Clinical Neurophysiology 121 (2010) 255–263

Contents lists available at ScienceDirect

Clinical Neurophysiology

journal homepage: www.elsevier.com/locate/clinph

Letters to the Editor

Motor evoked potential latency, motor threshold and electric field measurements as indices of transcranial magnetic stimulation depth

Dear Editor,

This letter is written in response to the paper "H-Coil: Induced electric field properties and input/output curves on healthy volunteers, comparison with a standard figure-of-eight coil", recently published by Fadini et al., at Clin Neurophysiol 2009;120:1174–82.

That study addresses an important issue and includes some valuable results which may contribute to our knowledge regarding the neuronal effects of different TMS coils. Yet, there are some serious methodological flaws and a great discrepancy between the results reported and the conclusions made by the authors. In addition there are several basic issues and assumptions of this study that must be addressed.

The study intends to compare the depths of stimulation of an H-coil version, partially similar to the coil used in Zangen et al. (2005), although different in certain key aspects, and a standard figure-8 coil.

Four key results relevant to this goal and the way they were treated in this study, will be discussed here.

1. Electric field distribution

1.1. Methods

Field decay profiles of the coils were measured in air. A more accurate comparison could have been achieved by performing measurements in saline using a dipole probe (Tofts and Branston, 1991), thus accounting for the electrostatic field induced at the scalp/air boundary. A rectangular probe in air measures the induced electric field but not the electrostatic component from surface charges that build up in the conductive medium. Moreover, it was shown (Roth et al., 2002) that in more realistic conditions such as a spherical model, the field decay rate with distance in saline is faster than in air. Hence, when comparing two coils with different configurations, measuring in air has a limited applicability to the measurement of the total electric field.

1.2. Results

The electric field intensities measured under Arms 1 and 5 of the H-coil used by the authors which were the arms placed over the motor cortex, were always between threefold and fourfold lower than the values measured under the figure-8 coil for the same stimulus output. Yet, both the resting and active motor thresholds were significantly higher for the figure-8 coil. The electric field required for threshold motor activation may be somewhat dissimilar for different coils due to inductive properties resulting in different pulse widths (Rudiak and Marg, 1994), but observed differences of that order of magnitude are very much unexpected and indicate on a serious methodological problem in this study. Moreover, the absolute intensities measured under Arms 1 and 5 at 70% stimulator output were below 35 V/m, while the resting motor threshold (RMT) was reached at just over 40% of stimulator output. This means that a field of approximately 20 V/m in air (which most probably would be even lower if measured in saline) was sufficient to induce a motor response. This is far below the range of intensities required to reach motor threshold (Epstein et al., 1990; Roth et al., 2002; Epstein and Davey, 2002; Roth et al., 2007). The inevitable conclusion is that there is a severe error at least in the measured electric field intensities under Arms 1 and 5.

1.3. Coil design

The H-coil used by the authors is significantly different in certain key aspects relative to the version described in the original work (Zangen et al., 2005). A number of important dimensions differ between the coils. For instance, the distances between Arm 1 and Arm 3 is 125 mm (compared to 95 mm), and that between Arm 4 and Arm 2 is 118 mm (compared to 78 mm) in the version used in Zangen et al. (2005). The difference in coils may explain the more rapid decay profile of the electric field measured by Fadini et al. (Fig. 4) when compared with the decay profile inferred from MT measurements in Zangen et al. (2005, Fig. 2). The decay profile in the latter study correlates well with unpublished measurements of the electric field profile at different depths in saline (and also with similar measurements of other H-coils (Roth et al., 2007)). The discrepancy in decay profiles might at least partially result from geometrical differences between the coils, and perhaps also from different distribution of windings (not reported by the authors).

In spite of all of the afore-mentioned limitations, the authors still report that the field decay rate was significantly faster for the figure-8 coil compared to all the arms of the H-coil used in their study. Yet, they curiously ignore these findings when reaching their stated conclusion that the H-coil had no advantage regarding the depth of stimulation.

2. Motor threshold measurements

Measurements of motor threshold can be used as a measure of depth of stimulation with TMS. In the past, this was assessed by relating the stimulator power output at motor threshold induced by various TMS coils with the depth profile of the electric field induced in each coil (Epstein et al., 1990; Rudiak and Marg, 1994). The fact that this method gave very similar depths for different coils, demonstrated the reliability of this approach. Using a similar approach, activation thresholds of the APB motor cortex as a function of distance from coil were used to compare the decay profiles of an H-coil version and a figure-8 coil, and a markedly slower rate of decrease of the effect with distance was found for the H-coil (Zangen et al., 2005, Fig. 2). Fadini et al. (2009) mention that for both coils the resting MT stimulator output values were similar to the thresholds found in Zangen et al. (2005) (when the coils were placed directly over the motor cortex). Yet the authors, when reaching their conclusions ignore the findings of Zangen et al. (2005) that demonstrate a clear advantage in depth penetration for the H-coil, and do not even discuss their own findings regarding the field decay rates as a function of distance measured for the H-coil relative to the figure-8 coil.

