The Maximum-likelihood Strategy for Determining Transcranial Magnetic Stimulation Motor Threshold, Using Parameter Estimation by Sequential Testing Is Faster Than Conventional Methods With Similar Precision

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Background: The resting motor threshold (rMT) is the basic unit of transcranial magnetic stimulation (TMS) dosing. Traditional methods of determining rMT involve finding a threshold of either visible movement or electromyography (EMG) motor-evoked potentials, commonly approached from above and below and then averaged. This time-consuming method typically uses many TMS pulses. Mathematical programs can efficiently determine a threshold by calculating the next intensity needed based on the prior results. Within our group of experienced TMS researchers, we sought to perform an illustrative study to compare one of these programs, the Maximum-Likelihood Strategy using Parameter Estimation by Sequential Testing (MLS-PEST) approach, to a modification of the traditional International Federation of Clinical Neurophysiology (IFCN) method for determining rMT in terms of the time and pulses required and the rMT value.

Methods: One subject participated in the study. Five researchers determined the same subject's rMT on 4 separate days–twice using EMG and twice using visible movement. On each visit, researchers used both the MLS-PEST and the IFCN methods, in alternating order.

Results: The MLS-PEST approach was significantly faster and used fewer pulses to estimate rMT. For EMG-determined rMT, MLS-PEST and IFCN derived similar rMT, whereas for visible movement MLS-PEST rMT was higher than for IFCN.

Conclusions: The MLS-PEST algorithm is a promising alternative to traditional, time-consuming methods for determining rMT. Because the EMG-PEST method is totally automated, it may prove useful in studies using rMT as a quickly changing variable, as well as in large-scale clinical trials. Further work with PEST is warranted.

Key Words: transcranial magnetic stimulation, motor threshold, excitability, parameter estimation by sequential testing, algorithm, maximum-likelihood strategy, method

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Motor threshold (MT) information acquired using single pulse transcranial magnetic stimulation (TMS) provides a noninvasive index of cortical excitability.[1,2] Determining the correct MT is important for determining the proper TMS dose for each subject and also is important with respect to safety.[3] MT can be determined when muscle groups are active (aMT) or when they are at rest (rMT).

MT can be determined either using EMG criteria, or visible movement.[4] The original guidelines published by the International Federation of Clinical Neurophysiology (IFCN) for measurement of MT[5] are time intensive and require determining MT using multiple stimuli approached from supramaximal to subthreshold, and averaging the two. Mills and Nithi (1997) proposed a refinement of the IFCN method designed to improve its efficiency and accuracy, but even this refinement typically requires delivery of more than 50 TMS pulses.[6,7] Even with a minimum 3-second interpulse interval, this method takes at least several minutes.

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Recently a procedure called the maximum-likelihood strategy (MLS) has become available as a means of more efficiently determining MT.[8] This strategy uses a commonly used mathematical algorithm called parameter estimation by sequential testing (PEST) to efficiently surround the threshold, depending on the single response to each intensity setting. The MLS-PEST method theoretically yields results comparable to the Mills-Nithi IFCN method in terms of accuracy, with fewer trials and in less time.[8] In the only study of this new technique, Awiszus studied 28 muscle groups in 4 subjects, and found no difference in rMT between the PEST method and the two other older techniques. The current study was designed to test the findings reported by Awiszus by comparing a modified Mills-Nithi procedure to the MLS-PEST in an active TMS laboratory. The current study is an extension rather than exact replication because, unlike the protocol used by Awiszus that used electromyography (EMG) recording to measure muscle activity in 28 muscles, we restricted the study to the hand, and visual determination of MT was also used. Additionally, we have incorporated the entire MLS-PEST algorithm into a feedback computer system controlling the TMS generator, which fully automates the MLS-PEST technique, and is thus theoretically faster. We therefore sought to directly compare the MLS-PEST method with a modified IFCN method in terms of the derived rMT value, the length of time, and the number of pulses required to find the rMT, using both visible movement and an EMG paradigm. We repeated the testing on several days to determine the day-to-day variability and repeatability of the 2 methods.

MATERIALS AND METHODS

The overall study consisted of 4 separate afternoons of TMS testing, with the same subject being tested (MSG) on all occasions. Visible movement was tested on the first two sessions, with EMG testing on the last 2. The study was conducted under the guidance of MUSC's IRB, who determined that individual consents were not needed because this was a simple method testing on one researcher.

