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A comparison of relative-frequency and threshold-hunting methods to determine stimulus intensity in transcranial magnetic stimulation

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HIGHLIGHTS

- Evaluated the latest International Federation of Clinical Neurophysiology recommendation for determining motor threshold.
- Adaptive threshold-hunting (PEST) determined threshold with fewer stimuli and with comparable results to the Rossini–Rothwell relative-frequency method.
- Equivalent results are obtained when targeting a supra-threshold MEP amplitude (1 mV).

ABSTRACT

Objective: Stimulation intensity (SI) in transcranial magnetic stimulation is commonly set in relation to motor threshold (MT), or to achieve a motor-evoked potential (MEP) of predefined amplitude (usually 1 mV). Recently, IFCN recommended adaptive threshold-hunting over the previously endorsed relative-frequency method. We compared the Rossini–Rothwell (R–R) relative-frequency method to an adaptive threshold-hunting method based on parameter estimation by sequential testing (PEST) for determining MT and the SI to target a MEP amplitude of 1 mV ($I_{1\ mV}$).

Methods: In 10 healthy controls we determined MT and $I_{1\ mV}$ with R–R and PEST using a blinded cross-over design, and performed within-session serial PEST measurements of MT.

Results: There was no significant difference between methods for MT (52.6 ± 2.6% vs. 53.7 ± 3.1%; $p = 0.302$; % maximum stimulator output; R–R vs. PEST, respectively) or $I_{1\ mV}$ (66.7 ± 3.0% vs. 68.8 ± 3.8%; $p = 0.146$). There was strong correlation between R–R and PEST estimates for both MT and $I_{1\ mV}$. R–R required significantly more stimuli than PEST. Serial measurements of MT with PEST were reproducible.

Conclusions: PEST has the advantage of speed without sacrificing precision when compared to the R–R method, and is adaptable to other SI targets.

Significance: Our results in healthy controls add to increasing evidence in favour of adaptive threshold-hunting methods for determining SI.

1. Introduction

The intensity of stimulation is a cardinal parameter in transcranial magnetic stimulation (TMS) studies, and is commonly determined by either setting stimulus intensity in relation to motor threshold (MT), or so as to achieve a motor evoked potential (MEP) of a predefined amplitude (usually 1 mV). In many TMS protocols, such as short-interval intracortical inhibition (SICI) and triple-pulse TMS, both approaches are needed to set conditioning and test pulse strengths (Ni et al., 2011; Ziemann, 2002). Accurate determination of MT is also critical for stimulus dosing that can have safety implications in interventional TMS (Rossi et al., 2009), and for the estimation of corticomotor excitability in investigational studies (Lemon, 2002). However, despite the importance of MT, a consensus as to the best method of determining it remains to be established.

A recent report of the International Federation of Clinical Neurophysiology (IFCN) has summarised the advantages and disadvantages of a range of MT estimation methods (Groppa et al., 2012). These include relative-frequency methods based on the Rossini–Rothwell (R–R) criterion or its variants (Rossini et al., 1994; Rothwell et al., 1999), the Mills-Nithi method that uses a two-threshold approach (Mills and Nithi, 1997), supervised parametric estimation (Tranulis et al., 2006), and adaptive threshold-hunting methods based on parameter estimation by sequential testing (PEST) (Awiszus, 2003; Awiszus et al., 1999) or a Bayesian variant (Qi et al., 2011). PEST models the probabilistic relationship

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between TMS and MEP amplitude, and predicts the stimulus intensity in a series of iterations to converge on MT in a relatively short number of trials. While the R–R method has been employed in the majority of TMS studies to date and has therefore become a *de facto* standard, the IFCN report recommended that 'the use of adaptive-threshold tracking procedures is preferable to other methods, if clinically feasible' (Groppa et al., 2012). There have however been relatively few reports comparing adaptive threshold-hunting and relative-frequency methods in a cohort of subjects under laboratory conditions.

