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Determination of motor threshold using visual observation overestimates transcranial magnetic stimulation dosage: Safety implications

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HIGHLIGHTS

- This is the largest study to date to systematically compare TMS motor thresholds (MTs) determined via electromyography (EMG) to those determined via observation of hand movement (OM).
- MTs determined via OM were on average 111% of those determined via EMG.
- OM-MT should not be assumed to be equivalent to EMG-MT, and may lead to stimulation outside of accepted safety standards.

ABSTRACT

Objective: While the standard has been to define motor threshold (MT) using EMG to measure motor cortex response to transcranial magnetic stimulation (TMS), another method of determining MT using visual observation of muscle twitch (OM-MT) has emerged in clinical and research use. We compared these two methods for determining MT.
Methods: Left motor cortex MTs were found in 20 healthy subjects. Employing the commonly-used relative frequency procedure and beginning from a clearly suprathreshold intensity, two raters used motor evoked potentials and finger movements respectively to determine EMG-MT and OM-MT.
Results: OM-MT was 11.3% higher than EMG-MT ($p < 0.001$), ranging from 0% to 27.8%. In eight subjects, OM-MT was more than 10% higher than EMG-MT, with two greater than 25%.
Conclusions: These findings suggest using OM yields significantly higher MTs than EMG, and may lead to unsafe TMS in some individuals. In more than half of the subjects in the present study, use of their OM-MT for typical rTMS treatment of depression would have resulted in stimulation beyond safety limits.
Significance: For applications that involve stimulation near established safety limits and in the presence of factors that could elevate risk such as concomitant medications, EMG–MT is advisable, given that safety guidelines for TMS parameters were based on EMG-MT.

1. Introduction

Transcranial magnetic stimulation (TMS) is gaining popularity as a therapeutic tool for alleviating depression, with great potential for use in other illnesses as well, and as an experimental method for establishing causal brain-behavior relationships. TMS dosage is generally set relative to the minimum intensity of the magnetic

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field necessary to elicit a reliable response in a target muscle when stimulating the motor cortex of an individual, the motor threshold (MT), with the assumption made that excitability in non-motor cortex is similar to that of motor cortex, or at least correlated. MT has become the standard for determining TMS dose due to its relationship with safety in regard to the possibility of inadvertent seizure, and to its efficacy and reproducibility in stimulating cortex.

The International Federation of Clinical Neurophysiology (IFCN) defined MT in a resting muscle (Resting MT; RMT) through the use of electromyography (EMG) in two seminal publications, first using an ascending relative frequency method to find the "level which induces reliable (usually around 100 μV) motor evoked potentials (MEPs) in 50% of 10–20 consecutive stimuli" (Rossini et al., 1994) and later using a descending relative frequency method to find a level at which an MEP of at least 50 μV occurs in at least 50% of 10–20 consecutive trials (Rothwell et al., 1999). The use of EMG to determine MT (EMG-MT) has the inherent advantage of providing a quantitative measure of muscle response. More important, MT based on EMG has been the basis for establishing IFCN guidelines for the safe use of TMS (Wassermann, 1998; Rossi et al., 2009). Rossi et al. (2009) reviewed the sixteen cases known at the time of inadvertent seizures, the most severe acute adverse effect caused by TMS, and reaffirmed the use of the limits on TMS parameters, established in relation to EMG-MT (Wassermann, 1998), in preventing inadvertent seizures.

However, a second method for determining MT has seen increasing use, in which EMG is not used, and instead the threshold estimation is performed by counting visually-detected movements of the target muscle (observed movement: OM-MT; Pridmore et al., 1998). This method has the advantage of being more convenient to perform, and simpler in a clinical setting since no expertise in EMG is necessary. There is currently no clear agreement among TMS users regarding the two methods (Anderson and George, 2009). A recent international consensus conference on TMS safety did lead to a general agreement that EMG-MT is more precise and that OM-MT may overestimate MT, but only 80% of participants endorsed these ideas and full consensus was not reached (Rossi et al., 2009). One recent study presented evidence that endorsed OM-MT as a reliable method of determining MT (Varnava et al., 2011).