Visible Movement Recording Method

Identical procedures were used on each of 2 separate days that were 4 days apart. The TMS subject (MSG), a 45-year-old man, sat upright in a chair and placed his dominant (ie, right) and relaxed hand at hip level on a specifically built contoured surface resembling the hand. Using a Neuronetics TMS figure-eight solid core device (model 2100; Neuronetics Inc), ZN applied a suprathreshold intensity of 50% machine output to the scalp over the dominant hand area of the left motor cortex until a visible movement in the fingers was observed. We initially identified this area by placing the TMS coil approximately 5 cm above the tip of the left ear using an imaginary line connecting it with the vertex. The best location was determined by systematically shifting of the coil position in an up-down and then forward-backward direction, preserving the TMS coil angle position of 45 degrees from the midline until the maximal right thumb movement had been achieved. Markers were placed on the scalp at this spot so that each experimenter (AM, CM, ZN, ZS, XL) could reliably hold the TMS coil in place throughout the experiment. On day one, half of the experimenters began with a modified version of the Mills-Nithi IFCN method and ended with the MLS-PEST. On day 2, the method used first for each experimenter was switched. Each experimenter was blind to the resting motor threshold (rMT) estimates of the others. Determination was performed serially for each experimenter, with the entire session lasting less than two hours.

For both the MLS-PEST and Mills-Nithi IFCN method of visible rMT determination, the frequency of stimulation was set at 1 pulse every 3 seconds. A response was defined as the observation of any finger movement on the right hand. The Mills-Nithi IFCN modification involved the following protocol: Pulses were delivered beginning with an intensity of 50% machine output. Resting motor threshold was defined as the average of two values referred to as the lower and upper rMT (LT and UT, respectively). The LT was the first value identified and was defined as the intensity at which less than three of six trials resulted in a response. Intensity was decreased in 2% decrements of maximum TMS machine output until the LT was found. Thus, the first intensity value tested was 50 and the intensity was then set at 48, 46, 44, etc, until the point at which no finger movement was observed (ie, the LT value). Once the LT was obtained, the TMS intensity was reduced 4% of maximum machine output below this value and then increased in increments of 2% of machine output until the first value associated with a successful response for three of six trials was identified: this was defined as the UT. The Mills-Nithi procedure estimates the threshold as the arithmetic mean of the "lower" (LT = largest stimulus strength with no success within 10 trials) and the "upper" threshold (UT = smallest stimulus strength with 10 successes within 10 trials). To reduce the amount of time needed for Motor Threshold determination, we employed a common modification of this procedure by decreasing the number of obligatory trials to "6", defining LT as no success within less than 3 of 6 trials and UT as at least 3 successes within 6 trials. To further minimize the number of trials needed for rMT determination, stimulation at a given intensity was discontinued at the point where criteria for UT or LT could no longer be met. Thus, if when determining LT, 4 pulses had been delivered at a specific intensity and no finger movement was observed it was not necessary for the experimenter to continue to apply stimulation for the obligatory 6 trials (a majority positive could no longer be met) and the next intensity setting was then administered.

MEP-EMG Recording Method

These 2 sessions followed the two sessions above by 2 weeks, with similar though not identical methods. The same