While these guidelines (if not yet a consensus) exist for determining MT, there are no comparable rules in place for selecting the intensity to achieve a MEP of predefined amplitude. The R–R method can be adapted to target a MEP with an amplitude other than that for MT, and PEST methods are well-suited to hunting for a target MEP amplitude of any value, however a comparison of these approaches for this purpose has not been reported.

Given the theoretical and practical advantages of PEST as well as the recommendations of the IFCN report, in the present study we have evaluated PEST against the R–R method for determining MT, investigated the application of PEST for targeting a MEP amplitude of 1 mV, and measured within-session variability in MT determined by PEST.

2. Methods

2.1. Participants

Testing was performed on 10 healthy, right-handed participants (18–30 yrs of age; 2 female). Participants gave informed written consent and completed a safety questionnaire prior to the study, which had the approval of the institutional Human Research Ethics Committee and conformed to the Declaration of Helsinki. Subjects were seated comfortably with arms resting on a cushion.

2.2. Electromyography (EMG)

MEPs were recorded from surface electrodes placed in a belly-tendon arrangement over the first dorsal interosseous (FDI) muscle of the right hand. The EMG signal was amplified ($\times$500), digitised (sample rate 10 kHz, band-pass filtering 0.02–20 kHz; Labview 8.6, National Instruments), and stored on a computer. All measurements were taken at rest. EMG was monitored throughout the sessions, and EMG data for 100 ms prior to each TMS was stored and checked off-line to confirm the absence of muscle pre-activation.

2.3. TMS

TMS was delivered through a 7 cm figure-of-eight coil connected to a MagStim 200^2 stimulator (Magstim Co., UK). The coil was held flat against the head and oriented in the parasagittal plane, and the optimal stimulation site for activation of the right FDI muscle was determined from initial exploration. All TMS was delivered at 0.2 Hz.

The TMS intensity corresponding to resting MT, and the intensity that gave a MEP of 1 mV amplitude ($I_{1\ mV}$), were determined using R–R and PEST methods. The order of R–R and PEST was pseudo-randomised, however MT was measured before $I_{1\ mV}$ in keeping with the usual procedure for experimental studies. To minimise the possibly-confounding influence of *a priori* information, three investigators were involved with testing, and blinding of investigators was performed as follows. Investigator 1 held the TMS coil during all experiments but was blinded to MEP amplitude and stimulus intensity once the optimal site had been determined. Investigator 2 managed the PEST method and set stimulus intensity as required, but was blinded to the R–R results. Investigator 3 carried out the R–R method and was blinded to the PEST results.

2.4. PEST method

A freeware program developed by Awiszus and Borckardt (2011) that employs a maximum-likelihood PEST strategy without *a priori* information was used. The program displays the TMS intensity to be delivered; the investigator inputs whether or not the trial was a success according to predetermined amplitude criterion, and a new intensity is then displayed for delivery. Confidence intervals of intensity estimates are displayed by the program during testing, and the target intensity is 'found' when 95% confidence intervals are within accuracy limits imposed by safety guidelines (Awiszus, 2011; Rossi et al., 2009). For MT, a trial was considered successful if MEP amplitude was >50 μV. For determining $I_{1\ mV}$, a success was an MEP amplitude of >1 mV. The number of stimuli delivered to determine MT and $I_{1\ mV}$ was recorded.

2.5. R–R method

The R–R guidelines do not nominate a starting intensity, and we chose 37% of maximum stimulator output (MSO) as our initial intensity as this corresponds to the default starting intensity of the PEST program. Stimulus intensity was increased in increments of 5% MSO until MEPs of >50 μV were consistently generated. Intensity was then decreased in steps of 1% MSO until the lowest intensity that elicited MEPs of >50 μV in 5 out of 10 stimuli was reached. The same protocol was used to determine $I_{1\ mV}$, with the target MEP amplitude limit set to 1 mV. The number of stimuli delivered to determine MT and $I_{1\ mV}$ was recorded.

