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ORIGINAL ARTICLE

Fast estimation of transcranial magnetic stimulation motor threshold

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Background
In Transcranial Magnetic Stimulation (TMS), the Motor Threshold (MT) is the minimum intensity required to evoke a liminal response in the target muscle. Because the MT reflects cortical excitability, the TMS intensity needs to be adjusted according to the subject's MT at the beginning of every TMS session.

Objective
Shorten the MT estimation process compared to existing methods without compromising accuracy.

Methods
We propose a Bayesian adaptive method for MT determination that incorporates prior MT knowledge and uses a stopping criterion based on estimation of MT precision. We compared the number of TMS pulses required with this new method with existing MT determination methods.

Results
The proposed method achieved the accuracy of existing methods with as few as seven TMS pulses on average when using a common prior and three TMS pulses on average when using subject-specific priors.

Conclusions
Our adaptive Bayesian method is effective in reducing the number of pulses to estimate the MT.
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Keywords TMS; motor threshold; Bayesian method

Transcranial magnetic stimulation (TMS) is a noninvasive neural stimulation technique that has broad applications.[1] TMS generates an electromagnetic field that passes through the scalp and induces an electrical current, which activates neurons in the cortex.[1] In motor cortex studies, if TMS is applied at an intensity above a threshold, the target muscle contralateral to the stimulated cortical neurons responds

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with a distinguishable electrical waveform, called the motor evoked potential (MEP). The International Committee of Clinical Neurophysiology (IFCN) defined the motor threshold (MT) as the minimum TMS machine output intensity that can induce reliable MEPs (usually >100 μV), with a probability of 50%.[2]

Most TMS studies require determining the MT accurately (i.e., with small difference between the measured MT and the true MT value) and precisely (i.e., with little variance), because the choice of stimulator intensity for each participant is adjusted according to their MTs. Earlier MT determination protocols were based on systematic search. According to the protocol for MT determination proposed by the IFCN,[2] the experimenter starts from a subthreshold intensity, then increase the intensity in steps of 5% machine output until 50% of 10 to 20 consecutive pulses can induce MEPs. In a revised IFCN protocol,[3] the experimenter starts from a suprathreshold intensity, then decrease it in steps of 2% or 5% until 50% MEP-induction can no longer be achieved in 10 to 20 consecutive pulses. Mills and Nithi proposed a protocol averaging an upper and lower threshold to determine MT. This protocol requires about 50 TMS pulses for accurate MT determination.[4,5]

Shortening MT determination has the potential to both save experimental time, discomfort to the subject, and reduce the likelihood of inducing physiological changes induced by multiple pulses. A breakthrough in MT determination was the introduction of the "best PEST" method, an adaptive method based on Parameter Estimation by Sequential Testing (PEST) and Maximum Likelihood (ML) regression.[6] Unlike other systematic methods, the "best PEST" is model based, in that it uses an S-shaped metric function to model the relationship between the probability of eliciting an MEP and the TMS intensity. At each trial, the intensity that is predicted to yield a 50% probability of generating an MEP according to the model is selected as the intensity for the next TMS pulse. This method is effective because at each trial the stimulation intensity is set to yield the highest (predicted) information gain.[7,8] Compared with the Mills and Nithi protocol, the "best PEST" has been shown to determine the MT with 24 TMS pulses on average in computer simulations,[6] and with 16 TMS pulses on average in experiment that used MEP to detect MT.[5]

Although prior knowledge of MT is often available before experiments and has the potential to speed up MT determination, it has not been thoroughly used in previous studies. Awiszus used two data points (MEP induction at 100% machine output and no MEP induction at 0% machine output) to initialize the "best PEST," which reflects the belief about MEP induction under extreme machine output conditions.[6] Borckardt et al.[9] found that if an experimenter has "a reasonably accurate guess" of MT and starts the PEST procedure with this guess, a nonparametric version of PEST required fewer trials, although the "best PEST" suffered a loss of accuracy.

Knowing when to stop the procedure can furthermore potentially speed up MT determination; care must be taken, however, to ensure that accuracy is not jeopardized by (too) early stopping. Mishory et al.[5] used a repeat-once stopping criterion that requires two consecutive estimations with the same MT prediction. Borckardt et al.[9] required that the difference between two consecutive estimations be lower than a threshold. In their freely distributed software, Borckardt et al.[9] used a progress bar to give "a rough visual estimate of how close the user is to reaching the rMT estimate"; no mathematical details were provided, however.

