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Stimulating deep cortical structures with the Batwing Coil: how to determine the intensity for Transcranial Magnetic Stimulation using coil-cortex distance

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Abstract

Transcranial magnetic stimulation (TMS) is increasingly used in cognitive neuroscience to probe non-motor cortical regions. A key question for such studies is the choice of stimulation intensity. Early studies used a simple metric such as 115% of motor threshold (MT) for non-motor regions; where MT is the stimulation intensity required to elicit a particular amplitude of motor evoked potential or visible muscle twitch when the coil is placed over primary motor cortex. Recently, however, it was demonstrated that this simple metric for stimulation of non-motor regions is inadequate – it could lead to over or under-stimulation depending on the distance between the coil and the cortex. Instead, a method was developed to scale the motor threshold based on coil-cortex distance, at least for standard figure-of-eight stimulating coils. Here we validate the same method for a ‘batwing coil’, which is designed to stimulate deeper cortical structures such as the medial frontal cortex. We modulated coil-cortex distance within-participant by inserting spacers of different thickness between coil and scalp. We then measured MT at each spacer. We show that for every millimeter between coil and scalp an additional 1.4% of TMS output is required to induce an equivalent level of brain stimulation at the motor cortex. Using this parameter we describe a linear function to adjust MT for future studies of non-motor regions-of-interest using the batwing coil. This is the first study to demonstrate the effects of coil-cortical distance on stimulation efficiency via a monophasic system using a batwing coil.

Keywords

motor cortex; MEP; MRI; EMG; human

1. Introduction

Transcranial magnetic stimulation (TMS) is now widely used to address cognitive neuroscience questions as it has both good spatial and temporal resolution and it can be used to make causal inferences (Bestmann, 2008). TMS can be used to probe both primary motor cortex (M1) and non-motor regions in cognitive studies. There are several ways in which TMS is used over non-motor regions. First, by delivering repetitive stimulation for a period

of time, a “virtual lesion” can be induced which disrupts subsequent behavior, e.g. primary visual cortex for visual imagery (Kosslyn et al., 1999). Second, TMS can be delivered in an event-related fashion within behavioral trials, thus revealing the precise time at which a particular brain region performs a function, e.g. the right angular gyrus for attentional reorienting (Chambers et al., 2004). Third, TMS can be used in a paired-pulse configuration, where one coil is placed over a non-motor region and the other over M1. By delivering a conditioning pulse over the non-motor area the functional connectivity with M1 can be determined (Koch and Rothwell, 2009). All these approaches to delivering TMS over non-motor regions require a careful choice of stimulation intensity. Whereas under-stimulation could reduce the chance of detecting experimental effects, over-stimulation could reduce the focality of the effect locally as well as extending stimulation to non-targeted remote brain regions and increasing the risk of an adverse event such as a seizure (Wassermann, 1998).

Early studies used a simple metric to determine the stimulation intensity for non-motor regions, such as 115% of motor threshold (MT) (e.g. Pascual-Leone et al., 1994). MT is defined as the minimum intensity of stimulation required to induce a visible muscle twitch (Varnava et al., 2011) or a particular amplitude of motor evoked potential (MEP) when electromyography (EMG) is recorded from the muscles (Rossini et al., 1994). However, the distance between the coil and cortex could influence stimulation efficiency (McConnell et al., 2001; Stokes et al., 2007; Stokes et al., 2005). Therefore, Stokes and colleagues (2007; 2005) developed a new method for determining stimulation intensity of non-motor regions based on the distance between coil and cortex. To do this they systematically varied the distance between the scalp and coil by adding different spacers of fixed width and then estimating MT for primary motor cortex. They derived a simple linear formula for calculating distance-adjusted MT (Stokes et al., 2005):

$$\text{distanceadjusted MT} = g \times (D_{\text{nonmotor}} - D_{\text{M1}}) + \text{MT}_{\text{M1}} \quad [1]$$

where distance-adjusted MT is defined for the non-motor region in % stimulator output, based on MT for the M1 (MT_{M1} , in % stimulator output), the distance between the scalp and the non-motor region ($D_{\text{non-motor}}$, in mm), the measured distance between the scalp and M1 (D_{M1} , in mm), and the distance-effect gradient (g , in % per mm). The parameter g indicates the extra amount of stimulator output (%) needed to reach an equivalent effect of TMS stimulation on the brain tissue for each millimeter increment in distance between coil and cortex. For a biphasic system with figure-of-eight coils, Stokes et al. (2007; 2005) and Varnava et al. (2011) calculated g as ~2.5-3.0%, i.e. an additional ~2.5-3.0% of stimulator output was required to induce an equivalent effect for each millimeter increment. For figure-of-eight coils, g was similar for different coil sizes of the same geometry (i.e. 70 mm vs. 50 mm) (Stokes et al., 2007). However, it is unknown whether the parameter will generalize to coils of different geometries and pulse profiles.

