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Variation in the response to transcranial magnetic brain stimulation in the general population

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Abstract

Objectives: The aim of this study is to describe the variability and other characteristics of the motor evoked potential (MEP) to transcranial magnetic stimulation (TMS) in a large database.

Methods: One hundred fifty one subjects, including 17 sib pairs, free of neurological or psychiatric disease and on no neuroactive medications were studied with uniform techniques. Nineteen were studied on 3 occasions. Measures included MEP threshold ($N = 141$) during rest and voluntary muscle activation and the response to paired TMS (subthreshold conditioning stimulus) at interstimulus intervals (ISIs) of 3, 4, 10, and 15 ms ($N = 53$).

Results: There was a large variability in all the measures. Approximately 40–50% of this appeared to come from within-subjects variation or experimental error. The MEP threshold data were skewed downward, but normalized with log transformation. The paired-pulse ratios (conditioned/unconditioned MEP) were normally distributed except those from the 3 ms ISI which had no lower tail and could not be normalized. There were subjects showing inhibition and others showing facilitation at all ISIs. There were no correlations in any of the data with age or sex, but MEP thresholds were highly correlated within sibs.

Conclusions: These data should be useful for planning, analyzing, and interpreting TMS studies in healthy and patient populations.

Keywords: Motor evoked potentials; Individual differences; Motor cortex

1. Introduction

Much of the transcranial magnetic stimulation (TMS) literature is devoted to the study of differences in the muscle response to motor cortex stimulation between groups of neurological patients and healthy individuals. However, one of the most striking aspects of the motor response to TMS is the degree to which healthy individuals differ and it is surprising, therefore, that interindividual differences have been largely ignored. While many laboratories have studied thousands of subjects over periods of years, none has published any compiled results. Moreover, since subjects have rarely been studied serially, there are a few estimates of the experimental error inherent to TMS techniques. Recently, we began studying a large sample of healthy individuals drawn from the general population in order to examine correlations between neurophysiological and behavioral characteristics and for detailed comparison to neurological and psychiatric patient groups.

In the present paper, I review this database in an effort to describe the range of variation in two commonly used measures, the motor evoked potential (MEP) threshold and the ratio of the conditioned to the unconditioned MEP in the paired-pulse paradigm first described by Kujirai et al. (1993) and to discuss some of its possible sources. Some of these findings were published in abstract form (Wassermann and Nguyen, 2001).

2. Subjects and methods

The subjects were 151 individuals (93 women, 58 men; age 18–76 years, mean 37.1 ± 12.7; Fig. 1). They were recruited for a variety of different studies and were either employees of the National Institutes of Health and or were recruited from the surrounding community through the NIH Clinical Research Volunteer Program. All were paid for participating. They were free from central nervous system (CNS) disease including psychiatric disorders and were on

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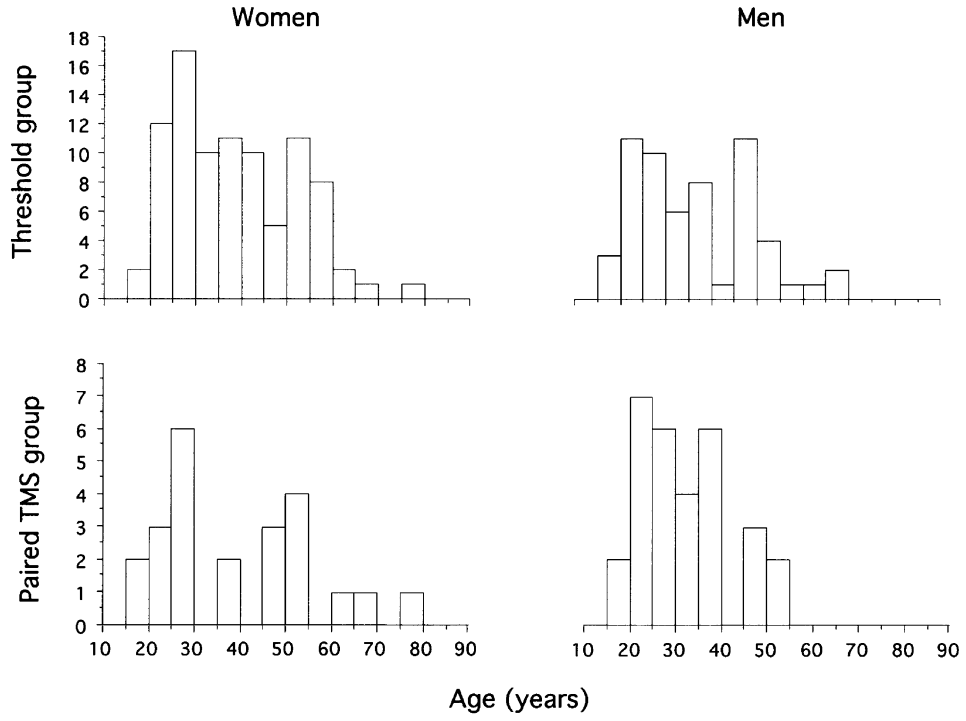