In this study, we propose to use Bayesian regression for PEST to add two modifications to the "best PEST" method to determine the MT quickly, accurately, and precisely. The first modification is to integrate prior MT data. The second modification is to determine a systematic and theoretically sound stopping criterion. The use of Bayesian regression in PEST is an established method in psychophysics,[10] but has not yet been applied to TMS in general, and MT determination in particular. The Bayesian framework has two potential advantages: The first advantage is that it is ideal for the systematic incorporation of prior knowledge.[11] After each trial, the likelihood that the MEP is generated by the model is combined with the prior probability distribution of MT probability to generate a posterior probability distribution of MT. This "posterior" can then be used to determine the threshold and to determine the intensity of the next pulse.[12,13] In this study, we leveraged two kinds of prior information separately: (1) A distribution of MTs is often available for the subject pool of the laboratory or the institution. We call this the common prior. (2) In multisession experiments, the MT determined in a previous session can be used to estimate the MT of the current session, because the MT measured from a same subject is relatively stable over time.[14] We call this the subject-specific prior. The second advantage of Bayesian regression is that it naturally lends itself to derive a stopping criterion based on the posterior probability to ensure a predetermined level of precision.[10,15] In this study, we thus hypothesized that combining prior knowledge with a posterior probability-based stopping criterion in the Bayesian PEST allows MT determination with fewer pulses than both the IFCN protocol and the "best PEST."

Materials and Methods

Experimental comparison of MT estimation methods

Ten right-handed subjects (five male and five female, age 27.7 ± 3.0 SD years) gave their informed consent for study procedures approved by the local institutional review board. We determined the resting MT of the right FDI in each subject with four methods: (1) IFCN protocol; (2) "best PEST"; (3) Bayesian PEST with common prior; and (4) Bayesian PEST with subject-specific prior. Because the true MT of the

subjects is unknown, we chose to use the MT estimated by the IFCN protocol as the standard for MT estimation. All subjects had their FDI resting MT previously measured with the IFCN protocol, at least 1 week before the experiment. For each subject, all four methods were tested in a pseudo random order, and a 10-mintue interval separated two consecutive methods within the session.

Single-pulse TMS

Focal single-pulse TMS was delivered with a figure-of-eight coil connected to a commercially available magnetic stimulator (Magstim 200). The coil was placed on the scalp at the optimal position for stimulation of the right first dorsal interosseus (FDI), and at a 45-degree with respect to the posterior-anterior direction toward the right. Surface electromyographic (EMG) electrodes were attached to the skin over the FDI muscle using electrode gel and tape. Signal was sampled at 2 kHz with differential amplifiers (Grass Instruments IP511) with a bandwidth of 1 Hz-1 kHz. Electrophysiologic signals from the muscle were amplified and recorded for analysis. Participants, who sat in a chair adjusted to a comfortable height, put their right hands on a soft pillow, and were instructed to relax during the stimulation session. A Lycra swim cap was worn over the head er to mark locations on the head so that the TMS coil could be reliably placed over same scalp regions during the course of the test session. The hotspot for FDI was determined with a standard protocol[16] at the beginning of each experimental session before MT estimation. A computer software displayed the EMG baseline activity, for which good resting condition was considered qualified if the amplitude remains within ± 20 μV. We used the criterion that any MEP peak-to-peak amplitude should be larger than 50 μV.

Description of MT estimation protocols

The IFCN protocol was performed as previously described.[3] We started from a suprathreshold intensity determined during hotspot hunting, and decreased it by steps of 2 % maximal stimulator output (MSO), until 5 of 10 consecutive TMS pulses can induce MEPs. If fewer than 10 pulses were delivered but more than five induced MEPs, the next lower intensity was tested.

The "best PEST" protocol was performed as previously described.[5] At first, two artificial data points, MEP induction at 100% MSO and no MEP induction at 0% MSO, were used to initialize the "best PEST." Accordingly, the first TMS trial intensity was set at 50% MSO. After each trial, all available data were used for ML regression to find the probit function of the MEP probability-TMS intensity relationship (the probit function is S-shaped function obtained with the cumulative distribution function associated with the normal distribution; see Supplementary Material). The threshold parameter of this function equals the estimated MT. The next TMS pulse intensity was set to this estimated MT and the procedure continued until the repeat-once criterion was met. The experimenter manually entered the TMS intensity and the resulting MEP observation (0 or 1) for each trial, as prompted by inhouse developed software. After the stopping criterion had been reached, a visual display on the computer screen indicated that the procedure should be stopped.

