Clinical Neurophysiology 126 (2015) 2337–2341

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

A comparison of two methods for estimating 50% of the maximal motor evoked potential

Julia B. Pitcher [a,*], Sebastian H. Doeltgen [a], Mitchell R. Goldsworthy [a], Luke A. Schneider [a], Ann-Maree Vallence [a], Ashleigh E. Smith [a], John G. Semmler [b], Michelle N. McDonnell [c], Michael C. Ridding [a]

[a] Robinson Research Institute, School of Paediatrics & Reproductive Health, University of Adelaide, Adelaide 5005, Australia
[b] Discipline of Physiology, School of Medical Sciences, University of Adelaide, Adelaide 5005, Australia
[c] School of Health Sciences, University of South Australia, Adelaide 5001, Australia

ARTICLE INFO

Article history:
Accepted 13 February 2015
Available online 28 February 2015

Keywords:
Corticomotor stimulus–response curves
Resting motor threshold
Ageing
Children
Motor evoked potential
First dorsal interosseous

HIGHLIGHTS

- Though desirable, it is often not feasible to construct corticomotor stimulus–response curves to set transcranial magnetic stimulation intensities.
- By analysing 176 corticomotor stimulus–response curves, we show that a motor evoked potential with amplitude 50% of maximum consistently occurs at 127–128% of resting motor threshold in healthy adults.
- A stimulus intensity adjusted to evoked a 1.0 mV MEP significantly underestimated this midpoint.

ABSTRACT

Objectives: Two commonly-used methods for setting stimulus intensities in transcranial magnetic brain stimulation studies were compared to determine which best approximated a motor evoked potential (MEP) of 50% of the maximal MEP amplitude (SI_{50}); a suprathreshold intensity relative to resting motor threshold (rMT) or adjusting the intensity to evoke an MEP amplitude of 1 mV.
Methods: Corticomotor stimulus–response curves and rMT for the right first dorsal interosseous (FDI) muscle of 176 subjects (aged 10–74 years) were retrospectively analysed.
Results: Regardless of subject age or sex, SI_{50} occurred at 127.5 ± 11.3% rMT. Except in young children, MEPs of 1 mV were significantly smaller than those evoked at SI_{50}.
Conclusions: In the inactive FDI muscle, a stimulus intensity of 127–128% rMT consistently gives the best approximation of SI_{50} in most subjects, except perhaps young children.
Significance: Setting TMS stimulus intensities relative to rMT provides a less variable inter-subject comparator, with respect to individual differences in corticomotor input–output characteristics, than adjusting the stimulator output to give an absolute MEP magnitude.

1. Introduction

There is still no clear consensus among transcranial magnetic stimulation (TMS) researchers or clinicians regarding the most appropriate method to determine and set test stimulus intensities. Undoubtedly, the most appropriate method for determining stimulus intensities depends largely on the hypothesis being tested. However, one of the most common approaches is to select a stimulus intensity that provides a test response (i.e., motor evoked potential; MEP) of a magnitude that lies near the midpoint of the corticomotor input–output relationship. In general, the two most prevalently used methods are, (1) an "Absolute Method", whereby the test stimulus is set to obtain a baseline MEP of approximately 1 mV peak to peak amplitude, most commonly used in paired pulse studies (Smith et al., 2009; Doeltgen and Ridding, 2010; Arai et al.,

* Corresponding author at: DX 640-517 Robinson Institute, School of Paediatrics and Reproductive Health, University of Adelaide, SA 5005, Australia. Tel.: +61 8 313 1301; fax: +61 8 313 0010.
E-mail address: julia.pitcher@adelaide.edu.au (J.B. Pitcher).

http://dx.doi.org/10.1016/j.clinph.2015.02.011
1388-2457/

2012; Pitcher et al., 2012; Vallence et al., 2012; Vallence et al., 2014), and (2) a "Relative Method", whereby the intensity is set to a predetermined intensity relative to each subject's resting motor threshold (rMT), often in the 120–150% rMT range (Di Lazzaro et al., 2012; Duque et al., 2012; Luber et al., 2012; Meister et al., 2012). The main rationale behind each of these methods is to attempt to avoid ceiling and floor effects; that is, to select a baseline or starting intensity that evokes an MEP equidistant in amplitude between resting motor threshold and the maximum amplitude MEP (i.e., MEP_{max}). Arguably the most accurate method of achieving this is to construct a full stimulus–response curve for each participant and directly determine the stimulus intensity at which 50% of MEP_{max} is obtained (SI_{50}). However, this is time-consuming and not always practical. Hence the ubiquitous use of either the Relative or Absolute methods described above. However, to our knowledge, there is no systematic evidence to support the use of either of these methods. Therefore, the aim of this study was to retrospectively reanalyse multiple archived corticomotor stimulus–response datasets as a single dataset, to determine the most accurate method of approximating SI_{50}. Specifically, we examined the curves to determine if SI_{50} was most accurately approximated by an absolute MEP amplitude (mV) or by a given stimulus intensity relative to rMT. We compared these relationships across a range of subject age groups.