Fig. 1. Histograms showing the age distributions for the men and the women in the threshold and paired TMS samples. The *y*-axes represent number of subjects.

no medications with known CNS effects. All gave written informed consent and the studies were approved by the Institutional Review Board of the National Institute of Neurological Disorders and Stroke. Detailed demographic data were not recorded. However, the group enrolled at that time in the protocol under which the studies were conducted was 71% Caucasian, 19% African–American, Asian, and 10% other. The group included both members of 17 sib pairs, as well as 19 women participating in studies of the effect of the menstrual cycle on cortical excitability. Paired TMS data were obtained in 53 individuals (23 women, 30 men; age 18–76, mean 35.0 ± 13.3; Fig. 1). Paired TMS data from the women in the menstrual cycle study are not reported, since they were obtained at predetermined points in the cycle and, therefore, probably had artificially decreased between-subjects variation. As shown previously (Smith et al., 1999, 2002) and in the present study, there is no detectable effect of the menstrual cycle on the MEP threshold. No menstrual cycle data were collected from the other women.

All studies were performed with Magstim 200® stimulators connected through a bistim® module to a 9 cm round coil (Magstim Co., New York, NY, USA). This was held with the center near the vertex in the optimal scalp position for producing a MEP in the right abductor pollicis brevis (APB) muscle. The position of the center of the coil was marked on the scalp and used as a reference. The EMG was recorded from the right APB with surface electrodes, amplified, and filtered (100/1000 Hz) before being digitized and stored for analysis using Spike2® or Signal® software and a Micro1401® interface from Cambridge Electronic Design (Cambridge, UK).

MEP thresholds were measured once, except in the women participating in the menstrual cycle study who were studied on 3 occasions, corresponding to the early and late follicular and the luteal phases. The resting MEP threshold was defined according to conventional criteria as the lowest intensity able to produce MEPs of at least 50 μV on 5 out of 10 consecutive trials of stimulation delivered at least 5 s apart while the muscle was monitored for relaxation with visual inspection of the EMG and playback through a loudspeaker. The stimulation intensity was always adjusted to a level where MEPs were produced consistently and then lowered incrementally until the MEP frequency fell below 5 out of 10. The criterion for the MEP during voluntary contraction, was an appropriately shaped and timed negative deflection in the EMG, higher than the preceding 100 ms of background activity, on 5 out of 10 consecutive trials delivered at least 5 s apart. We have recently abandoned this somewhat subjective method in favor of online rectification and averaging.

Paired-pulse TMS testing was done as follows: the conditioning pulse intensity was set at 10% below the active MEP threshold, as determined in the above mentioned procedure. The test pulse intensity was set at a level that consistently produced a MEP of 500–1500 μV and adjusted as needed thereafter, according to accepted methods (Ziemann et al., 1996b). Various interstimulus intervals (ISIs) were tested in individual studies, but all included 3, 4, 10 and 15 ms. At least 10 trials were conducted at each ISI and the isolated

Table 1
MEP thresholds (log mean (mean) ± standard deviation of log mean) in percent of maximum stimulator output and correlations with age.

	MEP threshold		Correlation with age (r)	
	Resting	Active	Resting	Active
All	1.68 (48.7) ± 0.091	1.57 (38.4) ± 0.104	0.065	0.095
Men	1.68 (48.7) ± 0.082	1.56 (37.1) ± 0.092	0.133	0.057
Women	1.68 (48.8) ± 0.096	1.58 (39.1) ± 0.111	0.039	0.083

test pulses were interspersed with a frequency of one out of 5 trials. The order of the ISIs varied randomly. The interval between trials also varied randomly by ≤20% around a mean of 6 s.

