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Distance-adjusted motor threshold for transcranial magnetic stimulation

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Abstract

Objective: To examine the relationship between coil–cortex distance and effective cortical stimulation using transcranial magnetic stimulation (TMS) in the left and right motor cortex. We also compare the effect of coil–cortex distance using 50 and 70 mm figure-eight stimulating coils.
Methods: Coil–cortex distance was manipulated within each participant using 5 and 10 mm acrylic separators placed between the coil and scalp surface. The effect of cortical stimulation was indexed by resting motor threshold (MT).
Results: Increasing distance between the coil and underlying cortex was associated with a steep linear increase in MT. For each additional millimetre separating the stimulating coil from the scalp surface, an additional ~2.8% of absolute stimulator output (~0.062 T) was required to reach MT. The gradient of the observed distance effect did not differ between hemispheres, and no differences were observed between the 50 and 70 mm TMS coils.
Conclusions: Coil–cortex distance directly influences the magnitude of cortical stimulation in TMS. The relationship between TMS efficacy and coil–cortex distance is well characterised by a linear function, providing a simple and effective method for scaling stimulator output to a distance adjusted MT.
Significance: MT measured at the scalp-surface is dependent on the underlying scalp–cortex distance, and therefore does not provide an accurate index of cortical excitability. Distance-adjusted MT provides a more accurate index of cortical excitability, and improves the safety and efficacy of MT-calibrated TMS.

Keywords: Transcranial magnetic stimulation; Coil–cortex distance; Motor threshold; Distance-adjusted motor threshold; Safety; Efficacy

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive method for inducing local increases in brain activity. The unique capacity to manipulate neuronal activity within the intact human brain has established TMS as an important technique within both experimental (Walsh and Cowey, 2000; Chambers and Mattingley, 2005) and clinical (Wassermann and Lisanby, 2001; Currà et al., 2002) neuroscience. In the laboratory, TMS is typically applied as a "virtual lesion" technique (Pascual-Leone et al., 1999) to examine the behavioural consequences of neural disruption. In contrast to natural lesions, however, TMS permits experimental control of both the location and duration of cortical disruption. Increasingly, TMS is also being used in conjunction with neuroimaging methods such as functional magnetic resonance imaging (fMRI: e.g., Bestmann et al., 2005) and event-related potentials (ERP: e.g., Taylor et al., 2006). The combination of stimulation and measurement enables the neurophysiological effects of TMS to be

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measured as well as the behavioural consequences. Clinical research has revealed the therapeutic potential of TMS, in particular for major depression (Wassermann and Lisanby, 2001), and the technique has also emerged as a potential diagnostic tool for detecting neuropathological changes in cortical excitability (Frasson et al., 2003).

In all of these domains, safe and effective application of brain stimulation requires accurate control over induced cortical excitation. Although TMS is widely considered a safe method for inducing cortical activity, over-stimulation increases the risk of known adverse effects, including headaches, nausea and in extreme cases, seizures (Wassermann, 1998; Machii et al., 2006). Furthermore, over-stimulation reduces the focality of the induced cortical excitation (Thielscher and Kammer, 2004). Conversely, under-stimulation may reduce the efficacy of a prescribed treatment in a clinical setting (Mosimann et al., 2002), and in the laboratory, decreases the likelihood of obtaining statistically significant results. Finally, random variations in the level of cortical stimulation across experimental conditions increase experimental error, reducing statistical power; and non-random variations will confound experimental contrasts, potentially yielding artefactual results.

Commercial stimulators express TMS intensity according to the percent of maximum stimulator output. However, the actual intensity of the generated electromagnetic field is determined by a number of stimulator-specific parameters such as the waveform and duration of the magnetic pulse, and induction coil properties such as size, shape and number of copper windings. Therefore, to provide a measure of stimulation intensity that can be generalised across different TMS-configurations, stimulation output is typically calibrated according to an overt and reliable physiological index of cortical excitation, such as an evoked motor response following stimulation of the contralateral primary motor cortex (M1). To provide a discrete index, the threshold of the motor response, or motor threshold (MT), is generally determined using a staircase method of titration (Rossini et al., 1994). TMS intensity expressed as a percentage of MT provides a measure of applied stimulation that can be generalised across coil geometry and stimulator types, and is used to define standard safety guidelines (Wassermann, 1998). However, MT does not provide a direct measure of intrinsic cortical excitability; several recent studies have demonstrated that MT is also strongly influenced by individual differences in the distance between the scalp and underlying motor cortex (Kozel et al., 2000; McConnell et al., 2001; Stokes et al., 2005).