2.6. Serial PEST

The variability of serial PEST measurement was evaluated in a subgroup of 7 subjects (22–25 years of age; 2 female) on a separate day. Using the protocol described above, MT was measured 4 times for each subject. Approximately one minute was required to perform each measurement, and measurements were performed at 4-min intervals. This timing was intended to simulate a protocol whereby MT might be tracked over time, such as following a neuro-modulatory intervention.

2.7. Data analysis

Sample variances were compared using an *F*-test of equality of variances after confirming data was normally distributed. After confirming no effect of order (R–R, PEST) using one-way ANOVA, linear regression and paired *t*-test analysis were used to compare number of stimuli and stimulus intensity between R–R and PEST methods for both MT and $I_{1\ mV}$. To further evaluate agreement between R–R and PEST, we calculated the intraclass correlation coefficient (ICC(A,1)) for stimulus intensities (McGraw and Wong, 1996). Comparison of serial PEST MT measurements was performed using one-way repeated measures ANOVA. All data are expressed as mean ± standard error.

3. Results

Fig. 1 summarises the group data for MT and $I_{1\ mV}$ estimated by the R–R and PEST methods. There was no difference between the group mean data for MT using R–R (52.6 ± 2.6% MSO) and PEST (53.7 ± 3.1%; $p = 0.302$). Likewise there was no difference between methods for estimating $I_{1\ mV}$ (66.7 ± 3.0% vs. 68.8 ± 3.8%, R–R vs. PEST, respectively; $p = 0.146$). The absolute difference in MT between methods was $\leqslant$ 5% MSO, and was < 5% MSO in 8/10 cases for $I_{1\ mV}$, except for 2 in whom the differences were 7 and 11%. The median of the absolute difference between methods was 2.3% MSO

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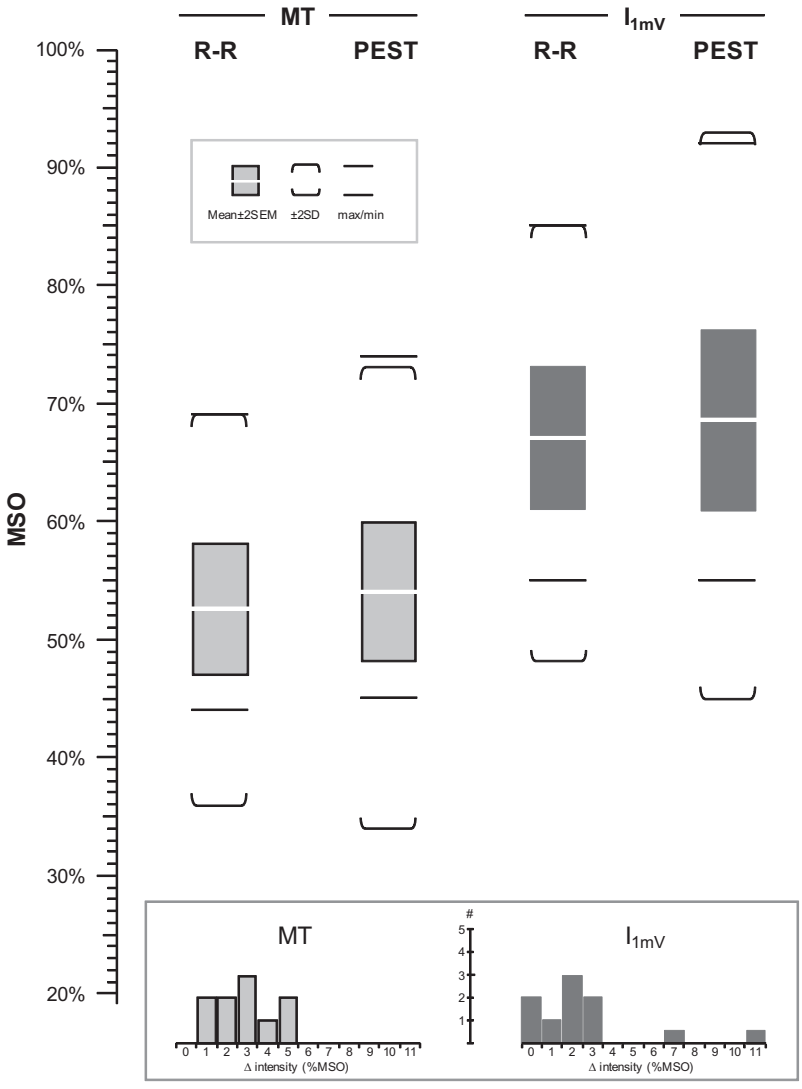