3. Results

Resting or active MEP thresholds were available for 141 individuals (89 women, 52 men; age 18–76 years; mean 37.3 ± 13.0). Two individuals (one man and one woman) had resting thresholds above the maximum output of the stimulators, so no resting values were entered for them. The mean MEP thresholds for men and women are shown in Table 1. Both the active and resting thresholds showed Gaussian distributions, somewhat skewed toward the lower range, which could be substantially normalized by using the log transform of the stimulation intensity (Fig. 2). Therefore, log intensity was used for determining the between-subjects coefficients of variation for the threshold measurements. These were 0.055 for the resting and 0.067 for the active threshold. There was no effect of sex or age on either the resting or the active threshold in the whole sample or when it was divided by sex (Table 1). Resting and active MEP thresholds were, however, highly correlated within individuals ($r = 0.82$).

In the group of women whose thresholds were measured on 3 occasions, there was no systematic change in either the resting or the active threshold across the 3 sessions ($P > 2.5$ by the Kruskal–Wallis test after normalization to the threshold from the first session) or between any two sessions (all $P > 0.05$ by the Wilcoxon test). Therefore, I assumed that the within-subjects variation between sessions was due to random sources or 'noise' in the technique and could be

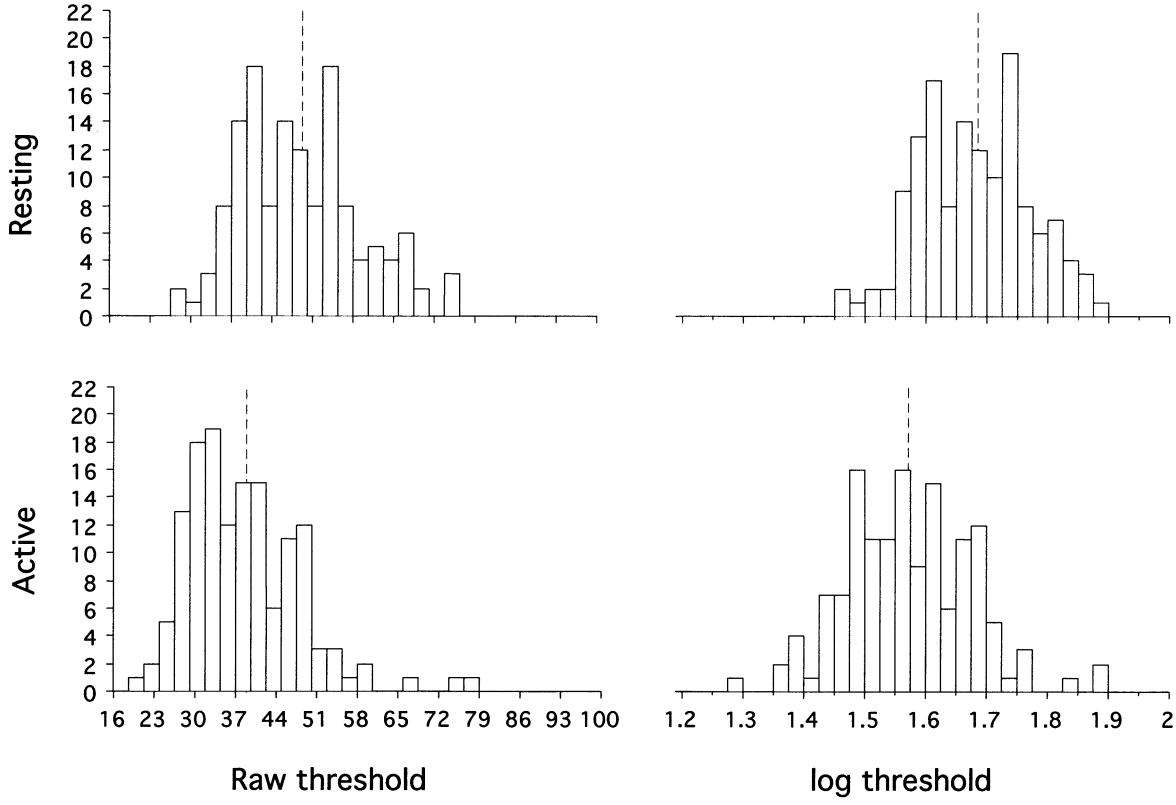

Fig. 2. Histograms showing the distribution of values for the resting and active MEP thresholds in raw and log transformed percentage of maximum stimulator output. The y-axes represent the number of subjects. The dashed lines show the mean.