The physical principles of electromagnetic induction state that the magnetic flux density decreases with distance; therefore, the effect of TMS is inversely proportional to the distance from the stimulating coil (Jalinous, 1991). In practice, scalp–cortex distance critically determines the minimum distance between the stimulating coil and the underlying cortical tissue. Consequently, individual variations in scalp and skull thickness directly influence the magnitude of the induced secondary current within underlying cortex. Previous studies have found that scalp–cortex distance influences the effect of TMS indexed by MT (Kozel et al., 2000; McConnell et al., 2001; Stokes et al., 2005), response to treatment (Mosimann et al., 2002), metabolic response indexed by fMRI (Nahas et al., 2000), and also neurophysiological response measured via intra-cranial recordings (Wagner et al., 2004)

Previously, we developed a novel technique to isolate the effect of distance from individual variations in cortical excitability (Stokes et al., 2005). By systematically varying the distance between the scalp surface and stimulating coil, we demonstrated a steep linear relationship between the scalp–coil distance and the percent of stimulator output required to reach MT. Specifically, using a Magstim Rapid system connected to a 70 mm figure-eight stimulating coil, we found that for each millimetre separating the scalp and coil surface, an additional ~2.9% of stimulator output (~0.064 T) was required to reach MT. The effect of distance has clear implications for studies that use MT as an index of cortical excitability, and in particular, for studies that use stimulation protocols calibrated to MT for stimulating cortical regions beyond M1. Anatomical analysis reveals substantial scalp–cortex distance variations between different cortical sites (Okamoto et al., 2004; Knecht et al., 2005; Stokes et al., 2005). Consequently, MT-calibrated TMS of non-motor regions with greater scalp–cortex distances than M1 will result in under-stimulation; whereas MT-base TMS of non-motor cortical regions that lie closer to the scalp will result in over-stimulation.

To account for the strong and quantifiable effect of distance, we derived a simple linear correction to calculate a distance-adjusted MT (Stokes et al., 2005):

$$\mathrm{AdjMT} = \mathrm{MT} + m \times (D_{\mathrm{Site}X} - D_{\mathrm{M1}})$$

where AdjMT is the adjusted MT in % stimulator output, MT is the unadjusted MT in % stimulator output, D_{M1} is the distance between the scalp and M1, $D_{\mathrm{Site}X}$ is the distance between the scalp and a second cortical region (Site*X*), and m is the distance-effect gradient. We argue that distance-adjusted MT provides a more direct index of cortical excitability than conventional MT, reducing the risk of over-stimulation (e.g., Chambers et al., 2006b), and increasing the validity of quantitative comparisons between cortical sites (e.g., Chambers et al., 2006a).

In the present study, we applied our previously validated 3-step method (Stokes et al., 2005) to further explore the application of AdjMT. In the first experiment, we examined the distance-effect characteristics in the right and left hemisphere, within participants using a standard 70 mm figure-eight induction coil. In the second experiment, we explored the effect of distance on MT using a 50 mm coil, which is becoming increasingly popular for inducing focal stimulation with reduced superficial artefacts (e.g., Muggleton et al., 2003). The results were consistent with our previous finding: distance significantly influences MT, and the relationship between MT and distance is well character-

ised by a steep linear function. In both hemispheres, and using both induction coils, we reveal an average distance-effect gradient of ~2.8% per mm. These results confirm and extend our proposal that AdjMT provides an accurate method to correct for the effect of distance on TMS efficacy.

2. Methods and materials

2.1. Participants

Twenty-four right-handed volunteers (16 male; 8 female; aged 19–28, 23.4 ± 2.8, mean ± SD) participated in the present study. Prior to testing, participants provided written informed consent, and were screened for contraindications to TMS (Wassermann, 1998). All experimental protocols were approved by the Human Research Ethics Committee at the University of Melbourne.