TMS subject (MSG) sat upright in a chair using the Brainsight Head Holder (Rogue Research Inc), and placed his dominant (ie, right) and relaxed hand on the same contoured surface at hip level. EMG electrodes were attached to the skin overlying the belly of his left abductor pollicis brevis (APB) and associated tendon with a ground on the back of his hand. Resting MT was determined on two sessions 4 days apart. Using a Magstim TMS device with a figure-eight coil ("Magstim SuperRapid"; The Magstim Company Ltd), ZN applied a suprathreshold intensity of 80% machine output to the scalp over the dominant hand area of the left motor cortex until a motor-evoked potential (MEP) of greater than 100 microvolts peak to peak was observed. We initially began the study by determining the Visible Movement Recording Method with a Neuronetics solid filled coil as the TMS device. However, for testing the MEP EMG Recording Method for MT determination we used a Magstim TMS device, which can be controlled by an external computer. The Neuronetics TMS machine lacks this feature. After determining the best location for APB stimulation, marks were placed on the scalp so that each experimenter (AM, FAK, ZN, ZS, XL) could reliably ensure that the TMS coil was in place throughout the experiment. (For the second EMG session only, the coil was rigidly mounted against the head on the head frame; see Fig. 1) A combination of analog and digital filtering was used to preserve the signal of interest (between 20 and 400 Hz). The EMG signal was band-pass filtered by a CED 1902 Signal Conditioner (Cambridge Electronic Design, Cambridge, UK) with cutoff frequencies of 0.5 Hz and 1000 Hz. Because of limitations in our hardware to specify a more stringent high-pass cutoff, the signal was further digitally filtered to remove any baseline drift by using a high-pass filter with a cutoff frequency of 25 Hz after sampling by a Micro 1401 mkII ADC (Analog to Digital Converter) (Cambridge Electronic Design, Cambridge, England) at 5 kHz and 16 bit precision. To reduce 60-cycle main-frequency noise, main-frequency artifact was estimated from the latter 0.5 seconds of data of each epoch, which is devoid of true EMG signal, via FFT (Fast Fourier Transform) and subtracted from the whole epoch. All processing was performed on a Dell computer, which then recorded and displayed each MEP on the screen. In the EMG-PEST mode, this output was integrated with the PEST algorithm, and then the results of this calculation were used by the Dell computer to control the subsequent settings on the Magstim TMS generator, allowing the PEST program to automatically change the TMS generator output setting according to the algorithm, until the final rMT was calculated.

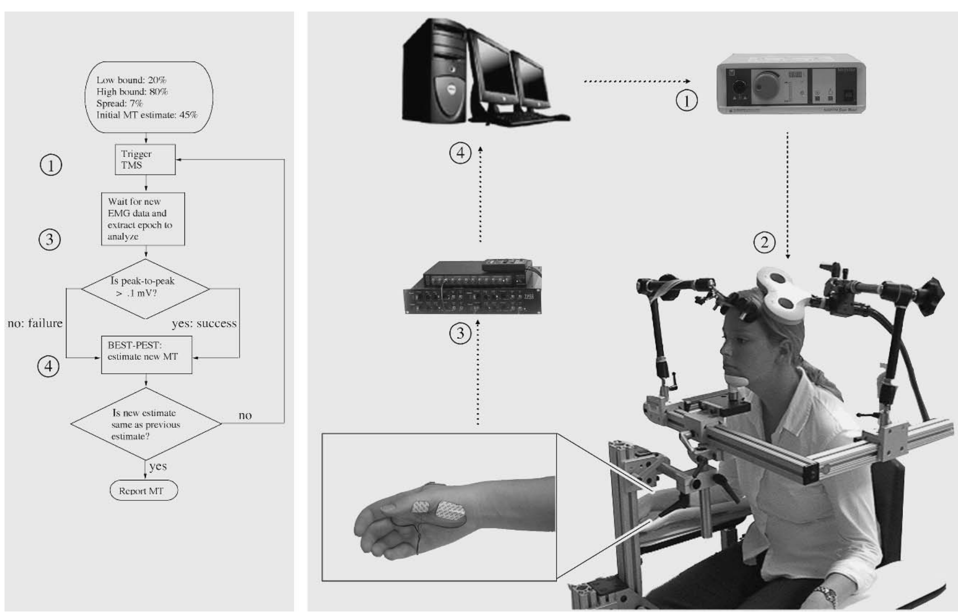

FIGURE 1. Setup for automated rMT determination using MLS-PEST and MEP-EMG This flow diagram indicates the setup for determining motor threshold via MLS-PEST using automated EMG capture and analysis. Numbered steps in the control flow diagram (left) correspond to the hardware diagram (right). Initial parameters are fed into the control program and the TMS generator is triggered (1). The attached TMS coil is placed over the scalp position controlling movement in the contralateral dominant hand. (2) The subject pictured is Emily Grenesko, a research assistant in the MUSC Brain Stimulation Laboratory. EMG lead placement for the APB muscle recording can be seen in the inset. The EMG hardware (3) records muscle activity triggered by the TMS machine and records and processes the EMG data. The Dell workstation (4) then calculates the peak-to-peak voltage of the MEP and passes the result to the MLS-PEST module, which determines a new TMS generator output based on whether the current pulse produced a supra-threshold EMG. The cycle then repeats itself until the rMT is found, typically taking less than 30 seconds.

