2009). Therefore, the data from this study provide evidence that single-pulse cTMS is not less safe than conventional single-pulse TMS.

Motor threshold versus pulse width

Fig. 2 shows the individual motor threshold as a function of pulse width for each of the 26 subjects. The mixed model analysis confirmed that the pulse width had significant effect on motor threshold ($F(2,50) = 4.464$, $p < .0001$). As expected, the motor threshold decreased with increasing pulse width ($ps < .0001$ for the three pairwise comparisons). The pulse energy at motor threshold also varied significantly with pulse width ($F(2,50) = 307$, $p < .0001$; see Fig. 3). As expected, the pulse energy increased with pulse width ($ps < .015$ for

the three pairwise comparisons); the threshold pulse energy for pulse widths of 60 μs and 120 μs was 5% and 45% higher, respectively, than the energy for pulse width of 30 μs .

Motor threshold rheobase and strength–duration time constant

By fitting model (4) to the motor threshold data separately for each subject, the rheobase and the strength–duration time constant were estimated to be $10.5\% \pm 2.5\%$ MA and 200 ± 33 μs , respectively. The rheobase and the time constant were strongly inversely correlated ($R = -.83$, $p < .0001$). It is not clear whether the high correlation between the individual rheobase and time constant is a real phenomenon or is an artifact of overfitting the data (2 parameters are estimated from each set of 3 motor threshold measurements). To address the potential issue of overfitting, the data were analyzed also under the assumption of identical time constant for all subjects, yielding $10.4\% \pm 1.4\%$ MA and 196 μs , 95% CI [181 μs , 210 μs], for the rheobase and time constant, respectively. These estimates may be more reliable than the individual fitting of both rheobase and time constant for each subject, since the total number of estimated parameters is greatly reduced (from 52 to 27). Indeed the distribution of the latter rheobase is narrower (standard deviation of 1.4% versus 2.5% MA). Nevertheless, the mean values from the two types of estimation are very similar, suggesting that the average results are relatively robust with respect to fitting approach. The rheobase and time constant estimates for both data fitting approaches are summarized in Table 1.

Input-output curves

Fig. 4 shows a representative set of IO curves for the three pulse widths from one subject. Fig. 5A summarizes the IO curve slope value as a function of pulse width in the 11 subjects for whom the slope could be estimated for all three pulse widths. Figures 4 and 5A demonstrate that pulse width has a significant effect on slope ($F(2,20.99) = 102$, $p < .0001$), with slope increasing with pulse width ($p < .0001$ for the three pairwise comparisons).

To explain the dependence of the IO curve on the stimulus pulse width, we constructed a simple quantitative model of the average MEP amplitude dependence on the TMS pulse parameters. The model is presented in mathematical detail in Appendix A and qualitatively summarized below. The unified IO model cascades the neural membrane response (2)–(3) from the strength–duration curve model and the conventional sigmoid-function IO equation (6). The rationale for this model is that the membrane depolarization of the directly stimulated cortical neurons occurs before the neural population summation in the corticospinal tract that gives rise to the sigmoid IO curve. The membrane depolarization increases with three factors related to TMS: the pulse amplitude, the pulse width, and the coupling between the TMS coil and the directly stimulated neurons (which, in turn, depends on factors such as the coil-to-cortex distance, head size, and neural population type and orientation relative to the induced electric field). Specifically, the neural membrane depolarization is driven by a product of these effects. Thus, increasing the pulse width or the coil-to-neuron coupling amplifies the effect of the stimulus pulse amplitude on the MEP amplitude, resulting in higher IO slope.

Another prediction of the unified model is that the IO slope is inversely proportional to the motor threshold since the motor threshold is inversely proportional to the product of the pulse width and coil-to-neuron coupling effects. Fig. 6 plots the IO slope versus motor threshold demonstrating that they are indeed strongly inversely correlated ($R = -.78$, $p < .0001$). Interestingly, since the coil-to-neuron coupling varies across subjects and is independent of pulse width, we expect that IO slope and motor threshold would be similarly correlated within each pulse width condition. Indeed, Fig. 6 indicates that such correlations exist and have comparable strength ($R = -.74$, $-.68$, and $-.62$, for 30, 60, and 120 μs pulse width, respectively; $p < .031$). Based on these correlations, we would expect that the

product of IO slope and motor threshold would not be dependent on pulse width. The IO slope $\times$ motor threshold product versus pulse width is plotted in Fig. 5B and compared with mixed model analysis. The analysis indicated that the hypothesis that IO slope $\times$ motor threshold is equal across pulse widths cannot be rejected ($F(2,21.09) = 0.67, p = .52$). Therefore, in contrast to the IO slope (Fig. 5A), the slope multiplied by the motor threshold (Fig. 5B) indeed does not vary with pulse width.