Fig. 1. Comparison of group data for MT and $I_{1\ mV}$ estimated with the R–R and PEST methods. The figure shows mean estimates (white line), 2 SEM range (filled box), 2 SD range (brackets) and maximum and minimum values (solid lines). The inset provides histograms (number of participants, vertical axis) of the absolute value of the difference between the R–R and PEST estimates (%MSO, horizontal axis), for MT and $I_{1\ mV}$.

for MT, and 1.6% MSO for $I_{1\ mV}$. Group mean MEP amplitude at $I_{1\ mV}$ was 1.1 ± 0.1 mV for R–R, and 0.97 ± 0.1 mV for PEST, and not significantly different between methods ($p = 0.322$). There was no difference in sample variances between R–R and PEST for MT ($F = 1.454$, $p = 0.586$) or $I_{1\ mV}$ ($F = 1.688$, $p = 0.447$). Data for MT and $I_{1\ mV}$ estimated by R–R and PEST for each individual are illustrated in Fig. 2.

There was good correlation between R–R and PEST estimates of MT (ICC(A,1) = 0.937, $p < 0.001$) and $I_{1\ mV}$ (ICC(A,1) = 0.915, $p < 0.001$; Fig. 3). For MT, the regression coefficient (r) was 0.954 ($p < 0.001$), and the y-intercept of the regression line was not significantly different to zero and the slope not significantly different to 1 (i.e. the identity function $y = x$). Likewise, for $I_{1\ mV}$, $r = 0.957$ ($p < 0.001$) and the regression line was not significantly different to the identity function. The number of stimuli required to determine MT using R–R was 56.8 ± 4.3, which was significantly greater than that for PEST (12 ± 0; $p < 0.001$), and this was also the case for $I_{1\ mV}$ (40.5 ± 5.9 vs. 12 ± 0, R–R vs. PEST, respectively; $p < 0.001$).

In all subjects, MT did not vary significantly with repeated measurement ($p = 0.180$; Fig. 4). Within-subjects variability in MT values was small, with a mean standard deviation across subjects of 1.2% MSO (range: 0.5–1.7%).

4. Discussion

Despite evidence from theoretical considerations and simulation studies that PEST algorithms can determine MT faster and with more precision than conventional methods (Awiszus, 2003; Borckardt et al., 2006; Qi et al., 2011), few studies have been performed to validate this approach in the human. In the present study, in human participants carried out using a blinded protocol, we demonstrate that PEST can determine both MT and $I_{1\ mV}$ in significantly fewer stimuli than the more conventional R–R approach, and that the estimates from these methods closely correspond. In addition, we show within-session MT measurements using PEST are consistent. This study provides further empirical support for the most recent IFCN recommendation for MT estimation, and demonstrates the utility of using this approach to target a MEP amplitude other than that for MT.