As in the visible movement testing, order was randomized and counter-balanced, and experimenters were kept masked from the determinations by others.

For the modified Mills-Nithi IFCN method of EMG rMT determination, the frequency of stimulation was set at 1 pulse in 3 seconds. A response was defined as an MEP of greater than 100 microvolts peak to peak. (The traditional definition has been 50 microvolts, however our signal detection software worked much better with 100 microvolts. We are refining this currently. Importantly, the same 100-microvolt criteria were used consistently for all studies on all days. Another reason for this stringent criterion (100 microvolts peak to peak) was to ensure that the program recorded definite responses from the muscle.) The Mills-Nithi IFCN modification involved the following protocol: Pulses were delivered beginning with an intensity of 75% absolute machine output. rMT was defined as the average of two values referred to as the lower and upper MT, respectively (LT and MT, respectively). The same algorithm used for the visible movement was used here, with MEP's replacing observed movement. As with the visible movement algorithm, to minimize trials needed for rMT determination, a given intensity was discontinued at the point where criteria for UT or LT could no longer be met.

MLS-PEST APPLICATION FOR BOTH VISIBLE AND MEP-EMG METHODS

The MLS-PEST determination relied on software available from http://www.med.uni-madgeburg.de/fme/ortho/forsch.htm. For the visible movement method, one pulse was delivered at this intensity and then the experimenter had to input whether or not a response was observed. (For the EMG method these steps were done automatically.) Based upon this input the next intensity setting was computed and then presented to the experimenter on the computer screen, who delivered it and again had to input the response status until a maximum-likelihood estimate was produced. Even after the maximum-likelihood estimate was produced, the software continued to generate intensity levels to be tried to further increase the precision of the rMT estimate. (For detailed description of the PEST algorithm, see the Appendix.) For the current study, it was decided to continue trying recommended intensities until the point where the rMT estimation provided by the software was the same (ignoring decimals) on any two subsequent trials. In addition to measuring rMT, both time in seconds and the number of pulses needed to determine rMT were recorded. Independent variables included (1) method of rMT determination; (2) experimenter, and (3) day.

Statistical Analyses

We used the Statistical Package for the Social Sciences (SPSS: Version 11) to conduct a 2 (method: MLS-PEST; Mills-Nithi IFCN) × 2 (day: 1; 2) × 5 (experimenter: E1; E2; E3; E4; E5) repeated measures factorial multiple analysis of variance (MANOVA) with rMT, time, and number of trials as dependent variables. We performed one MANOVA for the EMG determination and a separate MANOVA for the visible movement method.

We predicted that main effects of method would be found for both time and trials to determine rMT. Specifically, for both EMG and visible movement, we predicted that the MLS-PEST would require less time and fewer trials than the Mills-Nithi IFCN method. We did not predict a main effect of method, experimenter, or day on rMT estimate. We also did not expect any interactions.

RESULTS

Visible Movement Determination

As predicted, a 2 (strategy: MLS-PEST; modified Mills-Nithi IFCN) × 2 (day: 1; 2) repeated measures factorial MANOVA with rMT, time, and number of trials as the dependent variables revealed a main effect for strategy, [$F(3,2) = 46.00$, $P < 0.021$], but not for day. Also as predicted, no interactions emerged. Post-hoc univariate ANOVAs revealed that the MLS-PEST required significantly less time, [$F(1,4) = 32.84$, $P < 0.005$], and fewer trials, [$F(1,4) = 103.17$, $P < 0.001$], to obtain rMT compared with the modified Mills-Nithi IFCN method (Fig. 2). The MLS-PEST method determined a significantly larger rMT −41.6% versus 40.8% for IFCN [$F(1,4) = 9.85$, $P < 0.05$].

EMG Determination

(Note: Researchers noted that MEP rMT determination with the flat Magstim coil was more position sensitive than the rounded iron filled coil. For visit 2, a rigid frame supported the TMS coil. This resulted in better applications of the TMS device over the maximum spot for APB stimulation and in less variance of rMT values determined either by MEP-PEST or IFCN methods.) As predicted, a 2 (strategy: MLS-PEST; modified Mills-Nithi IFCN) X 2 (day: 1; 2) repeated measures factorial MANOVA with rMT, time, and number of trials as the dependent variables revealed a main effect for strategy, [$F(3,2) = 167.20$, $P < 0.006$] but not for day. Also as predicted, no interactions emerged. Post-hoc univariate ANOVAs revealed that the MLS-PEST method, compared with the modified Mills-Nithi IFCN method, required significantly less time, [$F(1,4) = 64.02$, $P < 0.001$], and fewer trials, [$F(1,4) = 339.85$, $P < 0.001$], to obtain rMT. There was no effect of strategy on rMT (Fig. 3).