The Bayesian PEST protocol was tested with both common and subject-specific priors. In both cases, and as illustrated in Figure 1, this method started from a prior distribution of MT, modeled by a Gaussian distribution with mean MT_0 and standard deviation σ_0. These parameters will be determined in computer simulations (see below). Bayesian probit regression was performed on all available data before the delivery of each TMS pulse. The intensity of the next TMS pulse was then set to be the MT predicted by the regression. After this next pulse, both the independent variable (the intensity) and the binary dependent variable (whether MEP is observed or not) were added to the entire dataset, and a new regression was carried out on the increased dataset to update the MT distribution probability (Figure 1). The procedure was iterated until the stopping criterion was met.

The stopping criterion used in the Bayesian PEST is based on the width of the MT posterior probability distribution.[15] Specifically, the (1-α)% probability interval of MT, the $_{(1-\alpha)}$PI, is the range of MT $[\theta_l, \theta_u]$ corresponding to

$$\int_{-\infty}^{\theta_u} Posterior(MT)dMT = \int_{\theta_l}^{\infty} Posterior(MT)dMT = 1-\frac{\alpha}{2}, \quad (1)$$

where "Posterior(MT)" is the posterior distribution of MT, and θ_l and θ_u are the lower and upper bounds of MT $_{(1-\alpha)}$PI. When θ_u-θ_l was less than a specific value, that we called "maximal $_{(1-\alpha)}$PI width," the MT estimation procedure was stopped.[10] The maximal $_{(1-\alpha)}$PI width will be determined in computer simulations, as we now discuss.

Computer simulations to determine MT prior distributions and maximal $_{95}$PI width

We generated synthetic TMS data with Monte Carlo simulations, by building 10 data generators with probit regression based on 10 datasets previously collected in TMS MT estimation, as previously described.[6,9] Each data generator was associated with one probit function determined by the data from one subject. Given a TMS intensity, the data generator stochastically generated 1 or 0 (MEP or no MEP) with probability calculated according to the probit function. The true MT of a data generator was equal to the value of the threshold parameter of the probit function.

Gaussian distributions were used to model the priors. The common prior mean MT_0 and standard deviation σ_0 were determined with the mean and standard deviation of the true MTs of the data generators. We found MT_0 = 40%