2. Methods

Raw MEP data collected for studies previously performed in our laboratories were re-analysed as a single dataset. Resting motor thresholds and corticomotor curves for the right first dorsal interosseous (FDI) muscles of 176 (110 males) neurologically-healthy subjects aged 10–74 years were extracted (Pitcher et al., 2009; Doeltgen and Ridding, 2010; Smith et al., 2011; Pitcher et al., 2012). All subjects gave informed, written consent and protocols were approved by local human research ethics committees and performed in accordance with the Declaration of Helsinki.

2.1. TMS and electromyography

TMS was performed by researchers with 2–15+ years of TMS experience. MEPs were recorded from the right FDI muscle using surface electromyography (EMG) with Ag–AgCl electrodes in a belly-tendon montage. EMG signals were sampled at either 2.1 or 5.0 kHz with a laboratory interface (CED 1401, Cambridge UK), bandpass filtered (20 Hz–1 kHz) (Digitimer D360, Welwyn Garden City, or CED 1902, Cambridge UK) and analysed offline. Single pulse TMS was delivered using a figure-8 coil with either 70 mm or 90 mm outer wing diameter connected to a Magstim 200^2 stimulator (The Magstim Co., Whitland, UK). The coil was held tangentially to the skull, with the handle pointing posteriorly and laterally at an angle of 45° to the sagittal plane, at the optimal scalp site to evoke a MEP in the relaxed FDI, inducing a current flow in the posterior–anterior direction in the underlying cortical tissue in a plane perpendicular to the estimated alignment of the central sulcus. All experiments were performed with muscles relaxed. The rMT was defined as the lowest stimulator intensity at which 5 MEPs with a minimum peak-to-peak amplitude of 50 μV were evoked from the resting FDI in 10 consecutive trials. Throughout the experiments, subjects were given high gain visual feedback of the EMG from the target muscle and instructed to attend to the muscle and maintain electrical silence. Any trials contaminated with EMG in the 100 ms prior to TMS were rejected offline prior to analysis.

2.2. Curve construction and analyses

The methods for obtaining the MEP data for the curves were broadly similar (Pitcher et al., 2009; Doeltgen and Ridding, 2010; Smith et al., 2011; Pitcher et al., 2012) with 5–10 MEPs recorded at stimulus intensities starting at 90% of rMT and incrementing to intensities above MEP_{max}. In half the studies, stimulus intensities were delivered in a pseudo-random order and, in the other half, intensity increased incrementally. Step increments included 3% and 5% of stimulator output, and 10% of rMT. All curves were refitted from the raw data for this study using the Marquardt–Levenberg algorithm for least-squares convergence and several secondary equation derivations, previously described in detail (Pitcher et al., 2003; Smith et al., 2011). The amplitude of the MEP at SI_{50} (mV) and the stimulus intensities (as a % rMT), at SI_{50} and which gave a 1 mV MEP, were measured from each curve.

The influence of subject age was examined using continuous (years; rMT only) and categorical (age group) methods. Groupings were based on a combination of findings from previous studies regarding maturation of the rMT (Eyre et al., 2001; Pitcher et al., 2012) and ageing-related changes to the corticomotor system (Pitcher et al., 2003; Ward and Frackowiak, 2003; Ward, 2006; Talelli et al., 2008).

2.3. Data and statistical analyses

Normal distribution and homogeneity of variance of the data were assessed using the Kolmogorov–Smirnov test and Levene's statistic, respectively, with age group as the factor. We also examined the data for differences due to coil diameter used (i.e., 70 mm or 90 mm) or stimulus intensity order (i.e., pseudorandom or stepwise) using one-way ANOVA. Curve characteristics were analysed using univariate analyses of variance with polynomial contrasts and Bonferroni's correction for multiple comparisons. Sex and age group were included as between-subjects factors. Post hoc analyses were performed using Tukey's HSD. All tests were two-tailed and statistical significance accepted at $P \leqslant 0.05$. All data are presented as means and standard deviations unless otherwise indicated.

3. Results

The data were not normally distributed and were log transformed for analysis. There were no differences in MEP amplitudes due to coil diameter and no differences in curves due to stimulus intensity order i.e., sequential or pseudo-randomised.

3.1. Resting motor threshold

Resting motor thresholds ranged from 26% to 77% of maximum stimulator output (MSO) (43.5 ± 8.8% MSO). There was a significant effect of age group ($F_{[5,175]} = 7.15$, $P \leqslant 0.0001$, $N = 176$), with rMT reducing steadily until 36–55 years (Fig. 1A). There was a main effect of sex on rMT ($F_{[1,175]} = 5.94$, $P = 0.02$, $N = 176$) being lower in males overall (42.2 ± 8.4% MSO) than in females (45.7 ± 9.2% MSO) and a main effect of age ($F_{[1,175]} = 14.36$, $P \leqslant 0.0001$, $N = 176$). There was also a weak age * sex interaction ($F_{[1,175]} = 4.5$, $P = 0.04$, $N = 176$) due to older females having higher thresholds. Regardless of sex, post hoc analysis indicated that children ⩽12 years of age had higher thresholds than 20–35 year olds ($P = 0.02$), 36–55 year olds ($P \leqslant 0.0001$) and 56–69 year olds ($P \leqslant 0.0001$), but not adolescents aged 13–19 years or the over 70 years participants. Similarly, 13–19 year olds had higher thresholds than either 36–55 year olds ($P = 0.003$) or 56–69 year olds ($P = 0.002$), but not 20–35 year olds ($P = 0.08$) or +70 year olds.