2.2. Apparatus

Cortical stimulation was delivered via a 2.2 T biphasic MagStim Rapid system (60 μs magnetic field rise time, 250 μs pulse duration) using either 50- or 70-mm figure-eight induction coil (MagStim). Prior to testing, structural T1-weighted magnetic resonance (MR) scans were acquired for each participant using a GE Signa 3T system ($1.3 \times 1.3 \times 1.3$ 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). As described previously in detail (Stokes et al., 2005), the distance between the participants' scalp and the stimulating coil was manipulated using custom-machined acrylic plastic separators, 5 and 10 mm in thickness.

2.3. Procedure

Primary motor cortex (M1) was localised in each participant by varying the precise scalp position of the stimulating coil whilst delivering magnetic pulses at a fixed output intensity. The optimal stimulation site, or 'hot-spot' (Rossini et al., 1994), was then marked to ensure that the same location was stimulated throughout the testing session. Tilt and coil orientation were held constant to avoid extraneous influences on effective stimulation. As described previously (Stokes et al., 2005), resting MT was defined as the lowest level of M1 stimulation required to produce a reliable twitch in the contralateral abductor pollicis brevis (APB), determined using an adaptive staircase measure (also see Kozel et al., 2000; McConnell et al., 2001). In this previous study, we showed that a binary measure of motor activity defined either by a visual twitch or electromyographic (EMG) recording provides reliable, and highly correlated, measures of MT (also see Pridmore et al., 1998; Conforto et al., 2004).

To examine the relationship between MT and coil–cortex distance, we randomly varied the distance between the scalp and stimulating coil using the 5 mm and 10 mm separators. This resulted in MT measures at three scalp–coil distances: 0 mm (Base-level MT; MT_0), 5 and 10 mm. We initially applied this method to the left and right hemispheres in 14 participants. The order in which the separators were used was randomised, and the order of hemisphere was counter-balanced across participants. To compare the effects of distance using a different coil diameter, we conducted a second set of measures in the right M1 of another 10 participants using a 50 mm stimulating coil. Finally, structural analyses of MR data determined the scalp–cortex distance in each participant at each stimulation site. Using the imaging software MRIcro, we applied a previously established procedure (McConnell et al., 2001; Stokes et al., 2005) to determine an average measure of M1 scalp–cortex distance across a volume spanning 16 voxels (~21 mm) in the sagittal plane and 7 voxels (~9 mm) in the coronal plane.

3. Results

3.1. The effect of scalp–cortex distance using a 70 mm TMS coil in the right and left motor cortex

With increasing distance between the scalp surface and stimulating coil, higher levels of stimulator output were required to reach MT. Fig. 1 illustrates the observed relationship between scalp–coil distance and MT in the left and right M1.

A two-way repeated measures analysis of variance (ANOVA) was performed on the data acquired using a 70 mm stimulating coil, including within-subjects factors of M1 Laterality (left vs right) and Scalp–Coil Distance (D_{0mm}, D_{5mm} and D_{10mm}). A significant main effect was observed for Scalp–Coil Distance [$F(2,20) = 521.3$, $p < .001$]. There was no significant effect of M1 Laterality ($F < 1$), and no interaction was detected ($F < 1$). Trend

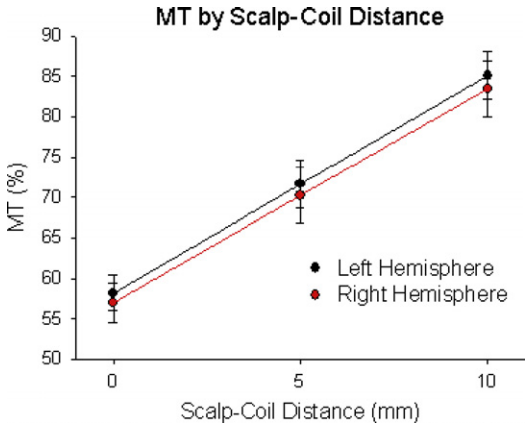

Fig. 1. The relationship between scalp–coil distance and MT using a 70 mm coil. Data points represent mean MT measured over the right (red) and left (black) M1. Error bars are ±1 SE.