3. MEP amplitudes

The size of the measured motor evoked potentials (MEPs) can provide important information about the stimulation site. This is however ignored in this study. The authors report that while the MEP amplitudes at threshold were not significantly different between the two coils, they found significantly larger MEP amplitudes for the H-coil compared to the figure-8 coil at higher values of simulator output (% RMT). This is most probably due to the recruitment of more stimulation sites relevant for the motor pathway, both superficially and in deeper layers. The authors however ignore this possibility and conclude that this indicates a non-focal but *definitely* not a deeper excitation by the H-coil. Correlation of the MEP amplitude data with the stimulation volume as derived from the electric field distribution, as a function of % RMT, would lead to more accurate conclusions regarding this issue.

4. MEP latencies

The authors measured MEP onset latencies of four muscles at intensities of up to 140% RMT, and found that, in general, they were not significantly shorter for the H-coil and indeed longer at threshold. Based solely on these observations, they reached the conclusion that the H-coil has no deeper effect as compared to the figure-8 coil. However, the assumption that MEP latencies can be linearly correlated with depth of cortical stimulation is an oversimplification and is not supported by the literature as detailed below.

It is known that MEP latencies elicited by electrical stimulation are significantly shorter than latencies induced by TMS (Edgley et al., 1990; Di Lazzaro et al., 1998). The effect of increasing the intensity also differs between electric and magnetic stimulation.

For electrical stimulation, the response latency has been shown to be sensitive to stimulus amplitude and electrode geometry. When applying electrical stimulation using scalp electrodes, it was shown in monkeys (Edgley et al., 1990) and humans (Burke et al., 1993) that increased stimulus intensity appears to shift the stimulation site down the cortico-spinal pathway as far as the medulla and dramatically reduced the latency time (Edgley et al., 1990). Another study found that electrical stimulation from implanted electrodes in the globus pallidus elicited a much shorter latency than TMS at threshold intensity (Kuhn et al., 2004). The latency for electrical stimulation could not be further reduced with increasing intensity, indicating that the most caudal location for excitation had been already achieved at the site of the implanted electrodes.

In contrast, when using magnetic stimulation and increasing the stimulus amplitude, the latency can be shortened by no more than 1–2 ms (Hess et al., 1987; Di Lazzaro et al., 1998). This corresponds to a transition between D-waves, believed to be generated by direct stimulation at the site of the pyramidal neurons, and I-waves believed to be induced by transverse interneurons (e.g. Amassian et al., 1987; Day et al., 1989). As an index of stimulation origin, a more precise marker of stimulation characteristics than EMG latency is the latencies of the cortico-spinal volleys measured in the epidural space of the spine, which can resolve these D-waves and I-waves (Di Lazzaro et al., 1998). Latencies of EMG measurements measured on the skin surface of the hand, represent a much coarser marker. The coil orientation – among other factors – plays an additional major role in any latency measurement. Thus, lateral–medial oriented TMS – but not anterior–posterior oriented TMS – induced D-waves at threshold intensities (Werhahn et al., 1994; Di Lazzaro et al., 2002). Hence it is quite clear that latency is sensitive to a complicated mixture of various neurophysiological parameters aside from depth of stimulation.

In contrast with electrical stimulation, there is no evidence of the ability of TMS to induce direct stimulation of motor cortico-spinal axons at a significant distance from the cortical layer. The primary orientation of the electrical field differs between electrical and magnetic stimulation, which may account for the different abilities to excite downstream axonal pathways. The area around the soma is a much more likely stimulation site for TMS, due to the greater density of sodium channels in the axonal hillock compared to further axonal sites, and due to the exponential decay of the membrane potential from the soma (Chan and Nicholson, 1986; Trachina and Nicholson, 1986; Ranck, 1975; Fox et al., 2004).

The EMG latency measurements in the ADM and APB muscles as reported by Fadini et al. (2009), indicate that the figure-8 coil induced stimulation with a shorter latency at threshold, but the latency time reaches a plateau with increased intensity. In contrast, the H-coil induced stimulation with a longer latency at threshold, but this latency decreased at a faster rate with stimulus amplitude (see Table 1). We performed APB latency measurements on four subjects, using the original H-coil version used in Zangen et al. (2005), and a standard figure-8 coil, but also tested higher % RMT intensities than those tested by the authors (see Table 1). This provided a more complete picture of the relationship of latency with stimulus strength. The prominent findings are:

(a) The results are quite similar when comparing the same % RMTs.

Table 1
Latency times (in ms) measured in the APB muscle at various percentages of resting motor threshold (% RMT). The regression slope (amplitude vs latency time) with its associated R^2 is also shown.

	% RMT						Slope (ms/% RMT)	R^2
	120	130	140	150	190	230		
Fadini et al.[a]								
Figure-8	24.4 ± 0.1	23.8 ± 0.2	23.9 ± 0.2				−0.025	0.60
H-coil	24.8 ± 0.1	24.6 ± 0.1	24.0 ± 0.1				−0.038	0.89
Roth et al.[b]								
Figure-8	25.0 ± 0.6	24.6 ± 0.6	24.6 ± 0.5	24.3 ± 0.5	24.0 ± 0.4	N/A	−0.013	0.88
H-coil	25.6 ± 0.5	24.8 ± 0.4	24.7 ± 0.6	24.5 ± 0.6	23.5 ± 0.2	22.8 ± 0.2	−0.023	0.96

[a] Fadini et al. (2009).

[b] Unpublished results (see text).