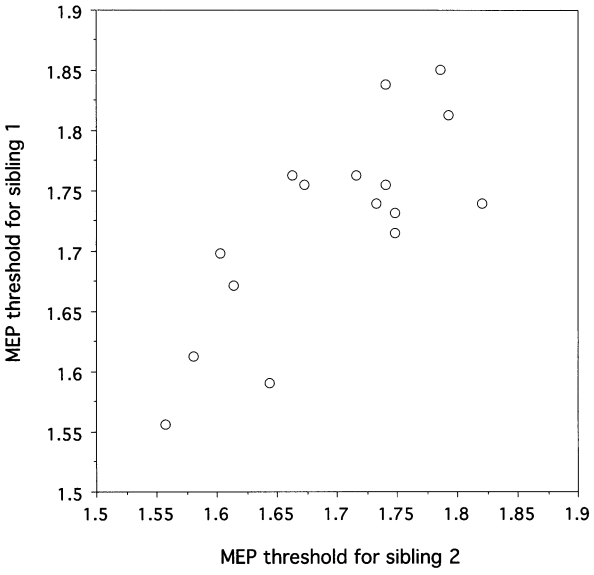

Fig. 3. Correlation of the resting MEP threshold between siblings. Scales are in log percentage of maximum stimulator output.

used to obtain an estimate of the contribution of the same sources to the between-subjects variation of the entire sample. In order to obtain a measure of the session-to-session variability, I pooled the individual data and computed the average coefficients of variation in the MEP threshold across sessions in the repeated sample. These were 0.058 ± 0.036 for the resting and 0.11 ± 0.05 for the active condition.

Among the 34 members of sib pairs, one had an unobtainable resting MEP threshold. The MEP threshold was highly correlated between members of sib pairs when tested at rest ($N = 16$ pairs, $r = 0.77$; $P = 0.0002$ by Fisher's r to z test; Fig. 3). During activation, the correlation was weaker, but still present ($N = 17$ pairs, $r = 0.57$; $P = 0.015$).

Paired TMS data were available for 53 subjects (23 women, 30 men; age 18–76; mean 36.6 ± 13.6; 4 additional men and 2 women were tested with ISI 3 ms). The mean and median ratios of the conditioned to the unconditioned MEPs and their coefficients of variation are shown in Table 2. Their distributions are illustrated in Fig. 4. The data for ISIs 4, 10, and 15 ms had an approximately normal distribution. However, the distribution for 3 ms was highly skewed, with no lower tail because the ratio approached zero (see discussion). There were no significant effects of age or sex on the ratio at any ISI (all $P \geq 0.19$ by analysis of variance (ANOVA)). There were weak correlations between the ratios from the long and short ISIs within individuals. However, the data from the 3 and 4 ms ISIs were more highly correlated with each other, as were the data from 10 and 15 ms (Table 3).