Table 1
Mean and standard error of the within-participants effect of scalp–cortex distance on MT using a 70 mm coil in the left and right M1

	MT_0	Scalp–M1 distance	Distance-effect gradient	R^2
Left M1	60.9 (2.5)	14.9 (0.7)	2.7 (0.1)	.99 (<0.01)
Right M1	60.8 (3.0)	15.6 (0.9)	2.8 (0.1)	.99 (<0.01)

analysis of scalp–coil distance collapsed across M1 Laterality revealed an exclusive linear term [$F(1,10) = 786.0$, $p < .001$; second order polynomial $F < 1$], and a linear regression ($y = 2.7x + 58$) performed on the mean scalp–coil distance MT values accounted for over 99% of the variance.

The effect of scalp–coil distance on MT was also well characterised by a linear function in both left and right M1 in individual participants (see Table 1). Repeated measures t-tests did not reveal any hemispheric differences for MT measured at the scalp surface [MT_0: $t(13) = .116$, $p = .909$], scalp–cortex distance [$t(12) = -.952$, $p = .360$], distance-effect gradient [$t(13) = -.529$, $p = .606$], or the reliability of the linear fit [$t(13) = -.131$, $p = .898$].

Correlational analyses revealed a significant relationship between MT_0 in each hemisphere [see Fig. 2a: $r(14) = .92$, $p < .001$]. Similarly, scalp–cortex distance measures were also correlated between left and right M1 [see Fig. 2b: $r(13) = .61$, $p = .027$]. However, neither the gradient nor the reliability of the distance effect correlated significantly between the hemispheres ($p = .158$ and $p = .710$, respectively; data not shown).

Collapsing across stimulation hemisphere, we observed a significant correlation between MT_0 and scalp–cortex distance [see Fig. 3a: $r(14) = .61$, $p = .021$], and also between MT_0 and the distance-effect gradient [see Fig. 3b: $r(14) = .66$, $p = .011$]. Despite the strong relationship between MT_0 and scalp–cortex distance, and between MT_0 and the distance-effect gradient, there was no evidence of a correlation between scalp–cortex distance and the distance-effect gradient [$r(14) = .08$, $p = .775$; data not shown].

3.2. The effect of scalp–cortex distance using a 50 mm TMS coil in the right motor cortex

Consistent with the coil distance effects described above, we also observed a strong relationship between increasing scalp–coil distance and MT using a 50 mm figure-eight stimulating coil (see Fig. 4).

Table 2
Mean and standard error of the within-participants effect of scalp–cortex distance on MT using a 50 mm coil in the right M1

	MT_0	Scalp–M1 distance	Distance-effect gradient	R^2
50 mm coil	59.6 (2.8)	17.0 (0.9)	2.8 (0.2)	.99 (<0.01)

We performed a mixed-model ANOVA with a fixed factor for Scalp–Coil Distance (0, 5 and 10 mm) and a random factor of Coil Diameter (50 vs 70 mm). A main effect was observed for Scalp–Coil Distance [$F(2,2) = 395.6$, $p = .003$], but not for Coil Diameter ($F < 1$). There was no significant interaction ($F < 1$). Linear regression ($y = 2.8x + 56$) performed on the mean scalp–coil distance MT values accounted for >99% of the variance. Linear functions also provided an excellent account of distance effects in each participant (see Table 2).

Independent samples t-tests compared individual estimates of MT obtained using a 50 mm coil with the right hemisphere data collected using a 70 mm coil. No significant group differences were observed for MT_0 [$t(21) = -0.2$, $p = .875$], scalp–cortex distance [$t(21) = 1.2$, $p = .261$], distance-effect gradient [$t(21) = 0.4$, $p = .722$] or the reliability of the fit [$t(21) = 0.1$, $p = .927$]. Consistent with the 70 mm coil data, a correlation was also detected between MT_0 and the distance-effect gradient [see Fig. 5: $r(10) = .84$, $p = .003$], and individual distance-effect gradients did not correlate with scalp–cortex distance ($p = .544$).

4. Discussion

The results of the present study confirm a strong linear relationship between coil–cortex distance and the efficacy of TMS (Stokes et al., 2005). Specifically, we observed that for each millimetre separating the stimulating coil from the scalp surface, and therefore underlying cortex, an additional ~2.8% of stimulator output (~0.062 T) was required to induce an equivalent level of cortical stimulation, defined by resting MT. This abrupt spatial gradient was consistent in both cerebral hemispheres, and using two different coil diameters.