Discussion

cTMS device

We presented the first use of a cTMS device in human subjects. This study demonstrated the safety, utility, and flexibility of cTMS for characterizing aspects of the neural response such as pulse width dependence and neural time constant that are not easily accessible with conventional TMS devices. The cTMS device enabled the generation of a range of pulse widths that is continuous and broader than the discrete pulse width selections implemented with conventional cosine TMS devices. In our study the pulse widths spanned a range of 1:4—wider than that in the previous studies with sinusoidal pulses: 1:3 (Barker et al., 1991), 1:1.4 (Rothkegel et al., 2010), and 1:2.3 (Kammer et al., 2011). The wider range of pulse widths could enable, in principle, higher regression accuracy for pulse width dependent measures. Furthermore, the simple and fast electronic control of the pulse width allowed interleaving of the pulse conditions, potentially reducing the impact of order effects and fluctuations of corticospinal excitability over time.

Strength–duration characteristics

Consistent with theoretical expectations and prior studies, the TMS pulse amplitude at motor threshold decreased with pulse width, whereas the pulse energy increased (Barker et al., 1991; Goetz et al., 2013; Kammer et al., 2011; Peterchev et al., 2008a; Peterchev et al., 2011a; Rothkegel et al., 2010). From the motor threshold strength–duration data we estimated a time constant of 196 μs , corresponding to a chronaxie of approximately $0.7 \cdot \tau_m = 137 \mu\text{s}$ (Ranck, 1975). This time constant estimate is 29% higher than the previously published value of $152 \pm 26 \mu\text{s}$ (Barker et al., 1991). The reason for this discrepancy is unclear, but may be related to various methodological differences including coil geometry, pulse shape, number and range of pulse widths, motor threshold definition, parameter estimation method, and number of subjects. It should be noted that even though Barker et al. and our study used different maximum pulse widths of 174.5 μs and 120 μs , respectively, these values are comparable since the near rectangular cTMS pulses produce the same amount of neural membrane depolarization as longer cosine pulses (Havel et al., 1997; Peterchev et al., 2008a). Potential advantages of our approach include the relatively large number of subjects, pulse width interleaving, log-transformation to normalize the data distribution, pooling the data from all subjects into a combined model assuming individual rheobase but common time constant, and use of frameless stereotaxy for reliable coil positioning. Finally, it is encouraging that despite methodological differences, the discrepancy between the time constant estimate in Barker et al (1991) and in our study is relatively small.

For posterior–anterior orientation of the induced electric field, indirect waves in the corticospinal tract, which are associated with interneuron stimulation, have lower threshold than direct waves, which are associated with pyramidal axon stimulation (Di Lazzaro et al., 2004). Therefore, the strength–duration time constant we derived likely corresponds to interneurons. Our study did not explore whether there is a difference between the time constant for indirect and direct waves. Barker et al. (1991) reported a time constant for magnetic stimulation of the ulnar nerve at the wrist ($150 \pm 55 \mu\text{s}$) that is very close to the

cortical time constant they estimated ($152 \pm 26 \mu\text{s}$). This observation suggests that corticospinal pyramidal axons, which are similar to myelinated motor axons and express the same dominant sodium channel phenotype (Caldwell et al., 2000; Tzoumaka et al., 2000), may also have a similar time constant to the cortical interneurons putatively characterized in our study. The strength–duration time constant of the pyramidal axons could be explored in future studies, for example by using lateromedial coil orientation that, unlike posterior–anterior orientation, induces direct waves at threshold (Di Lazzaro et al., 2004).