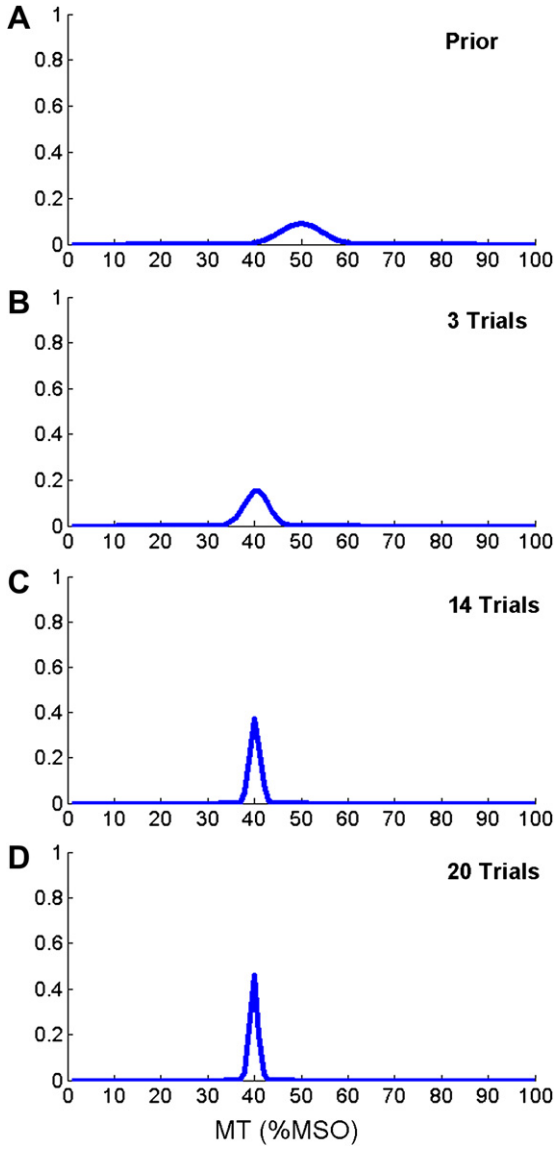

Figure 1 Illustration of the probability distributions of MTs after different number of trials in the Bayesian PEST procedure. The true MT in this simulated subject was 40% MSO. In each panel, the *x*-axis represents MT in % MSO, and the *y*-axis represents probability. **A**, The prior is a Gaussian distribution with mean 50% MSO and standard deviation 4.5% MSO. **B**, Posterior MT distribution after three trials. **C**, Posterior MT distribution after 14 trials. **D**, Posterior MT distribution after 20 trials.

MSO and σ_0 = 8% MSO. To determine the maximal $_{95}$PI width for Bayesian PEST with the common prior, we selected the largest maximal $_{95}$PI width that enabled the Bayesian PEST to yield an average estimation error not significantly different from that of the simulated "best PEST" with the repeat-once criterion.[5] We tested maximal $_{95}$PI widths of 21, 11, 9, 7, 6, and 5% MSO.

Because the mean MT_0 of the individual subjects was not available, we assumed that the prior mean MT_0 was in the range defined by MT ± 10% MSO for each data generator, where MT was the true MT of the corresponding data

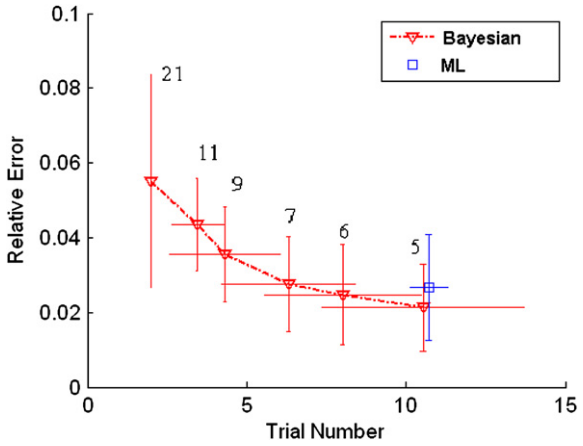

Figure 2 Comparison of stopping trial and relative error of "best PEST" (ML) and Bayesian PEST. Mean relative errors of 10 data generators as a function of stopping trials, for the "best PEST" (square) and for different maximal $_{95}$PI width (21, 11, 9, 7, 6, and 5 from left to right) for the Bayesian PEST (triangles). The maximal $_{95}$PI width tested is labeled as a number next to each triangle data point. Horizontal bars represent ± 1 standard deviation for stopping trials; vertical bars represent ± 1 standard deviation for the relative error.

generator. The standard deviation σ_0 of the subject-specific prior was taken as 3% MSO (see Supplementary Material for rationale). To determine the maximal $_{95}$PI width for Bayesian PEST with the subject-specific prior, we tested maximal $_{95}$PI widths of 5, 7, and 9% MSO. We selected the maximal $_{95}$PI width that enabled the Bayesian PEST to yield an average stopping error not significantly different from that given by the "best PEST" with the repeat-once criterion[5] when MT_0 was in the range of MT ± 5% MSO. This range of true MT ± 5% MSO for MT_0 was chosen based on our observations in the laboratory that the difference of between-session MT in healthy subjects is less than 5% MSO. This observation is consistent with the data shown in Figure 2,[14] in which six of seven healthy subjects had between-session MT differences less than 5% MSO.

To evaluate the stopping error, we compared the estimated MT against the true MT of the corresponding data generator, and used the relative error as stopping error:

$$Relative\_Error = \frac{|True\_MT - Model\_Estimated\_MT|}{True\_MT} \quad (2)$$

We repeated 50 simulation runs to evaluate the relative error for each condition. Further details and rationale of the computer simulation can be found in the Supplementary Material.

Data analysis

We compared the MTs determined with each method with those measured by the IFCN protocol by paired *t* test and Pearson's correlation, taking the IFCN protocol has the published standard recommendation for MT estimation.

We also examined the individual differences among the MTs measured by all methods. We considered a difference of 5% MSO from the IFCN estimation a large deviation because the IFCN protocol recommended TMS intensity steps of 2-5% MSO.[3] To evaluate the speed of each method, we compared the numbers of trials with paired t tests. The significance level for all statistical tests was $P < .05$.