The present data are consistent with the results of previous investigations relating coil–cortex distance to changes in effective stimulation. For example, previous studies have demonstrated a strong link between observed MT and scalp–cortex distance measured at M1 using structural MR (Kozel et al., 2000; McConnell et al., 2001; Stokes et al., 2005). Similarly, in non-motor cortex, scalp–cortex distance reduces the efficacy of therapeutic TMS (Mosimann et al., 2002), as well as the induced neural response to TMS measured via fMRI (Nahas et al., 2000), and intracranial recording (Wagner et al., 2004). To examine the effect of distance more directly, we developed and validated a method for reliably establishing the relationship between distance and effective TMS (Stokes et al., 2005). We systematically varied the distance between the scalp and coil surface using measured separators to determine the relationship between coil–cortex distance and MT. In two separate experiments of this previous study, we showed that increasing scalp–coil distance was associated with a steep linear increase in the amount of stimulator output required to reach MT. Initially, we used 10 separators ranging by 1 mm increments from 1 to 10 mm, however in the second

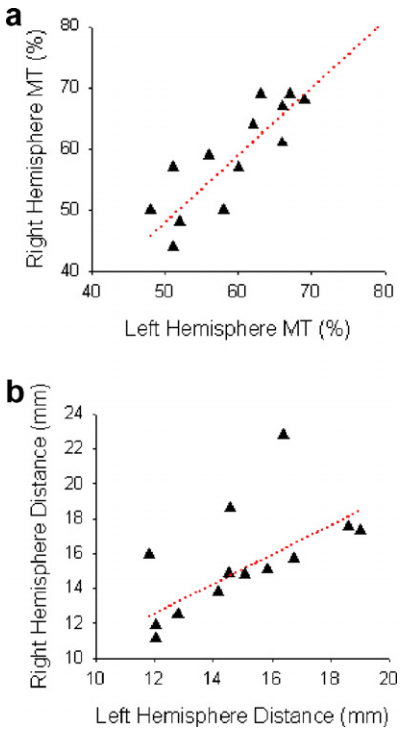

Fig. 2. Inter-hemispheric correlations for MT_0 and scalp–cortex distance using a 70 mm coil. (a) Individual measures of MT at the scalp-surface over the right and left M1, and the between-hemisphere linear regression is shown in red. (b) The distance between the scalp surface and underlying cortex for left and right M1, and the linear regression in red.

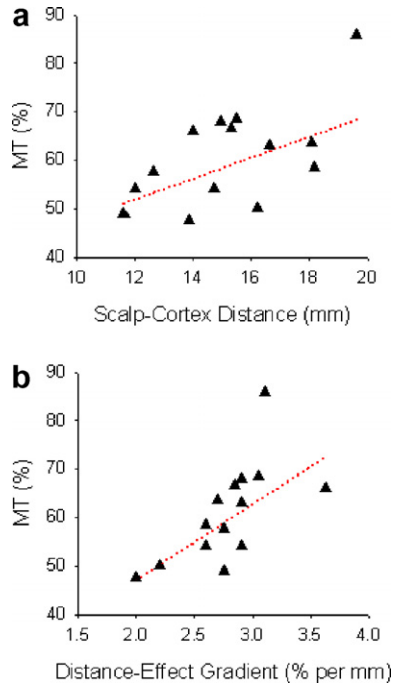

Fig. 3. Correlation between MT_0 and estimates of scalp–cortex distance and the distance-effect gradient using a 70 mm coil. (a) Scalp-level MT as a function of individual measures of scalp–M1 distance in each participant, collapsed across cerebral hemisphere. The linear regression between MT and scalp–M1 distance is shown in red. (b) Scalp-level MT as a function of individually estimated distance-effect gradients, collapse across hemisphere, and the linear regression in red.

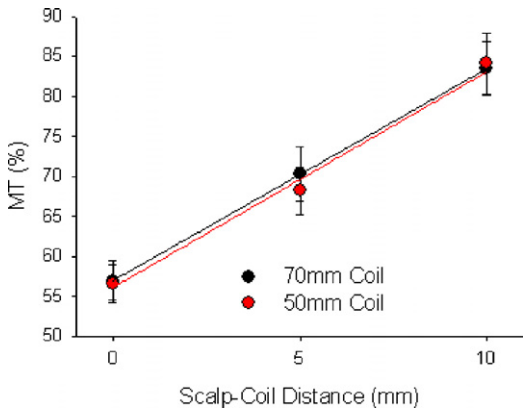

Fig. 4. The relationship between scalp–coil distance and MT using a 50 mm (in red) and 70 mm (in black) TMS coil. Data points represent mean MT measured in the right hemisphere. Error bars are ±1 SE.

experiment we found that an abbreviated procedure produced an equally reliable estimate of the distance-effect gradient using only three distance-varied measures of MT. Hence, in the present study, we applied this more efficient method to examine the effect of distance in two separate cortical sites within the same participants and using two commercially available coil diameters. Under all circumstances, we identified a steep linear function relating scalp–coil distance and MT.