A potential accuracy limitation of the strength–duration rheobase and time constant estimates in this work, as well as in previous TMS studies, stems from the fact that all motor threshold data points were collected for pulse widths shorter than the strength–duration time constant. In this pulse width range, the motor threshold is affected significantly by both the rheobase and the time constant. On the other hand, for pulse widths significantly longer than the time constant the motor threshold is approximately equal to the rheobase and the effect of the time constant is insignificant. Such data could potentially provide a more reliable estimate of the rheobase. Generating very long TMS pulses, though, is technically challenging. As demonstrated in this study and in prior papers (Barker et al., 1991; Peterchev, 2011; Peterchev et al., 2008a; Peterchev et al., 2011a), longer pulses, especially as they approach and exceed the strength–duration time constant, consume more energy, require a larger capacitor, produce more heating, and have higher peak coil current compared to shorter pulses. An alternative device topology for flexible pulse shaping (Goetz et al., 2012a) could potentially minimize the required capacitor size and energy storage, making the device smaller and safer compared to cTMS devices, but even with this approach the energy storage and peak coil current would increase for longer pulses.

Energy efficiency

The energy efficiency comparison among pulse widths showed that, as expected, brief pulses are more energy efficient, consistent with previous studies of cosine pulses (Barker et al., 1991; Kammer et al., 2011), with our evaluation of cTMS using a filter modeling the neural membrane response (Peterchev et al., 2008a; Peterchev et al., 2011a), and with simulations (Goetz et al., 2013). Whereas the energy efficiency improvement going from $120 \mu\text{s}$ to $60 \mu\text{s}$ is substantial (28%), the improvement going from $60 \mu\text{s}$ to $30 \mu\text{s}$ is marginal (5%). This is expected since the rate of energy reduction with decreasing pulse width slows down for briefer pulses even for ideal rectangular electric field pulses (Peterchev et al., 2008a). Furthermore, longer cTMS pulses are less rectangular and closer to a cosine shape. Using various neural response models, we previously showed that the near rectangular electric field pulses generated by the cTMS device are more energy efficient than conventional cosine pulses (Goetz et al., 2012b; Peterchev et al., 2008a; Peterchev et al., 2011a). Thus some of the loss of efficiency for longer pulses could be attributed to the less efficient pulse shape, in addition to pulse width.

Input–output characteristics

We showed that the IO curve slope increases with TMS pulse width. This observation is consistent with data from peripheral nerve electric stimulation (Boerio et al., 2008).

We developed a simple model combining conventional strength–duration and input–output curve models to explain this phenomenon. Our model showed that the IO curve slope is directly proportional to the magnitude of membrane depolarization of the neurons directly stimulated by TMS, which is a function of pulse width and shape. The neural membrane depolarization and consequently the IO slope are monotonically increasing functions of pulse width. The same mechanism drives the pulse width dependence of the motor

threshold, and is thus responsible for the shape of the motor threshold strength–duration curve.

Furthermore, our model showed that both the IO slope and the motor threshold depend on the strength of the TMS coil coupling to the directly stimulated neurons. Therefore, the neural membrane depolarization as a function of pulse width drives the pulse width dependence of the IO slope and motor threshold, whereas the coil-to-neuron coupling strength contributes to the interindividual variability of these measures. Indeed we showed that the IO slope is inversely proportional to the motor threshold both within and across pulse width conditions (see Fig. 6).

Thus, our quantitative model explains the observation by Rothkegel et al (2010) that the IO curve characteristics become independent of pulse width when normalized to the motor threshold. This observation could enable comparisons among studies using devices with different pulse widths (Rothkegel et al., 2010). In fact, our model supports an even broader claim that normalization of the IO curve to the motor threshold can largely compensate for the effect of not only pulse width but pulse shape as well, since the pulse width and shape both affect the neural membrane depolarization, that, in turn, affects the IO slope and motor threshold. This observation is relevant as long as the neural population stimulated by the various pulse shapes and widths is the same, which is likely the case near threshold for matched direction of the dominant electric field pulse phases.

Normalizing the IO slope by multiplying it by the motor threshold (or by other related measures such as the IO curve inflection point) removes the slope dependence on the pulse shape and width, as well as the dependence on factors such as the coil-to-cortex distance. The resulting IO slope $\times$ motor threshold product can therefore be used as a measure of corticospinal tract summation and muscle response that may provide more sensitive characterization of individual differences than the IO slope alone.

A limitation in this study is that we used least-squares fitting of the IO curve data which is standard in the literature but may underestimate the curve slope due to the shifting spread and skewness of the MEP variability along the IO curve (Goetz and Peterchev, 2012). Future work could use more sophisticated fitting approaches for the IO curve (Goetz and Peterchev, 2012). Nevertheless, the relative differences in slope among the various pulse widths, which is a key finding in the present work, should be present regardless of systematic error in the IO slope estimation.