Results

Demonstration of MT distribution change in Bayesian PEST

A Bayesian PEST simulation that demonstrates the change in MT distribution after incoming data is available is shown in Figure 1. The true MT of the artificial data generator is 40% MSO. The prior is a broad Gaussian distribution with mean at 50% MSO and standard deviation at 4.5% MSO (Figure 1**A**). As the number of pulses available increases, two changes happen to the estimated distribution of MT (Figure 1**B-D**): (1) the mean shifts towards the true MT (the accuracy increases), and (2) the standard deviation of the estimator decreases (the precision increases). The second change will eventually allow the posterior distribution to satisfy the $_{(1-\alpha)}$PI criterion.

Using computer simulations to determine maximal $_{95}$PI width

To determine the maximal $_{95}$PI width for the Bayesian PEST with common prior, we compared the "best PEST" and the Bayesian PEST in simulation. The "best PEST" stopped, on average, at 10.7 ± 0.6 (mean ± standard deviation) trials with a relative error of 0.027 (Figure 2, squares). As the maximal $_{95}$PI width decreased, the stopping error of Bayesian PEST decreased, but the number of TMS trials required increased. Bayesian PEST was as accurate as the "best PEST" (paired t test, $P = .605$, relative error 0.027) for maximal $_{95}$PI width equal to 7% MSO. For this condition, the Bayesian PEST stopped after 6.3 ± 2.1 (mean ± standard deviation) trials, which is significantly lower than that of "best PEST" (paired t test, $P < .0001$). The maximal $_{95}$PI width was thus determined as 7% MSO for the Bayesian PEST with common prior.

To determine maximal $_{95}$PI width for the Bayesian PEST with subject-specific prior, we considered maximal $_{95}$PI widths of 5, 7, and 9% MSO with MT_0 within the range MT ± 10% MSO. The top row of Figure 3 shows the stopping error (Figure 3**A**) and the number of trials (Figure 3**B**) when the maximal $_{95}$PI width was 5% MSO. In the range of true MT ± 5% MSO, the average stopping relative error was below 0.021 (Figure 3**A**), and the average number of trials was less than 15 (Figure 3**B**). The middle row of Figure 3 shows the stopping error (Figure 3**C**) and the number of trials (Figure 3**D**) when the maximal $_{95}$PI width was 7% MSO. In the range of true MT ± 5% MSO, the average stopping relative error was below 0.027 (Figure 3**C**), which was equal to the stopping error of the "best PEST" (Figure 2 square), and the average number of trials was less than 6 (Figure 3**D**). The lower row of Figure 3 shows the stopping error (Figure 3**E**) and the number of trials (Figure 3**F**) when the maximal $_{95}$PI width was 9%. In the range of true MT ± 5% MSO, the average stopping relative error was not lower than 0.027 (Figure 3**E**). In light of these simulations results, the maximal $_{95}$PI width was determined as 7% MSO for the Bayesian PEST with subject-specific prior.

Experimental comparison of MT estimation methods

Our experiment results showed the Bayesian PEST with subject-specific prior required the fewest number of TMS pulses (Figure 4**A**). Specifically, the number of pulses are 29.9 ±11.6 (mean ± SD) for the IFCN method, 12.2 ±5.5 for the "best PEST" method, 6.6 ± 2.6 for the Bayesian PEST with common prior, and 2.7 ± 0.5 for the Bayesian PEST with subject-specific prior. The subject-specific prior required fewer pulses than the common prior (paired t test, $P < .001$), which itself required fewer trials than the no prior "best PEST" (paired t test, $P = .016$). Finally, the "best PEST" required fewer pulses than the IFCN method (paired t test; $P = 0.0046$), as previously reported[5] (Figure 4**A**).

There was no difference in average in the estimated MTs between the IFCN, the "best PEST," the Bayesian PEST with common prior, and the Bayesian PEST with subject-specific prior (Figure 4**B**). Specifically, for paired t test on the null hypothesis that the estimated MTs of two methods are the same, the P value for the "best PEST" and the IFCN method was .31, the P value for the Bayesian PEST with common prior and the IFCN method was .84, the P value for the Bayesian PEST with subject-specific prior and the IFCN method was >.99. The difference was 0.7 ± 2.1% MSO between the "best PEST" and the IFCN method, 0.2 ± 3.1% MSO between the Bayesian PEST with common prior and the IFCN method, and 0.0 ± 1.6% MSO between the Bayesian PEST with subject-specific prior and the IFCN method. The MT estimated by the IFCN method and by the "best PEST" were significantly correlated with coefficient 0.95 ($P < .001$), the MT estimated by the IFCN method and by the Bayesian PEST with common prior were significantly correlated with coefficient 0.879 ($P < .001$), and the MT estimated by the IFCN method and by the Bayesian PEST with subject-specific prior were significantly correlated with coefficient 0.986 ($P < .001$).