Here we took the same approach as Stokes et al. (2007; 2005) to derive a distance-adjusted MT formula for the batwing coil. The batwing coil, so called because of its shape (Fig. 1a), is designed to stimulate deeper cortical structures, such as the leg area in the motor cortex (e.g. Roy and Gorassini, 2008). Importantly, this same coil could be used to stimulate other deep non-motor regions, such as the pre-supplementary and supplementary motor areas of dorsomedial frontal cortex. There is a burgeoning literature about the neurocognitive function of dorsomedial frontal cortex, including studies with fMRI, EEG, neurophysiology and lesions in humans (see reviews by Nachev et al., 2008). It would thus be very useful to be able to stimulate dorsomedial frontal cortex using TMS, as this could provide causal evidence for the importance of these structures, and moreover, their activity at precise moments in time. Although the standard figure-of-eight coil has been used to stimulate the

dorsomedial frontal cortex (e.g. Mars et al., 2009), the batwing coil is a preferred choice because the coil geometry allows efficient stimulation of deeper cortical regions.

In this study we first acquired a high-resolution structural MRI image for each participant in order to calculate the distance between the scalp and cortex. Next, we used TMS to measure MT at the primary motor cortex while we varied the distance between the scalp and coil using three spacers of different thickness (3, 6 and 9 mm). We aimed to calculate the distance-effect gradient, g , and to derive a linear formula for distance-adjusted motor threshold with the batwing coil that could be useful for future studies.

2. Material and Methods

2.1 Participants

Eighteen healthy young adults (6 female, aged 18-22 yrs, 1 left handed) participated in this study. All participants provided written informed consent according to an Institution Review Board protocol at the University of California at San Diego, and passed TMS safety screening.

2.2 Apparatus

In the first session, a high-resolution T1 structural MRI image was acquired (3D FSPGR: slice thickness, 1mm; TR, 7.8 sec; TE, 3 sec; matrix, 192×192; FOV, 256; 172 sagittal slices) from a GE Signa 3T scanner at the Center for functional MRI at University of California, San Diego. In the second session, TMS was delivered via a monophasic Magstim 200-2 system (54 μ s magnetic field rise time, 225 μ s pulse duration; Magstim, Whitland, UK) and a 70-mm batwing coil (type no. 15411; see Fig. 1a). Surface EMG was recorded from the first dorsal interosseous (FDI) of the right hand via 10-mm-diameter Ag-AgCl hydrogel electrodes (Medical Supplies, Inc, Newbury Park, CA). A ground electrode was placed over the styloid process (wrist) of the right ulna. The EMG signal was amplified via a Grass QP511 Quad AC Amplifier System Grass amplifier (Grass Technologies, West Warwick, RI), with a band-pass filter between 30 Hz and 1 kHz and a notch filter at 60 Hz. A CED Micro 1401 mk II acquisition system was used to sample data at 2kHz. Data were displayed and recorded to disk using CED Signal v4 (Cambridge Electronic Design, Cambridge, UK).

2.3 Procedure

Hotspotting and motor thresholding—The coil was positioned on the left M1 for each participant (Fig. 1b). The coil was initially placed 5 cm lateral and 2 cm anterior to the vertex and repositioned to where the largest MEP was observed consistently. Since coil orientation can affect stimulation efficiency (Brasil-Neto et al., 1992), the coil handle always pointed back and 45° lateral from the midline, which is the optimal orientation for eliciting a motor hand response in M1. MT was defined as the minimum stimulator output required to induce MEPs of 0.1 mv peak-to-peak amplitude in 5 out of 10 consecutive stimulations (Rossini et al., 1994). MT was determined using a method of limits. The stimulation intensity was continuously increased or decreased by 2% of maximum stimulator output until a minimum intensity was found to meet the MT criterion. To examine the relationship between MT and coil-cortex distance, we randomly modulated the distance between the scalp and coil for participants by inserting plastic spacers of different thickness (3, 6 and 9 mm) between the scalp and coil. This allowed us to measure four MTs for each participant: scalp-level MT (no spacer), and MT at spacers of 3, 6 and 9 mm in thickness.

