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Reliability of the 'observation of movement' method for determining motor threshold using transcranial magnetic stimulation

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ABSTRACT

The aim of this study was to establish the reliability of the observation of movement (OM) method for obtaining motor threshold (MT) in transcranial magnetic stimulation (TMS). MTs were obtained on separate days, following separate hunting procedures, for both left and right motor cortex (M1), with one or multiple estimates obtained from the same hemisphere within a single session. MTs obtained using the OM method were highly reliable and reproducible on different days (left M1: $r = .98$, $p < .0001$; right M1: $r = .97$, $p < .0001$). MTs were not influenced by the order of acquisition when two hemispheres were stimulated in the same session [$F(1,22) = .12$, $p = .73$] or by the collection of additional MTs as part of the distance-adjusted procedure [$F(1,23) = .74$, $p = .40$]. The results verify the reliability of the OM method and confirm its viability for the safe and efficient application of TMS to the left and right M1. The OM method is a reliable technique for obtaining MT and is relatively simple and quick to run. It therefore provides an effective procedure for research and clinical applications.

1. Introduction

Over the last decade, transcranial magnetic stimulation (TMS) has developed into a valuable technique for experimental and clinical neuroscientists studying the function and dysfunction of the human brain. TMS is a non-invasive neurostimulation technique based on the principle of electromagnetic induction. During TMS a brief current is passed through a stimulating coil over the scalp, inducing electrical currents in the underlying cortex (Wagner et al., 2009). The induced current activates neuronal axons, causing action potentials. Recent years have witnessed a rapid increase in the application of TMS as a 'virtual lesion' technique to examine behavioural consequences of neural disruption (Pascual-Leone et al., 1999), as a therapeutic aid in psychiatric settings (Wassermann and Lisanby, 2001), and as a diagnostic tool for detecting neuropathological changes in cortical excitability (Frasson et al., 2003). Its potential has been further enhanced by combining TMS with simultaneous measures in other electrophysiological (e.g. electroencephalography) or imaging modalities (e.g. functional magnetic resonance, near-infrared spectroscopy) or with exposure to neuroactive drugs (pharmaco-TMS) (see Ziemann, 2011 for a recent review), thus enabling the neurophysiological effects of TMS to be measured as well as behavioural consequences.

The increasing popularity of TMS highlights the necessity for safe, effective and reliable application of brain stimulation. This requires an appropriate level of electric current to be induced within a target region. Over-stimulation increases the risk of known adverse effects (Rossi et al., 2009) and reduces the focality of the induced excitation (Thielscher and Kammer, 2004), while under-stimulation may reduce the efficacy of a prescribed clinical treatment (Mosimann et al., 2002) or reduce the likelihood of detecting a statistically significant result under experimental conditions. Appropriate levels of stimulation intensity are typically determined according to a measure of cortical excitability known as 'motor threshold' (MT). MT is defined as the minimum stimulation, applied to the scalp overlying motor cortex (M1), required to induce an overt motor response in the contralateral hand muscle (Kozel et al., 2000; McConnell et al., 2001; Stokes et al., 2007). MT can be used to calibrate the dose of TMS at M1, as well as other brain areas if adjusted to account for individual variations in scalp-to-cortex distance (i.e. distance-adjusted MT: Stokes et al., 2005, 2007).

Two methods can be used by clinicians and researchers to determine a motor response in the hand muscle: one involves recordings using electromyography (EMG) and the other relies on the observation of a muscle twitch. In the earliest studies MT has been estimated by recording motor evoked potentials (MEPs) of the resting muscle of the abductor pollicis brevis (APB) with an EMG

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(Barker et al., 1985). One disadvantage of the method, however, is that MEP amplitude can be highly variable both within and between subjects (Kiers et al., 1993; Säisänen et al., 2008; Jung et al., 2010), thus reducing the repeatability and accuracy of the results (Julkunen et al., 2011). More recently, many have adopted the simpler and more convenient visualisation or 'observation of movement' (OM) method in which MEPs are replaced with observed movements of the thumb or fingers following stimulation of the contralateral motor cortex. Since it does not require EMG, the OM method reduces the time and expense of the procedure, as well as the need for specialist training (Schutter and van Honk, 2006).

There is currently a lack of consensus on which of the two techniques is best for determining the motor threshold (Anderson and George, 2009). Only a few studies have directly compared the MTs produced by the EMG-assisted method with those from the OM method, yielding different results. Some researchers have found that the two produce different MTs (Conforto et al., 2004; Hanajima et al., 2007), while others found the two are strongly related and yield similar estimates of cortical excitability (Pridmore et al., 1998; Stokes et al., 2005; Balslev et al., 2007). In spite of the limited and equivocal research, the OM method appears to be the method of choice for many researchers and clinicians in experimental (Fierro et al., 2000; Pourtois et al., 2001; Denslow et al., 2005; Göbel et al., 2006; Oliveri and Vallar, 2009; Hoffman et al., 2010; Seifert et al., 2010; Van der Werf et al., 2010; Ishibashi et al., 2011) and clinical applications (Cohen et al., 2004; Epstein et al., 2007; Goyal et al., 2007; Mogg et al., 2007; Borckardt et al., 2008; Fitzgerald et al., 2008; Vercammen et al., 2009; Barth et al., 2011). Since MTs are the stimulation intensity around which safety parameters for TMS are defined (Wassermann, 1998), it is critical to determine the reliability of this popular and simpler technique.