The MTs estimated by each method for individual subjects are shown in Figure 4**C**. The estimation difference between IFCN method and "best PEST" for all subjects was below 4% MSO. The estimation difference between Bayesian PEST with common prior and IFCN method for one subject was 6% MSO ("+" marker in Figure 4**C**), and for the other of nine subjects was below 5% MSO. The

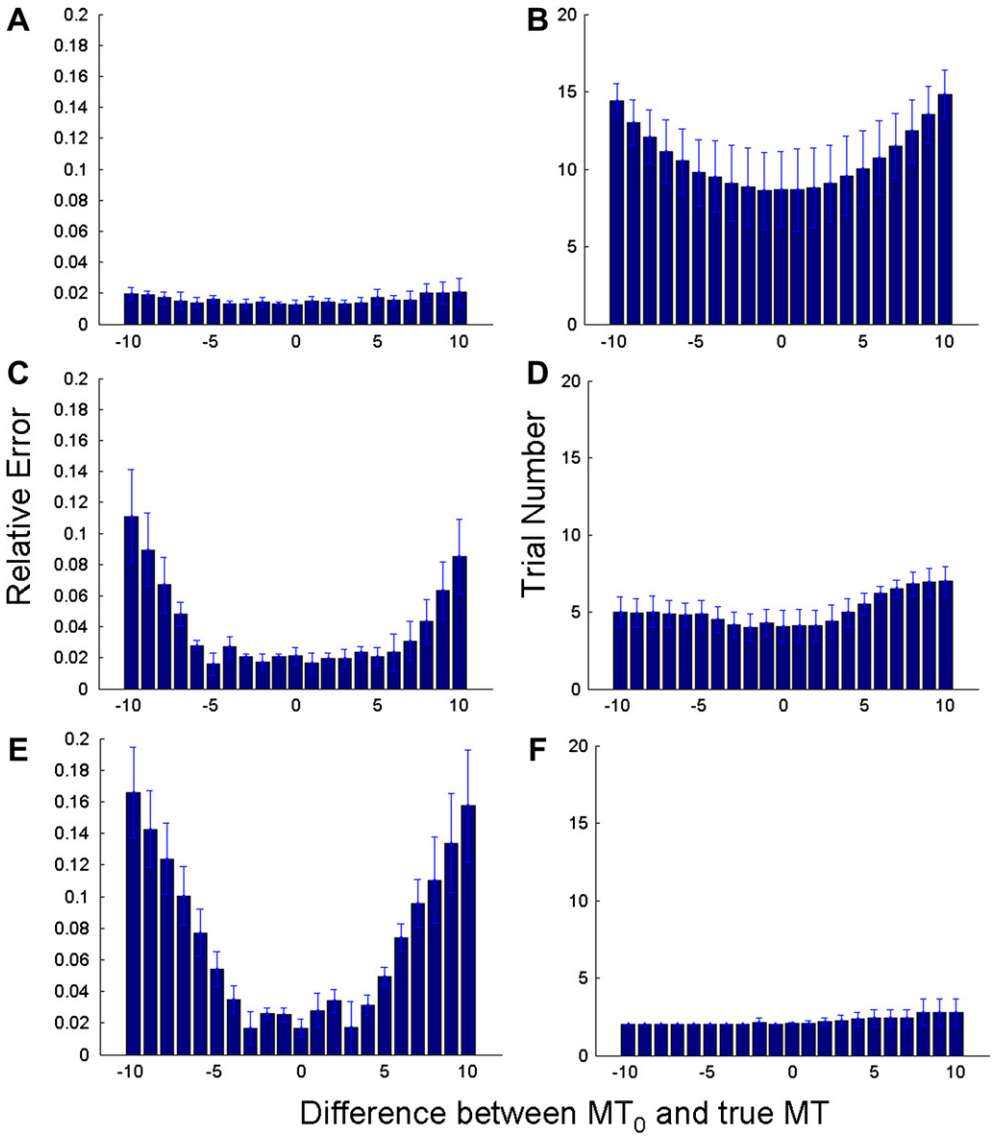

Figure 3 The stopping relative error and the number of trials of Bayesian PEST when the maximal $_{95}$PI widths were equal to 5 (**A**, **B**), 7 (**C**, **D**), and 9 (**E**, **F**) % MSO. In each subplot, the MT_0 changes from true MT −10% MSO to true MT +10% MSO. Bars represent average ± 1 standard deviation across results of 10 data generators. When the maximal $_{95}$PI width was 7% MSO and MT_0 was in the range of true MT ± 5% MSO, Bayesian PEST stopping relative error was less than the "best PEST" stopping relative error 0.027, therefore we selected the maximal $_{95}$PI width of 7% MSO.

estimation difference between Bayesian PEST with subject-specific prior and the IFCN method was below 3% MSO for all subjects. We considered a difference of 5% MSO from the IFCN estimation a large deviation because the IFCN recommended using 2-5% MSO as step size for MT estimation. Thus, except for one subject in the Bayesian PEST with common prior, all deviations are acceptable.

Discussion