Localizing the ‘hot spot’ with MRI—The MRI images were co-registered to participants’ heads using a magnetic tracking device (minibird 500, Acension Tech) and

MRI co-registration software (MRIReg and MRICro). A scalp coordinate of the stimulation location was recorded in the co-registered structural MRI space. As described previously in Varnava et al. (2011), the distance between M1 scalp surface and underlying cortex was estimated using an automated procedure based on a mesh model of the cortical surface, defined using the segment routine in SPM 8 (Wellcome Department of Cognitive Neurology, London, UK). For each participant, we took the mean distance of the 100 cortical voxels nearest to the scalp site of stimulation as our estimate of scalp-cortex distance at M1. Varnava et al. (2011) showed that this automatic estimation method is reliably correlated with a manual estimation method.

2.4 Data analysis

We defined three different types of coil distance: a) Coil-scalp distance is the distance between the coil and scalp, which is the thickness of spacers. There were 4 coil-scalp distances: 0 (no spacer), 3, 6 and 9 mm, b) Scalp-cortex distance is the distance between the stimulation spot on the scalp and its underlying cortical surface, which is estimated from MRI images using an automatic procedure (see section 2.3), c) Coil-cortex distance is the sum of scalp-cortex distance and coil-scalp distance. To explore the relationship between MT and coil-cortex distance, we performed several analyses.

First we examined whether there was a significant difference in MT for different spacers (coil-scalp distance) by conducting a repeated measures analysis of variance (ANOVA). As previous studies showed that MT rose as coil-scalp distance increased for the standard figure-of-eight coil (Stokes et al., 2007; Stokes et al., 2005; Varnava et al., 2011), we also expected a linear relationship between MT and coil distance for the batwing coil.

Second, as the linear term accounted for the most variance (see Results), we derived the distance-effect gradient for each participant and for the group using a linear regression fit:

$$Y = g \times X + C \quad [2]$$

Where Y is MT, X is the coil-scalp distance, C is a constant, and g is the distance-effect gradient.

Third, because distance-adjusted MTs for non-motor regions of interest need to be derived based on the distance between the coil and cortex (rather than the distance between the coil and the scalp), we modified the above formula for average coil-cortex distance using a linear regression fit.

3. Results

3.1 The relationship between MT and coil-scalp distance

We systematically modulated coil-scalp distance and measured MT at each coil-scalp distance (spacer) for each participant. There was an orderly increase of MT with increasing distance: $38.9 \pm 7.6\%$ (no spacer), $43.0 \pm 8.3\%$ (3mm), $46.9 \pm 9.3\%$ (6mm) and $51.8 \pm 9.7\%$ (9mm) of maximum stimulator output (Fig. 1c). An ANOVA showed there was a significant main effect of coil-scalp distance on MT, $F(3,51)=212$, $p<0.001$ and a trend analysis found a significant linear component, $F(1,17) = 262$, $p<0.001$, but no significant higher order components, $p's>0.07$. This shows that the relationship between MT and coil-scalp distance is well represented by a linear function.

3.2 Estimating the parameter 'g'

The linear fit for the group was $MT = 1.4 \times \text{coil-scalp distance} + 38.3$ ($R^2 = 0.99$, $p<0.001$, see Figure 1c). The R^2 values of all fits for each participant were in the range of 0.95~1.

Thus, the distance-effect gradient 'g' was 1.4% / mm (i.e. 1.4% extra stimulator output is needed for each extra mm between coil and scalp). The high R^2 value indicates that distance is a powerful determinant of stimulation efficiency at the range of coil-cortex distances tested in this study. Nevertheless, we note that we only probed at a small number of distances (albeit those which are applicable for most TMS studies). The true underlying effect is non-linear according to the Biot-Savart law.

Consistent with previous findings (Stokes et al., 2007; Varnava et al., 2011), the individual distance-effect gradient correlated positively with scalp-level MT ($R^2=0.27$, $p<0.05$, see Fig. 1d). Thus, people with larger scalp-level MT require higher field strength to reach the MT as coil-cortex distance increases.

3.3 A formula for non-motor distance-adjusted intensity for the batwing coil

To correct MT for a non-motor region, one would need to know the distance-effect gradient and the cortical distance difference between the non-motor region and M1. Thus we modified the above formula to estimate adjusted MT based on coil-cortex distance by conducting another linear regression fit. Note again that coil-cortex distance is the sum of coil-scalp distance plus scalp-cortex distance. For primary motor cortex, coil-cortex distance was: 14.26 ± 2.24 (no spacer), 17.26 ± 2.24 (3 mm), 20.26 ± 2.24 (6 mm) and 23.26 ± 2.24 mm (9 mm). Now the linear function was: distance-adjusted MT = $1.4 \times$ coil-cortex distance + 18.6 ($R^2 = 0.99$, $p<0.001$, Fig. 1e). Thus, by formula 1 the recommended distance-adjusted MT for non-motor regions for the batwing coil and monophasic stimulator systems can be derived as follows:

$$\text{distanceadjusted MT} = 1.4\%/\text{mm} \times (D_{\text{nonmotor}} - D_{\text{M1}}) + \text{MT}_{\text{M1}} \quad [3]$$

where distance-adjusted MT is MT for the non-motor region in % stimulator output, MT_{M1} is MT for the M1 in % stimulator output, $D_{\text{non-motor}}$ is the distance between the scalp and non-motor region in mm, D_{M1} is the distance between the scalp and M1 in mm.

