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

B.I. Silbert, H.I. Patterson, D.D. Pevcic, K.A. Windnagel, G.W. Thickbroom *

Australian Neuro-Muscular Research Institute and Centre for Neuromuscular and Neurological Disorders, M518, University of Western Australia, Nedlands, WA 6009, Australia

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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

* Corresponding author. Tel.: +61 8 93464479; fax: +61 8 9346 3487.
E-mail address: gary.thickbroom@gmail.com (G.W. Thickbroom).

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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 (×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 ⩽ 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