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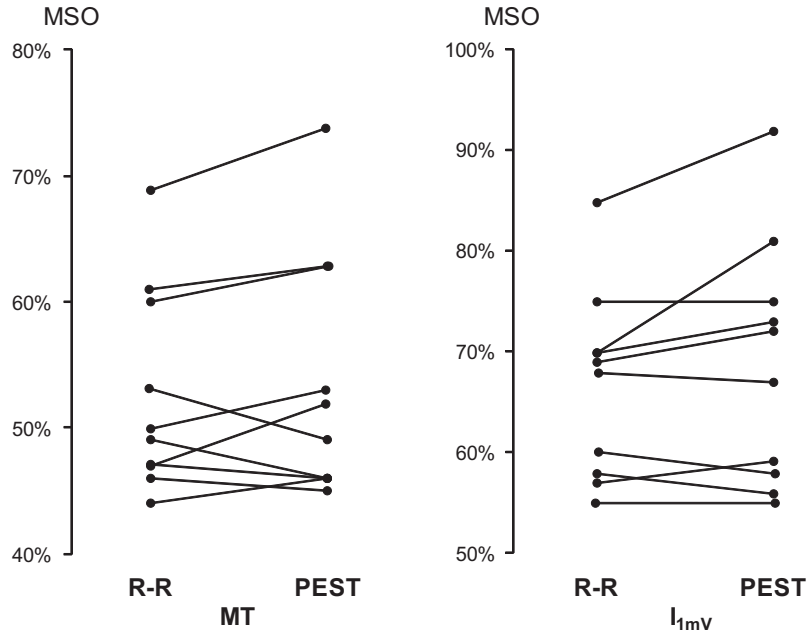

Fig. 2. Individual participant data: comparison of MT and $I_{1\ mV}$ estimated with the R–R and PEST methods for each individual ($n = 10$).

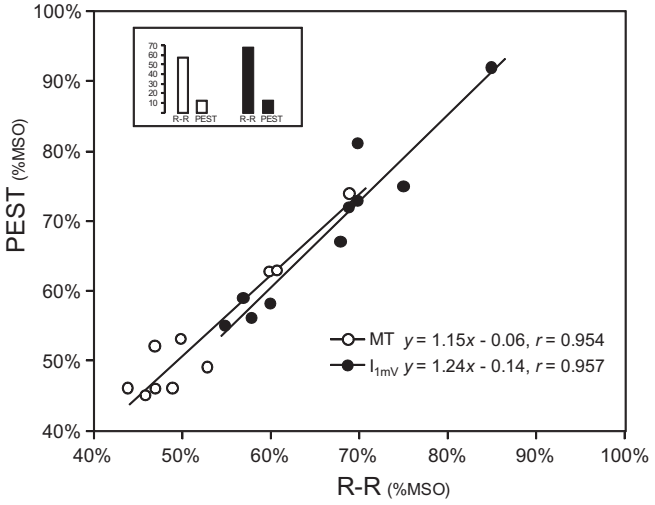

Fig. 3. Scatter plot and regression lines of MT and $I_{1\ mV}$ estimated with the R–R vs. PEST methods. Inset indicates the mean number of stimuli delivered using R–R and PEST to obtain the estimates of MT (white) and $I_{1\ mV}$ (black).

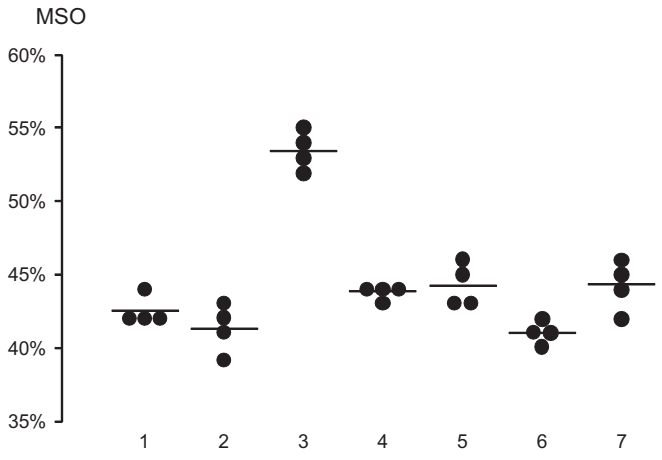

Fig. 4. Individual participant data: MT estimated by PEST for each individual ($n = 7$) on 4 occasions at 4-min intervals, and mean MT for each individual (black line).