4. Discussion

The current study demonstrates that coil-cortex distance is a key factor determining TMS efficiency for a monophasic system with a batwing coil. Specifically, we show that for every millimeter increment between the cortex and coil, an additional 1.4% of TMS output is required to induce an equivalent level of brain stimulation at the motor cortex. Although the full relationship between coil-cortex distance and motor threshold is nonlinear according to the Biot-Savart law, it is approximately linear at the range of coil-cortex distance that is tested here and that is applicable for most TMS studies. We thus derive a linear formula (see formula 3 above) that can be readily adopted by other investigators to choose stimulation intensity for the batwing coil. This will be useful for studies that use the batwing coil to probe deeper subregions of dorsomedial frontal cortex and the superior parietal lobe.

The present finding agrees with the linear relationship between coil-cortex distance and MT reported in previous studies using the figure-of-eight coil and a biphasic system (Stokes et al., 2007; Stokes et al., 2005; Varnava et al., 2011). However, whereas those studies showed that an additional 2.5-3.0% power was required to induce an equivalent TMS effect on the motor cortex with every millimeter increment of coil-cortex distance, here we estimate that parameter as 1.4% / mm. This difference presumably relates to different stimulator systems (biphasic vs. monophasic, in our case) and/or different coil shapes (figure-of-eight vs. batwing, in our case). Coil geometry determines the shape of magnetic field so it likely influences the gradient of MT against coil-cortex distance. In fact, the lower slope seen here is predictable based on the observation that the thresholds are on average lower for this

combination of pulse shape (monophasic) and coil type (batwing), and with the positive relationship between threshold and slope demonstrated in previous studies (Stokes et al., 2007; Varnava et al., 2011).

The distance-adjusted method has the advantage of avoiding under- or over-stimulation of a particular region of interest. It is also useful for studies that aim to compare the stimulation effects on multiple brain regions. Given that scalp-cortex distances are different among brain regions (Stokes et al., 2005), unadjusted scalp-level MT could produce a significant but artificial stimulation effect. For example, if region A has a smaller cortical depth than region B, then stimulation with unadjusted scalp-level MT may cause a greater behavioral effect when TMS is administered over region A relative to region B. This could lead to a false inference that region A is more critical for behavior than region B. In other words, while a researcher could conclude that a behavioral difference relates to a functional difference between the two regions the reality could be that the behavioral difference relates to a difference in the stimulation efficiency of the two regions. We therefore recommend that researchers should equate MT carefully between regions of interest.

It may seem that unadjusted MT is adequate for the batwing coil with the monophasic system because the distance-effect gradient is low. However, if one tries to stimulate a deeper cortical structure, such as pre-supplementary motor area, the deviation from adjusted MT will accumulate so that stimulation with unadjusted MT would likely fall below the required intensity. Thus, one should carefully adjust MT for a deeper cortical structure based on cortical distance.

5. Conclusion

We have calculated the distance-effect gradient for the batwing coil and a monophasic TMS system. We observed that a millimeter increment between the coil and cortex demands an additional 1.4% power to induce an equivalent TMS effect on underlying brain tissue. This parameter can be readily used by other researchers to adjust stimulation intensity for the batwing coil depending on the depth of the structure they wish to stimulate. We anticipate increased usage of the batwing coil in cognitive neuroscience because the coil geometry allows efficient stimulation of deeper cortical regions of the dorsomedial frontal cortex such as the supplementary and presupplementary motor areas and regions of the superior parietal lobe.

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Figure 1.

a. Geometry of the batwing coil; b. The coil was placed over the left primary motor cortex and EMG was recorded from the right hand; c. Coil-scalp distance of left M1 was significantly correlated with MT, $R^2=0.99$, $p<0.001$; d. The distance-effect gradient was significantly correlated with scalp-level MT, $R^2=0.27$, $p<0.05$; e. Coil-cortex distance of left M1 was significantly correlated with MT, $R^2=0.99$, $p<0.001$. Error bars in all panels indicate $\pm 95\%$ confidence intervals.