Only four studies have been published in which a direct comparison of the two methods of determining MT has been made, with varying results (Balslev et al., 2007; Conforto et al., 2004; Hanajima et al., 2007; Pridmore et al., 1998). In Pridmore et al. (1998), six subjects were tested, and in five of those six, OM-MT was lower than EMG-MT. In two others, EMG-MT was slightly lower than OM-MT, on average by less than 2% of total stimulator output (Balslev et al., 2007 (4 subjects); Conforto et al., 2004 (14 subjects)). In the fourth study testing ten subjects, EMG-MT was much lower than OM-MT, on average by 6% of total stimulator output (Hanajima et al., 2007). One difficulty in comparison is that in two of these studies EMG was measured from a particular muscle, yet OM was performed counting any motion from the entire hand and wrist (Conforto et al., 2004; Pridmore et al., 1998).

In examining the four studies comparing the two methods for estimating MT, it is concerning that in two of them the reported data indicated that use of OM-MT to establish subsequent TMS dosage could lead to adverse outcomes in some individuals. In Conforto et al. (2004), one subject had an OM-MT much higher than his or her EMG-MT. The difference was 14% of stimulator output, which corresponded (using the group mean EMG-MT, as no individual MTs were provided) to an OM-MT 132% of EMG-MT. In Hanajima et al. (2007), while individual MTs were not reported, on average the OM-MTs were 113% higher than EMG-MTs, presumably with some individuals having even higher percentage differences. Because the parameters for safe use of TMS were based on EMG-MTs (Wassermann, 1998; Rossi et al., 2009), the use of such OM-MTs to establish dosage in subsequent repetitive TMS sessions could result in overstimulation. Overestimation of MT leads to stimulation at a higher intensities above true MT. In single pulse TMS studies, this results in decreased focality. In rTMS studies or clinical settings, this results in stimulation trains that exceed established safety limits and could lead to accidental seizures. For example, if the OM-MT of the subject in Conforto et al. (2004) whose threshold was 32% higher than his/her EMG-MT was used to establish the TMS dose for a typical depression treatment, the treatment parameters used would exceed safe limits. Typically, the device might be set at 100% MT, applying 4 s trains at 10 Hz. As consensus safe limits are based on EMG-MT, the patient would be receiving an intensity of over 130% EMG-MT, where safe train duration is actually 2.9 s (Rossi et al., 2009; Table 5), and would thus be receiving an unsafe, potentially seizure-inducing dose.

With these considerations in mind, we found OM-MT and EMG-MT for each of a larger group of twenty subjects and focused our attention on individual variability in OM-MT and EMG-MT differences, to determine how well OM-MT estimates EMG-MT, and whether OM-MT is adequate to prevent stimulation at potentially unsafe levels. It should be noted that while the most recent IFCN consensus guidelines included other methods for finding MT such as adaptive staircases and the two-threshold method, and recommended using adaptive staircasing where possible (Groppa et al., 2012), we used the traditional relative frequency method (Rothwell et al., 1999) in the present study, as it is still the most commonly used method of estimating MT in both clinical and research situations.

2. Methods

2.1. Subjects

Twenty healthy adult volunteers (8 female, mean age 40 ± 13 years, range 19–62) were recruited, gave written informed consent, and were paid for participation in one of several healthy control TMS studies, approved by the New York State Psychiatric Institute Investigational Review Board. Subjects were excluded if they were over the age of 65, had a history of any Axis I psychiatric disorder including substance abuse or dependence as determined by the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Non-Patient Edition (SCID-I/NP; First et al., 1998) or history of any neurological disease or other illness that would present a risk with TMS. All subjects were screened with physical and neurological examinations, blood and urine testing, urine drug screens, and pregnancy tests for women of childbearing capacity.

2.2. Transcranial magnetic stimulation (TMS)

This study used a Magstim 200 TMS device (Magstim Co., Whitland, Wales, UK) and a 70 mm figure-8 coil. Consecutive stimuli were separated by 7–10 s to avoid carry-over effects. Stimulation intensity was initially set at 48% of the maximum device intensity, a suprathreshold level for which most individuals. Maintenance of optimal coil orientation was assisted by Brainsight computerized frameless stereotaxy system (Rogue Research, Montreal, Canada). This system uses an infrared camera to monitor the positions of tracking devices attached to the TMS coil and to the subject's head. The relative positions of the coil and the target site(s) on the subject's head were tracked in real time, and allowed the coil to be placed and maintained to within 1 mm of the site chosen during MT determination.