Previous reports evaluating PEST have most often used a computer modelling approach, on the basis that the value of MT is a known. Awiszus (2003) collected TMS recruitment-curves from multiple muscles in 4 male participants and then used this data to perform Monte-Carlo simulations comparing PEST and IFCN threshold measurements, with the modelling predicting the superiority of PEST. Borckardt et al. (2006) used computer simulations to compare 5 variants of PEST, and described some subtle differences between methods that led them to conclude that the choice of method could be guided by the experimental circumstances. They provided a downloadable version of their software that was employed in the present study. In the human, Mishory et al. (2004) compared PEST with a modified Mills–Nithi procedure and concluded PEST was faster and derived a similar result, although this study was performed in only one subject. More recently, Qi et al. (2011) have described a PEST variant based on Bayesian statistics, and used computer simulations as well as measurements in 10 control subjects to compare this to the Rothwell IFCN method (Rothwell et al., 1999) and to the PEST method as described by Awiszus (2003). While the primary purpose of this study was to compare these two PEST variants, they confirmed that both of these were faster than the IFCN method and achieved the same result in the subject group.

In the present study we have taken the R–R MT estimation protocol that has become the *de facto* standard, and compared it to PEST in a cohort of healthy participants under laboratory conditions. For this comparison, we incorporated a blinded methodology. While both the R–R and PEST methods are in principle objective, there nonetheless remain potential sources of bias. In the R–R method the choice of starting intensity, number of stimuli at any given level, and intensity increments or decrements could be subject to operator decisions. In either method an operator may be tempted to overlook 'outliers' or to repeat measurements. With our rigorous approach, we have confirmed the advantages of PEST over R–R.

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We also report on the application of PEST to target a MEP of amplitude greater than that used to define MT. It is now common to target a MEP of 1 mV amplitude, and under some circumstances achieving this in the shortest possible time is important, especially when multiple adjustments are required within a session (Cash et al., 2010; Ni et al., 2011; Wagle-Shukla et al., 2009). We modified MT estimation by PEST and R–R to target this amplitude, and again confirm the accuracy and speed of PEST in achieving this useful experimental value.

While the median difference between PEST and R–R estimates of MT was just 2.3% MSO, on an individual basis differences of up to 5% MSO were observed. Unfortunately, while R–R has been a *de facto* standard for some time, it cannot be considered the definitive measure of MT, and it has been reported that the approach has mathematical and statistical flaws (Awiszus, 2011; Tranulis et al., 2006). Thus, the difference in MT cannot be attributed to PEST, and the source of these differences cannot be determined from the present data. It is noted that the variation of PEST MT taken with repeated measurements was small, supporting confidence in this method. While $I_{1\ mV}$ was also within 5% MSO when estimated by PEST or R–R for the majority of participants ($n = 8$), a somewhat greater difference was observed in two individuals. The significance of this is not certain, however the median difference in the PEST and R–R $I_{1\ mV}$ estimates (1.6% MSO) was comparable to that for MT. Additionally, the regression between PEST and R–R for both MT and $I_{1\ mV}$ was not significantly different to the identity function, and ICCs were high. Overall, these data indicate that PEST and R–R are targeting the same underlying values.

We conclude that PEST as implemented and made available by Awiszus and Borckardt (2011) has the advantage of speed without sacrificing precision when compared to the R–R IFCN method, and that it is adaptable to other stimulus intensity targets. We acknowledge that our study has evaluated R–R and PEST under control conditions, and the effectiveness of PEST remains to be determined under other conditions such as active motor threshold, in clinical studies or in studies that modulate brain excitability such as with non-invasive brain stimulation protocols. Refinements to PEST methods may further improve speed and precision (Qi et al., 2011). Our results add to the increasing evidence in favour of adaptive threshold-hunting methods for determining stimulus intensity and are consistent with the most recent recommendation of the IFCN for threshold estimation (Groppa et al., 2012).

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The authors report no conflicts of interest.

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