Initially, we examined the effect of scalp–coil distance in the left and right motor cortex in right-handed participants using a standard 70 mm figure-eight coil. Consistent with previous TMS studies (e.g., Triggs et al., 1999), we did not identify any differences between the magnitude of MT in either hemisphere. Moreover, in both cerebral hemispheres we identified a linear function relating scalp–coil distance to observed MT. On average, individually determined linear functions explained more than 99% of the variance, and within-participant comparisons did not reveal any significant hemispheric differences for the distance-effect gradient, or for the reliability of the linear fit. Similarly, factorial analyses revealed only a significant main effect of distance. These results suggest that the effect of distance is equivalent in both hemispheres. Finally, a trend

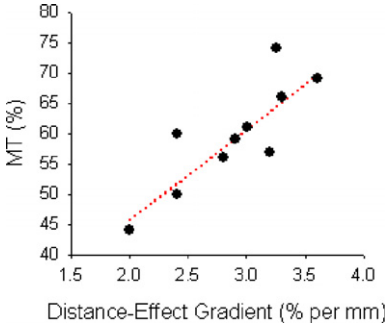

Fig. 5. Correlation between MT_0 and the distance-effect gradient using a 50 mm coil. Data points represent individual participants, and the linear regression is shown in red.

analysis revealed an exclusive linear component relating distance to MT, consistent with previous evidence of a linear distance-effect relationship (Stokes et al., 2005).

The pattern of effects obtained with a 50 mm figure-eight stimulating coil was strikingly similar to the 70 mm coil results. Interestingly, no group differences were observed between MTs measured via either coil size, providing important empirical evidence that the reduction in magnetic field strength associated with a 20 mm reduction in coil diameter does not significantly reduce effective stimulation. Furthermore, and crucial to the current study, no significant differences were observed between the average distance-effect gradients of individually fitted functions, or the reliability of these linear fits. Factorial analysis revealed a main effect for distance, but no other significant terms. These results imply that the effect of distance does not depend on coil size between 50 and 70 mm. Overall, the present results confirmed our previous conclusion that coil–cortex distance critically determines the level of induced cortical stimulation. Furthermore, the reliability of the observed distance relationship further validates a distance correction using an efficient empirical method to model the distance-effect gradient by systematically manipulating scalp–coil distance. The present study, therefore, provides additional validation of the proposed linear distance correction in two cortical sites, and using two difference different coil sizes.

The present findings also shed further light on the basis of the distance-effect gradient. Although the principal aim of the current study was to characterise the distance-effect gradient in both hemispheres, and using two coil sizes, we also examined the relationship between the individual parameter estimates to provide hints toward other factors that may influence the effect of distance on effective stimulation. These additional analyses revealed a significant correlation between the degree of the distance-effect gradient and MT measured at the scalp surface. Furthermore, scalp-level MT was correlated between the hemispheres, although no significant correlation was detected between the distance-effect gradient calculated in each hemisphere. This pattern of relationships indicates two apparently independent sources of variance. The first, shared between the cerebral hemispheres, correlates with MT but not the distance-effect gradient; and the second, independent of hemisphere, correlates with both MT and the degree of the distance effect. Presumably, the first source of variance corresponds to individual variations in cortical excitability that directly influence MT. The second source of variance, however, might correspond to random variation in the lateral position of the coil with respect to the targeted motor representation. Because the strength of magnetic field generated by the figure-eight coil configuration also declines with lateral distance from the central peak (Jalinous, 1991), variation in the precise positioning of the coil over the motor representation will directly influence the observable effect of cortical stimulation. Specifically, we would expect MT to increase with further lateral displacement of the coil from the ideal position. Indeed, a recent study comparing two methods of M1 localisation found that the 'hot-spot' localisation procedure results in lower estimates of MT than using a less accurate fixed approach (Conforto et al., 2004). If the effect of distance also increases with increasing lateral distance from a central peak, then subtle variations in the precise lateral positioning of the coil over the target location will result in distance-effect gradient variations that co-vary with scalp-level MT, as observed in the present study. Although MT and distance-effect gradient variations were minimal (SE = 2.8%; and SE = 0.1% per mm, respectively), they nevertheless highlight the importance of accurate M1 localisation for any MT-based calibration procedure.