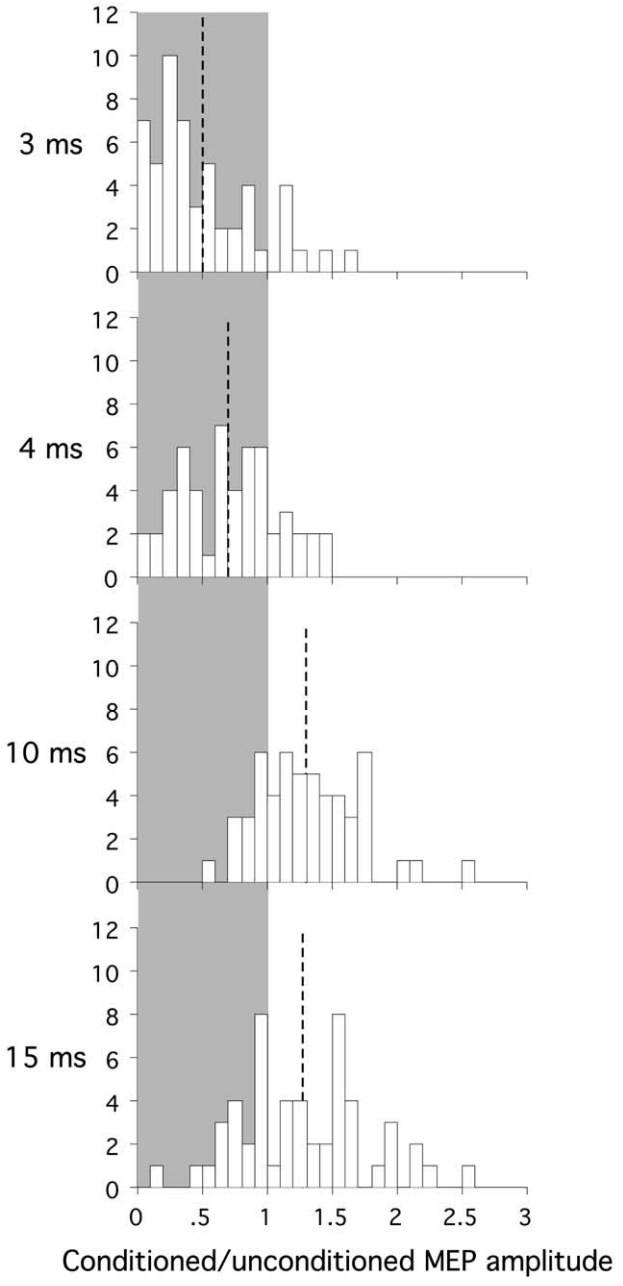

Fig. 4. Histograms showing the distribution of values for the ratio of the conditioned to the unconditioned MEP amplitude at interstimulus intervals (ISIs) of 3, 4, 10, and 15 ms. The y-axes represent number of subjects. The dashed lines indicate the mean for each ISI and the shaded area contains the values showing an inhibitory effect of the conditioning stimulus.

Table 2
Paired-pulse MEP amplitude means, medians, and variability across subjects

ISI	Mean	Median	Standard deviation	Coefficient of variation
3	0.497	0.384	0.394	0.793[a]
4	0.708	0.707	0.377	0.532
10	1.305	1.279	0.390	0.299
15	1.273	1.235	0.497	0.391

[a] Highly skewed distribution, see text.

Table 3
Correlations between the conditioned/unconditioned MEP ratios at different ISIs

ISI	4	10	15
3	0.689	0.198	0.336
4		0.297	0.310
10			0.626

4. Discussion

The MEP threshold varies widely in the healthy population. Based on a comparison of the within-subjects variability in the 19 individuals who were tested on 3 occasions with the between-subjects variability in the entire sample, I estimate that experimental error and other unstable determinants of threshold may account for about 36% of the across subjects variability at rest and about 50% during voluntary activation. If there was any underlying, but undetected, variation in the thresholds due to the menstrual cycle, this might have caused me to overestimate these percentages slightly. Potential sources for experimental error in threshold determination are many, but are most likely to include electrode placement, coil placement, stimulation (trial) frequency, and, in the resting state, subthreshold activation of corticospinal outputs. I note here that the round coil was used intentionally because it contacts the head around its entire circumference and is not subject to rotation in the 'roll', 'pitch' or 'yaw' axes. Therefore, my estimates of error magnitude may be too conservative for studies using hand-held 8-shaped coils, which contact the scalp at a single point around which they are free to pivot. Other factors may be beyond the control of the experimenter, such as asynchronous firing of motor units with phase cancellation, causing variable MEP amplitude and morphology (Magistris et al., 1998) and other unknown physiological sources of variability in the MEP amplitude.

The remaining between-subjects variability in MEP threshold presumably results from relatively stable biological differences between individuals. These are largely unknown, but have been studied in at least one instance and there are grounds for further speculation. Previous studies (Kozel et al., 2000; McConnell et al., 2001) indicate, unsurprisingly, that MEP threshold increases with the distance from the coil to the underlying cortex. However, cortical volume decreases with age, even in young, healthy subjects, particularly men (Gur et al., 2002). Therefore, if brain volume was a significant contributor to the variation in MEP threshold, one would expect to detect a relationship between age and MEP amplitude in a sample of this size. As mentioned in Table 1, no such relationship was found.

Our sibling data suggest that the MEP threshold has a very significant genetic input. Such a factor (or factors) might operate at the level of skull thickness or the pattern of cortical sulcation. On the other hand, it could be an intrinsic neuronal property. For instance, the activity of cation channels is a heritable characteristic (Singh et al., 1999), and has been implicated by drug studies (Ziemann et al., 1996a; Chen et al., 1997) as a determining factor in MEP threshold.