Our results showed that the Bayesian PEST with posterior $_{95}$PI stopping criterion is a fast, precise, and accurate MT determination method. Our experiment showed that, on average, the common prior requires seven TMS trials and the subject-specific prior requires as few as three TMS trials (Figure 4**A**). The MT determined by the Bayesian PEST methods were not different from that estimated by the IFCN method (Figure 4**B**), except for one subject, for which a 6% MSO difference was found between the MT estimated by IFCN method and the MT estimated by Bayesian PEST with common prior (Figure 4**C**).

Introduction of prior knowledge in the Bayesian framework can largely speed up the determination of the MT. It may seem surprising that MT can be estimated in as few as three trials when a subject-specific prior is available. This can be understood as the prior information accounts for the information provided by multiple trials. Indeed, a posterior

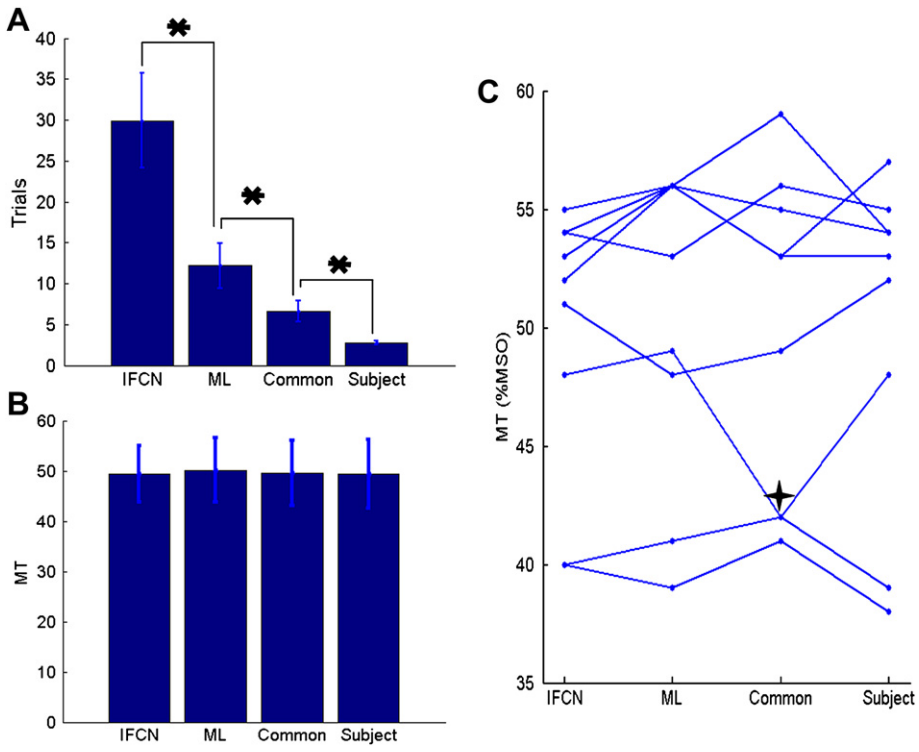

Figure 4 Comparison of MT determination methods. **A**, Average number of pulses used. **B**, Average MT estimated. **C**, Single subject MTs measured. For one subject there was a 6% MSO difference between MT measured by the IFCN method and the Bayesian PEST with common prior (filled circle); for all other subjects, this difference was less than 5% MSO. All error bars represent ± 1 standard deviation. "ML," "best PEST" with the stopping-once criterion; "Common," Bayesian PEST with common prior; "Subject," Bayesian PEST with subject-specific prior. The marks "*" indicate statistically significant differences. The mark "+" indicates the MT measured by Bayesian PEST was 6% MSO lower than the MT measured by IFCN method, for the subject.