The practical implications of a steep distance-effect gradient are revealed by structural examinations of MR scans demonstrating significant inter- and intra-individual variations in the depth of cortical sites (Okamoto et al., 2004; Knecht et al., 2005; Stokes et al., 2005). For example, the average scalp–cortex distance of the middle frontal gyrus of the prefrontal cortex is significantly less than the average distance measured between the scalp and motor cortex (Stokes et al., 2005). Consequently, an uncorrected MT-calibrated stimulation protocol applied to the prefrontal cortex will result in systematically higher levels of cortical excitation than intended. Intra-individual differences in scalp–cortex distance may underlie some instances of adverse reactions to stimulation of non-motor regions that nevertheless adhered to safety guidelines set for MT-calibrated M1 stimulation (i.e., Wassermann, 1998). Indeed, a recent review found that adverse effects, including seizure, were most commonly observed following unadjusted MT-calibrated stimulation of the frontal cortex (Machii et al., 2006). Substantial distance variations will inevitably result in some individuals receiving levels of cortical stimulation that far exceed safety recommendations (Wassermann, 1998). In addition to the adverse effects of over-stimulation, it is also important to consider the potentially adverse consequences of under-stimulation in the clinical environment: the efficacy of treatment regimes calibrated to unadjusted MT will be reduced for patients with higher than expected scalp–cortex distance (e.g., Mosimann et al., 2002).

Poor control over cortical stimulation also has important implications for research applications. As noted above, MT-calibrated stimulation of non-motor regions that vary in scalp–cortex distance relative to the motor cortex may result in under- or over-stimulation. Unadjusted MT-calibrated stimulation of non-motor cortical regions with large average scalp–cortex distances will thus reduce the likelihood of detecting significant experimental effects. Conversely, over-stimulation of brain areas with scalp–cortex distances less than M1 will increase the extent of activation beyond the intended structure via two distinct mechanisms: increased volume of stimulated tissue directly under the coil (Thielscher and Kammer, 2004), and increased transsynaptic stimulation of connected brain

regions (e.g., Ruff et al., 2006). Over-stimulation therefore raises the potential for mistakenly attributing effects caused by inadvertent activation of non-targeted brain regions to the intended stimulation site. Consequently, to ensure more accurate control of cortical stimulation, we propose that MT should be adjusted according to the effect of distance we have demonstrated.

The present data also provide preliminary evidence that individual differences in distance-effect gradients reflect random variations in the lateral displacement of the peak magnetic field and the targeted cortical representation. If the lateral gradient in magnetic field geometry is the principal source of variation, group estimates of the underlying distance-effect gradient may provide a more stable correction than individually determined values. We therefore recommend the use of the distance-effect gradient revealed in the current study for use with the same stimulation configuration:

$$\mathrm{AdjMT}\% = \mathrm{MT} + 2.8 \times (D_{\mathrm{Site}X} - D_{\mathrm{M1}})$$

where AdjMT is the adjusted MT in % stimulator output, MT is the unadjusted MT in % stimulator output, D_{M1} is the distance between the scalp and M1, and $D_{\mathrm{Site}X}$ is the distance between the scalp and a second cortical region (Site*X*). For use with other TMS configurations, however, we recommend the application of the distance manipulation described here, and elsewhere (Stokes et al., 2005), to determine the appropriate distance-effect gradient. Similarly, the proposed method could be applied to examine the distance-independent relationship between MT and coil position, including orientation and tilt angle.