There was also great between-subjects variability in the paired-pulse ratio data. This data set provides no estimate of the within-subjects reliability of the paired-pulse technique. However, Boroojerdi et al. (2000) repeated paired-pulse studies 3 times in 4 healthy subjects and found a variation across measurements of 37 and 23% for the pooled inhibitory and excitatory ISIs, respectively. Their coefficients of variation of 0.67 and 0.21 across subjects correspond fairly well to our own (Table 2). However, it is important to note the skewness of the distribution of values for our 3 ms data (Table 2; Fig. 4). This means that estimates of the variability for the inhibitory ISIs based the standard deviation, (e.g. the coefficient of variation) may give an inflated estimate of the true variability. This could account for Boroojerdi et al.'s higher estimate of between-subjects variability at the shorter ISIs, which included 2 and 3 ms. This finding also implies that parametric statistical tests may be inappropriate for group comparisons of these values. Despite this element of uncertainty, the data suggest that a substantial portion of the apparent variation across subjects in our study is due to error or unstable within-subjects factors. The potential contributors to error are similar to those listed above for the MEP threshold. However, electrode and coil placement are less likely to contribute, because the stimulation intensity was adjusted to account for differences in apparent excitability and the dependent variable (ratio) is a relative, rather than an absolute measure.

While the paired-pulse method has been used quite successfully to compare various neurological and psychiatric patient groups to healthy subjects (Ridding et al., 1995; Ziemann et al., 1997a,b; Greenberg et al., 2000) virtually all of the reported patient data lie within the range that I found in this sample of healthy individuals.

At least one stable source of interindividual variability in the paired-pulse response has been detected, if not fully explored. In a previous study (Wassermann et al., 2001) of a subsample ($N = 46$) of these subjects, we showed that paired pulse excitability was significantly correlated with a stable behavioral trait, i.e. the tendency to experience anxiety and other negative emotions, particularly in men ($r = 0.63$), where the data were free from random effects of the menstrual cycle. This suggests that these associated behavioral and physiological traits accounted for roughly 40% of the variance. In women the correlation was weaker but still present ($r = 0.48$), accounting for about 23% of the variance. These substantial effects suggest that a significant portion of the variability in the response to paired TMS is accounted for by potentially important biological differences between individuals. Such hidden variations (endophenotypes) may also pose significant confounds in group studies.

With regard to the correlations within the paired-pulse data, the greater correlation between the paired-pulse ratios within the inhibitory (3 and 4 ms) and facilitatory (10 and 15 ms) ISIs suggest that paired-pulse inhibition and facilitation may vary independently within individuals. It is also noteworthy that appreciable numbers of individuals showed facilitation at ISIs of 3 and 4 ms and inhibition at 10 and 15 ms. While perhaps surprising to some, these values lay on the tails of normal distributions and did not appear to come preferentially from either sex or any particular band of the age spectrum. The correlations between the data from the different ISIs suggest that at least some of these tendencies reflected stable individual variation.

No correlations with age or effect of sex were found in the paired-pulse data. An earlier report claimed that older subjects showed less intracortical inhibition (Peinemann et al., 2001). This study, rather than a population-based, correlational design, was a comparison between two relatively small groups of individuals who may have differed systematically on other measures beside age. While an effect of the magnitude suggested by their study was clearly absent in ours, as with threshold, the question of a weak effect of age on MEP ratio remains, since older individuals, particularly men, were relatively poorly represented in our sample.

We have reported before on the effects of ovarian hormones on paired-pulse excitability (Smith et al., 1999, 2002). This is a potential source of both within- and across-subjects variability. However, there seem to be no overall differences between men and women when the group of women is large enough for random sampling to negate cyclical effects.

Another potential source of variability that has not been addressed to date is the time of study. Presumably, circadian variations in arousal, circulating hormone levels, and other factors affecting neural function could influence cortical and spinal excitability.

This is by far the largest and one of the most diverse samples of individuals ever included in a reported TMS study. The techniques described are conventional and the degree of care and precision used in the experiments are likely comparable to those of most laboratories. From the degree of variability both within- and across-subjects, it is possible to say conclusively what TMS users have long believed, i.e. that neither the MEP threshold nor the paired-pulse ratios, as measured here, will be useful as clinical tests for individual subjects or even for comparisons between groups with minor differences. Clearly, if such tests are to be had, refinements in TMS methods will be necessary. Some of these are already available, for instance the triple pulse technique of Magistris et al. (1998), which eliminates the variability in the MEP due to asynchronous firing of motor units. On the positive side, it is also possible to state with confidence that the MEP to single and paired TMS is a sensitive measure of corticospinal function and has the potential to reveal far more than it has to date. Particularly striking is the potential of TMS to detect physiological endophenotypes and correlations with behavioral traits that may be the result of genetic variations.

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