DISCUSSION

Using either visible movement or EMG methods, we found that the MLS-PEST method consistently took less time and fewer pulses to determine the rMT. These data from a

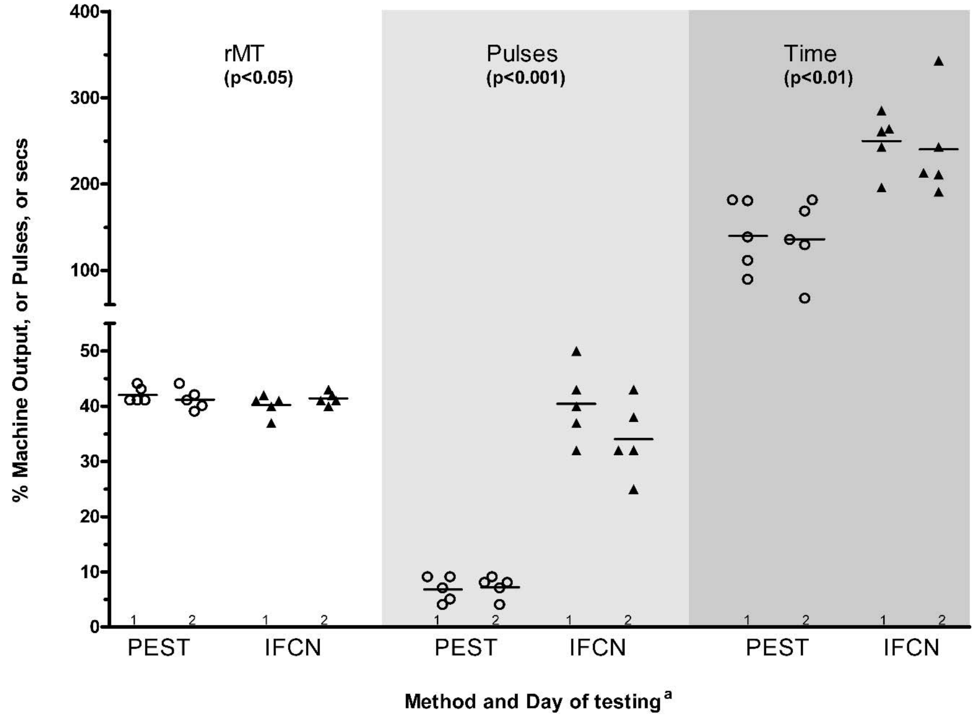

FIGURE 2. rMT Values; number of TMS pulses, required for rMT determination; time, needed for rMT determination in testing using visible movement recording method. ○–MLS-PEST method; ▲–Mills-Nithi IFCN Method. [a]Day of testing is shown by number on x-axis.