In addition to providing a more accurate calibration method for non-motor TMS applications, AdjMT could also provide a standard measure for motor cortex studies that focus explicitly on cortical excitability. For example, a number of recent investigations have examined the relationship between cortical excitability, indexed by MT, and a range of physiological (Bütefisch et al., 2003), pharmacological (Oliveri and Calvo, 2003), and psychiatric (Pascual-Leone et al., 2002) variables. However, our present data imply that MT comparisons made across participants will depend, at least in part, on variations in scalp–cortex distance (also see Kozel et al., 2000; McConnell et al., 2001; Stokes et al., 2005). The effect of distance, therefore, will add experimental noise to the dependent variable, assuming that scalp–cortex distance variations are not related to variations in the independent variable. However, if the scalp–cortex distance varies systematically with the experimental manipulation, then observed differences in unadjusted MT will be confounded by variations in scalp–cortex distance. For example, such distance-effect confounds might be particularly problematic for studies comparing MT across groups defined by age, as normal ageing is associated with changes in scalp–cortex distance (Kozel et al., 2000; McConnell et al., 2001). Consequently, unadjusted MT does not provide an acceptable index of cortical excitability in the presence of group differences in scalp–cortex distance. In such cases, we propose that AdjMT could provide an index of cortical excitability that is less dependent on scalp–cortex distance. However, as a minimal requirement, we recommend the use of individual measures of scalp–cortex distance to regress out the effect of distance. Similarly, if MT is to provide a useful diagnostic tool in clinical settings (Frasson et al., 2003), normative data will need to be based on a distance-independent measure of cortical excitability.

Correcting for the effect of distance is also important for TMS studies that compare the effects of stimulation across different cortical sites. Multi-site experimental designs are used to dissociate, and also *associate*, the effects of stimulation at different cortical locations. Furthermore, multi-site experimental designs also provide a powerful method to control for non-specific effects of cortical stimulation. However, quantitative comparisons between different stimulation conditions that vary in scalp–cortex distance will be confounded unless the effects of distance are accounted for. Although we recommend AdjMT as an optimal correction, output intensities could also be corrected for distance without reference to MT:

$$\mathrm{Output}_{\mathrm{site2}} = \mathrm{Output}_{\mathrm{site1}} + 2.8 \times (D_{\mathrm{site2}} - D_{\mathrm{site1}})$$

where $\mathrm{Output}_{\mathrm{site1}}$ and $\mathrm{Output}_{\mathrm{site2}}$ represent the percent of absolute stimulator output for Site 1 and Site 2, respectively, and D_{site1} and D_{site2} represent their cortical distances. Correcting for the effect of distance between experiment sites will therefore increase the validity of quantitative comparisons (e.g., see Chambers et al., 2006a).

Increasingly, TMS applications are adopting more precise methods for positioning the stimulating coil (Herwig et al., 2001b). For brain regions with an easily indexed overt effect, such as an evoked motor response or visual phosphene (Stewart et al., 2001), the stimulating coil can be functionally localised for each individual using a 'hot-spot' search method as applied in this study. However, for cortical regions without a robust functional marker, coil localisation can be problematic. Early TMS applications typically applied rule-of-thumb measures [e.g., PFC = 5 cm rostral to the M1 'hot-spot' (Pascual-Leone et al., 1996)], however such heuristics can be highly inaccurate (Herwig et al., 2001a). Scalp–cortex reference systems, such as the international 10–20 system for electrode placement (Klem et al., 1999), provide a standardised coil positioning system that is useful for group averages, but does not account for individual differences in cortical anatomy, yielding substantial individual variation in the precise location of cortical stimulation (Okamoto et al., 2004). However, with increasing access to MR facilities, and reducing cost of commercial TMS/MR registration systems, experimenters have increasingly begun to use individually acquired MR scans to guide coil placement. We view the issue of scalp–cortex distance variations highlighted in this study as a logical extension of the general problem of individual variation in cortical anatomy. Similarly, the proposed solution, distance-adjusted stimu-

lation protocols, is in practice a direct extension of MR-guided TMS.

Over the last two decades, TMS has continued to gain prominence in both clinical and experimental neuroscience. The unique capacity to stimulate the intact human brain non-invasively establishes the unique position of TMS in the spectrum of available techniques. Nevertheless, more technical research is needed to fully understand the parameters that determine effective stimulation. The paucity of TMS technical research contrasts with the extensive literature on the technical aspects of neuroimaging methods such as fMRI and ERP. The present study documents at least one significant parameter in TMS that can be easily quantified, and therefore, easily accounted for using a simple linear correction.

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