In the present study, we test the reliability of the OM method for obtaining MT, as well as distance-adjusted MT (daMT). We obtain MTs on separate days, following separate hunting procedures, for both left and right M1, with one or multiple estimates obtained from the same hemisphere. Our results show that MTs obtained from left and right motor cortex, using the OM method, are highly reliable and are unaffected by the order of acquisition when both hemispheres are stimulated in the same session or when multiple estimates are collected. These results verify the reliability of the OM method and confirm its viability for the safe and effective application of TMS.

2. Materials and methods

2.1. Participants

Twenty four volunteers (12 male; 12 female; aged 19–30, 23.7 ± 3.7, mean ± SD) participated in the present study. All were deemed right-handed according to the Briggs and Nebes Handedness Questionnaire (Briggs and Nebes, 1975). Participants were screened for contraindications to MRI and TMS (Wassermann, 1998) prior to testing and provided informed consent. The experimental protocol was approved by the School of Psychology Ethics Committee at Cardiff University.

2.2. Apparatus

Cortical stimulation was delivered via a biphasic MagStim Rapid system (60 μs magnetic field rise time, 250 μs pulse duration) using a 2.2 T 70-mm figure-eight induction coil. Prior to testing, structural T1-weighted magnetic resonance (MR) scans were acquired for each participant using a GE Signa 3 T system (1 mm × 1 mm × 1 mm, sagittal acquisition). TMS/MR registration was performed using a magnetic tracking device (miniBIRD 500, Ascension Tech) and MRIcro/MRIreg interface software (Rorden and Brett, 2000). The distance between the scalp and stimulating coil was manipulated using custom-machined acrylic plastic separators, 3.17 mm, 5.63 mm and 9.03 mm in thickness.

2.3. Procedure

As in previous studies (Kozel et al., 2000; McConnell et al., 2001; Stokes et al., 2007) MT was defined as the minimum stimulator output required to induce a visible twitch in the APB muscle of the contralateral hand on 5 of 10 consecutive pulses delivered at a rate of ≤0.5 Hz to the motor cortex. For each participant, the stimulating coil was positioned over M1, and the lowest stimulator output to induce a motor response was determined using an adaptive staircase method (Kozel et al., 2000; McConnell et al., 2001; Stokes et al., 2005). The coil was held tangentially to the surface of the scalp oriented 45° to the midline dividing the two brain hemispheres. The location of M1 was determined by varying the position of the coil while delivering magnetic pulses until a reliable twitch in the contralateral hand was observed. The optimal stimulation site, or 'hot-spot' (Rossini et al., 1994), was then marked with a semi-permanent marker to ensure that the same location was stimulated throughout the testing session. Tilt and coil orientation were then held constant to avoid extraneous influences on effective stimulation. Stimulator intensity was increased after trials in which an observable motor response was present on less than 5 out of 10 trials and decreased for trials in which a motor response was present on ≥5 of 10. Intensity was increased or decreased by steps of 5%, 2% and 1% until MT was found, with the step-size reduced after each reversal.

MTs were determined within individual participants in three separate sessions run on three separate days, following separate hunting procedures, at least 24 h apart. In session 1 MTs were established for both left and right M1 when the distance between the scalp and stimulating coil was 0 mm (base-level MT: first estimate of MT_0). The order of hemisphere stimulation was counter-balanced across the sample. Session 1 took approximately 10 min to complete. In sessions 2 and 3, MTs for left and right M1 were obtained at coil–scalp distances of 0 mm (second estimate of MT_0), 3.17 mm, 5.63 mm and 9.03 mm. The order of coil–scalp distances was randomized across the sample and the order of hemisphere stimulation was counterbalanced across participants in sessions 2 and 3. Each session was completed in approximately 20 min. The average lapsed time between the first estimate of MT_0 in session 1 and the second MT_0 estimate in session 2 was 53.44 h (just over 2 days: SD = 48.68). To avoid possible expectancy effects, the experimenter was blind to the participant's previous MT estimate. With the stimulating coil positioned tangential to the scalp surface, the separators were placed between the coil and the scalp while maintaining the alignment of the virtual cathode over the marked scalp location.

Finally, we used an automated procedure to estimate the distance between the scalp surface and underlying cortical surface. First, we extracted a volume of grey matter using the segment routine in SPM 8 (Wellcome Department of Cognitive Neurology, London, UK). Next, we fitted a mesh model of the cortical surface, which was then used to calculate the distance between cortex and a given scalp coordinate. In this study, we calculated the distance between the cortical surface and the scalp location stimulated during MT, and transformed to voxel-space using miniBIRD/MRIreg. For stability, we used the mean distance of the 100 nearest cortical voxels. To validate this automated method of calculating scalp–cortex distances against previously established, but more labor-intensive manual procedures (see McConnell et al., 2001; Stokes et al., 2005), we also calculated scalp–cortex distances using the manual method for comparison. There was no difference in the