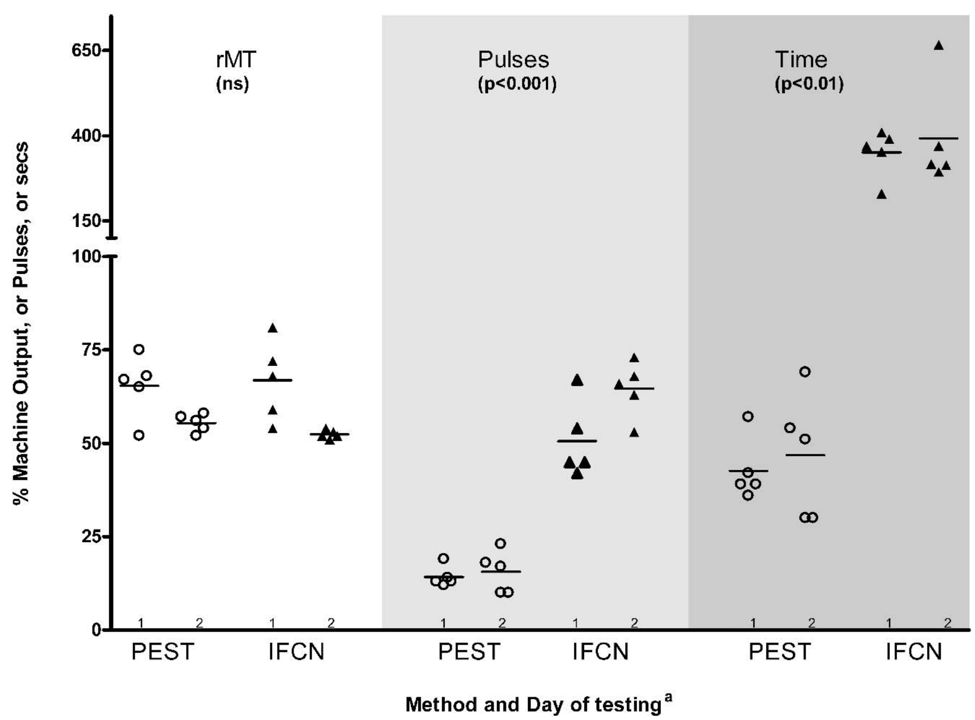

FIGURE 3. rMT Values; number of TMS pulses, required for rMT determination; time, needed for rMT determination in testing using MEP-EMG movement recording method. ○–MLS-PEST Method; ▲–Mills-Nithi IFCN Method. [a]Day of testing is shown by number on x-axis.

group of researchers familiar with TMS support the notion that the MLS-PEST method is faster and more efficient than the conventional methods for determining rMT. We also failed to find a significant difference in the actual rMT value obtained by the PEST or traditional methods when EMG was used. It is unclear whether the 0.8% difference in rMT found using visible movement has clinical or research significance.

These studies are not a formal comparison of the 2 approaches. This sample size is not sufficient for establishing absolute equivalence of the 2 methods for determining rMT. Rather, this work highlights the potential advantages of using the PEST approach.

As a continuation of Awiszus' work, which analyzed a potentially unlimited number of threshold estimates, we have demonstrated that a limited number of end-point estimates of MT, using the PEST algorithm, can provide useful and consistent information regarding recorded MT.

An important note of caution can be seen in the results from the 2 different EMG sessions, where the minor introduction of a rigid coil holder produced noticeable, although not significant, differences in measured rMT. Thus, the rMT measurement, despite advances in efficiency of sampling such as the PEST algorithm, is still dependent on accurate and consistent coil positioning.

There is ever mounting evidence that repeated daily prefrontal rTMS has clinically significant antidepressant effects.[9–16] Large-scale multisite clinical trials are being organized which are beginning to involve TMS inexperienced clinicians. In these trials, and in clinical use, accurately and efficiently determining rMT is important. The current study suggests that MLS-PEST is a more efficient method of determining rMT than are traditional methods. The fully automated MLS-PEST EMG method may have wide applications. However, further work is warranted with the PEST approach to determine whether there are subtle differences in rMT obtained and whether it can be widely adopted in clinical and research settings.

APPENDIX

The PEST algorithm is based on the probability p to obtain a success at a particular magnetic stimulus strength m and was modeled by a cumulative Gaussian distribution as

$$p(m,t,s) = \frac{1}{s\sqrt{2\pi}} \int_{-\infty}^{m} e^{\frac{(\tau-t)^2}{2s^2}} d\tau$$

with parameters t ("threshold" corresponding to the stimulus strength for which $P = 0.5$) and s ("threshold spread" corresponding to the extra amount of stimulus strength that is necessary to increase p from 0.5 to 0.84).

The log-likelihood function L for an experiment during which n stimuli were applied that yielded j successes at magnetic stimulus strengths of $ms_1,..., ms_j$ and k failures at stimulus strengths of $mf_1,..., mf_k$ (where $j + k = n$) was defined as

$$L(t,s) = \sum_{t=1}^{j} \ln[1 - p(ms_t,t,s)] + \sum_{t=1}^{k} \ln[p(mf_t,t,s)]$$

where ln denotes the natural logarithm. The values of t and s that maximized L were defined as the maximum-likelihood threshold estimate and the maximum-likelihood threshold spread estimate respectively.[8]

The PEST algorithm per definition does not impose any limits on the number of stimuli. Therefore we implemented a constraint on the number of end-point stimulations where the algorithm stopped when two similar next estimates were obtained.

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