Conclusion

The cTMS device generates efficient, adjustable near rectangular electric field pulses, enabling study of the pulse width dependence of cortical excitability measures such as motor threshold and IO curve. The time constant and rheobase quantifying the TMS motor strength–duration curve could potentially be useful as noninvasive biomarkers for brain based disorders and therapeutic interventions. We estimated the average strength–duration time constant in healthy humans to be 196 μ s. The IO curve slope increases with pulse width, which can be explained by the same membrane depolarization mechanisms that determine the motor threshold strength–duration relationship. The product of the IO slope and the motor threshold removes this interdependence and may provide a potentially sensitive measure of individual corticospinal tract summation and muscle response.

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Appendix A

We present a simple quantitative model of the average MEP amplitude dependence on the TMS pulse shape, pulse width, and coil-to-neuron coupling. This model, diagrammed in Fig. A1C, combines the low-pass filter approximation of neural membrane response (equations 2–3 in the main text) used in the strength–duration curve model (Fig. A1A), followed by the conventional sigmoid-function IO model (Fig. A1B; equation 6). The rationale for this model is that the membrane depolarization of the directly stimulated cortical neurons occurs before the neural population summation in the corticospinal tract that gives rise to the sigmoid IO curve. Parameter g is a gain that characterizes the coupling between the TMS coil and the directly stimulated neurons and hence depends on factors such as the coil-to-cortex distance, head size, and neural population type and orientation relative to the induced electric field. The depolarization factor $r(\tau_m, \tau_p)$ is defined in equation (2). Parameters V'_0 and s' are, respectively, inflection point and spread that characterize the neural membrane action potential threshold and population summation in the corticospinal tract, respectively, and are independent of the pulse width and coil coupling to the directly stimulated neurons in the cortex. The unified model in Fig. A1C can be expressed as a modified sigmoid curve

$$y = y_1 + \frac{y_h - y_1}{2} \left(1 + \operatorname{erf} \left(\frac{V_c g r(\tau_m, \tau_p) - V'_0}{s' \sqrt{2}} \right) \right). \quad (\text{A1})$$

Expression (A1) can be rearranged in the form of the conventional sigmoid curve (6) where

$$V_0 = \frac{V'_0}{g r(\tau_m, \tau_p)} \quad (\text{A2})$$

and

$$s = \frac{s'}{gr(\tau_m, t_p)}. \quad (\text{A3})$$

Combining equations (7) and (A3), the maximum slope of the unified IO model is

$$m = \frac{y_h - y_l}{s' \sqrt{2\pi}} gr(\tau_m, \tau_p). \quad (\text{A4})$$

Thus, the IO slope is directly proportional to the coil-to-neuron coupling gain g . The depolarization factor $r(\tau_m, t_p)$ is a monotonically increasing function of the pulse width t_p ; therefore, the IO curve slope m is an increasing function of t_p as well. Furthermore, the depolarization factor r is affected by the pulse shape, and thus implicitly models the pulse shape dependence of the IO slope as well.

The unified IO model (A1) can be related to the strength–duration model (4) since both use the depolarization factor, $r(\tau_m, t_p)$, to explain the effect of pulse width. Thus, the modeled motor threshold can be expressed as a function of the parameters of equation (A1)

$$V'_{th} = \frac{1}{gr} \left[V'_0 - \sqrt{2} s' \operatorname{erf}^{-1} \left(1 - 2 \cdot \frac{y_{th} - y_l}{y_h - y_l} \right) \right] \quad (\text{A5})$$

where $\operatorname{erf}^{-1}(\cdot)$ is the inverse error function and y_{th} is the MEP threshold level, equal to $\log_{10}(50 \mu\text{V})$. Based on the strength–duration curve equation (4), the rheobase is therefore

$$V_{th\infty} = \frac{1}{g} \left[V'_0 - \sqrt{2} s' \operatorname{erf}^{-1} \left(1 - 2 \cdot \frac{y_{th} - y_l}{y_h - y_l} \right) \right]. \quad (\text{A6})$$

As expected, the motor threshold and the rheobase are inversely dependent on the coil-to-neuron coupling gain, g .