after N trials can be viewed as the prior before the N + first trial, and having a prior at the beginning is equivalent to starting with multiple trials.

Previous psychophysics studies suggested that Bayesian PEST requires at least 20 samples to be collected because of the concern that too few samples may not be sufficient for threshold estimation.[10,12] In this study, fewer samples are adequate because there are two major differences between our study and these studies: (1) We focused on the field of TMS and used sound domain-specific prior, whereas other studies usually examined the algorithm in general and used uniform prior.[12] (2) TMS has a minimal tunable intensity unit that is 1% MSO. Our estimates based on the results of Alcala-Quintana and Garcia-Perez[12] indicate that after 10 trials, the error of MT estimation can be as small as 0.2% MSO, which is lower than the possible 1% MSO tunable in TMS experiments.

Our current Bayesian method has three possible limitations. First, we used Gaussian distribution to model the prior for MT. Because true MT cannot be less than 0% MSO in experiment, the Gaussian prior is in theory only suitable for modeling the prior knowledge when its tail is small below zero. However, even if a Gaussian prior has a relatively large tails outside the range 0 and 100% MSO, subsequent Bayesian PEST sampling will reduce the tail. Furthermore, as our results show, and at least for healthy subjects, the prior distributions are largely contained within the 0-100% MSO range. If the MTs are expected to be near the 0% MSO boundary (which would generate very large tails with a Gaussian prior), bounded prior distributions such as the Gamma distribution can be used.

Second, if the mean of the prior is different from the true MT, both the number of trials and error increase (Figure 3). When the prior is neither a uniform distribution nor the same as the true distribution, a bias is introduced into the MT estimation. However, the stopping criterion can mitigate effect of the prior bias: As the number of pulses increases, precision improves together with accuracy (Figure 1), the $_{95}$PI stopping criterion controls the stopping accuracy (Figures 2 and 3). With our assumption that the difference between the MT_0 and true MT is within 5% MSO, this amount of prior bias can be well controlled by 7% MSO maximal $_{95}$PI width; the relative error is then lower than the relative error of the "best PEST" (0.027). If in a particular clinical or experimental setting, it is important that the MT is determined with a very high accuracy (for safety reasons for instance), then the assumption can be made that the difference between the prior mean MT_0 and true MT can be as large as 10% MSO; in this case, a stopping criterion of 5% MSO maximal $_{95}$PI width should be chosen. As a result, the relative error will decrease (Figure 3**A**) and the number of trials will increase (Figure 3**B**). If a safer (although presumably longer)

approach is required, ML regression can be used for the final MT estimation based on all collected data. In such case, Bayesian regression could then only be used for determination of the next sampling intensity. The effect of prior with this "hybrid" method would thus only bias which intensities are sampled, but would not affect the final MT estimation.

Third, because the Bayesian PEST uses all previous data, erroneous data are a potential problem for both "best PEST" and Bayesian PEST. During MT estimation process, MEP identification may be inaccurate because of the volitional muscle twitch or simply wrong data entry. Nonparametric PEST[9] does not explicitly uses all data and is robust against erroneous data. Besides careful experimental operation, a systematic evaluation of the robustness of these techniques or the development of robust Bayesian regression for PEST may be necessary in future studies.

In our study, as in Awiszus,[6] we assumed that the hotspot, defined as the optimal position that has the lowest MT on the scalp for placing the TMS coil, had already been found before MT estimation. In actual TMS experiments, however, locating the hotspot is not a trivial task. Further, hotspot location and MT determination are often carried out simultaneously. TMS studies would thus greatly benefit from adaptive methods that extend our proposed Bayesian adaptive MT determination method with the addition of priors in two-dimensional space to concurrently optimize the sampling location and the sampling intensity.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.brs.2010.06.002