Parameter r drives the pulse shape and width dependence of the IO slope and motor threshold, whereas parameter g contributes to the interindividual variability of these measures. Since the effect of g and r is opposite for motor threshold and for IO slope, the product of IO slope and motor threshold,

$$m \cdot V'_{th} = \frac{y_h - y_l}{\sqrt{\pi}} \left[\frac{V'_0}{s' \sqrt{2}} - \operatorname{erf}^{-1} \left(1 - 2 \cdot \frac{y_{th} - y_l}{y_h - y_l} \right) \right], \quad (\text{A7})$$

is independent of either r or g , and is dependent only on parameters characterizing neural membrane action potential threshold, corticospinal tract summation, and muscle response.

A

B

C

Figure A1.

Block diagrams of the conventional strength–duration model (equations 2–4) (A), conventional IO response model (equations 5 and 6) (B), and novel unified model combining the strength–duration and IO models to account for the effect of TMS pulse shape, pulse width, and coil-to-neuron coupling. TMS device capacitor voltage V_C represents the TMS pulse amplitude and y is the log-transformed MEP amplitude. The dashed block in models A and C represents the low-pass filtering behavior of the membrane of the neurons directly activated by the TMS pulse. The model parameters are defined in the text.

Highlights

Controllable pulse parameter TMS (cTMS) is used to characterize the pulse width dependence of motor threshold and input–output (IO) slope in this first-in-human cTMS study.

Average strength–duration curve time constant for motor cortex is estimated to be 196 μ s, 95% CI [181 μ s, 210 μ s].

IO slope increases with pulse width and is inversely correlated with the motor threshold both across and within pulse width, consistent with the predictions of a novel quantitative model.

Figure 1.
cTMS electric field pulse waveforms recorded with a search coil and normalized to unity amplitude for pulse widths of 30, 60, and 120 μs .

Figure 2.

Motor threshold of 26 subjects measured as percentage of maximum TMS pulse amplitude (% MA) at pulse widths of 30, 60, and 120 μ s. The corresponding log-average values of the motor threshold are 75.8%, 47.1%, and 34.7% MA, respectively. The motor thresholds for the various pulse widths are significantly different ($p < .0001$ for the three pairwise comparisons). These data were fitted to a first-order model of the neural membrane resulting in rheobase and membrane time constant estimates given in Table 1.

Figure 3.

Dependence of pulse energy at motor threshold on pulse width for the same 26 subjects as in Fig. 2. Markers and error bars show log-average and standard deviation, respectively.

Within each plot all levels are significantly different ($p = .014$ for $60 \mu\text{s}$ versus $30 \mu\text{s}$; $p < .0001$ for all other pairwise comparisons).

Figure 4.

Example IO curves of one subject (34 year old female) for pulse widths of 30, 60, and 120 μ s. The markers show measured data points and the solid lines show the best-fitting cumulative Gaussian model. The vertical axis is logarithmic.

Figure 5.

IO curve slope (A) and IO slope multiplied by motor threshold (B) of 11 subjects for pulse widths of 30, 60, and 120 μs . Markers and error bars show log-average and standard deviation, respectively. Subject with missing IO slope estimate for 30 μs pulse width is omitted from the plots. As expected from the inverse correlation between IO slope and motor threshold (Fig. 6), the dependence of IO slope on pulse width seen in panel A vanishes when IO slope is multiplied by motor threshold in panel B.

Figure 6.

Individual IO curve slope as a function of motor threshold for pulse widths of 30, 60, and 120 μ s. The IO slope is inversely correlated with motor threshold both across the pulse width range ($R = -.78$, $p < .0001$) and within each pulse width ($R = -.62$ to $-.74$, $p < .04$). The axes are logarithmic.

Estimates of the motor threshold rheobase and time constant based on the strength–duration data of 26 subjects shown in Figure 2. The rheobase and time constant were estimated by fitting the motor threshold data to a leaky integrate-and-fire neural response model, under two alternative assumption: both parameters have individual values (first row) or rheobase has an individual value and time constant has the same value for all subjects in the group (second row).

Table 1

Model	Number of estimated parameters	Rheobase (% MA)		Strength–duration time constant (μs)		
		Mean	SD	Mean	SD	95% CI
Individual rheobase; individual time constant	52	10.5	2.5	200	33	—
Individual rheobase; group time constant	27	10.4	1.4	196	—	[181, 210]