A simulation study of the mechanisms that govern direct activation of pyramidal tract neurons in Transcranial Magnetic Stimulation

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ABSTRACT

Transcranial magnetic stimulation (TMS) is widely used to stimulate the motor cortex. In this work we calculated the electric field induced by a figure-eight coil in an idealized finite element model of the motor cortex. This field is used to predict the response of pyramidal tract neurons (PTNs). Results show that PTN stimulation occurs where they bend after entering the white matter. Also, biphasic current waveforms are found to be more efficient than monophasic waveforms. This model successfully explains several experimental observations made during stimulation of the motor cortex with TMS, and may help to identify the mechanisms involved in direct stimulation of PTNs.

KEYWORDS: TMS, motor cortex, pyramidal tract neurons, PTN, finite element, FEM

INTRODUCTION

Transcranial magnetic stimulation (TMS) of the hand motor area elicits, at threshold, descending motor volleys with latencies longer than the volley recruited by electrical anodal stimulation (aTES). These are termed I-waves and they are thought to result from indirect trans-synaptic activation of pyramidal tract neurons (PTNs) [1]. When pulse intensity is increased, an earlier small wave appears with the same latency as the earliest volley elicited by aTES. This volley is termed a D-wave and is thought to result from direct activation of PTNs. Although several works have confirmed this D- and I- wave hypothesis [2]-[4] much is still unclear about the mechanisms that govern PTN activation.

According to the cable equation for TMS [6] neural stimulation is determined by the spatial derivative of the electric field parallel to the neuron. However stimulation at lower thresholds can occur even if the field is homogeneous, provided that the neuron bends [5] or terminates [7]. More recent works have suggested that regions where the electric conductivity changes abruptly (e.g. at grey matter – white matter interfaces) may serve as activation sites for neurons that cross them [8]. This happens because, at these interfaces, the electric field is discontinuous, which leads to highly localized and strong field gradients that may influence neural activation. The large number of possible activation mechanisms makes it difficult to predict the activation site of a given neural population. The situation is further complicated by the fact that neural activation in TMS is also highly depended upon the current pulse's waveform, and the initial direction of the current in the coil [4].

In this work we aim to determine the precise activation site of PTNs and the mechanisms that determine their direct stimulation by TMS pulses. To do so we created an idealized model of the hand area of the motor cortex. The electric field induced by a figure-eight coil inside this model was then calculated using the finite element method (FEM). Finally, a discretized version of the cable equation was solved to model the response of an idealized PTN to the induced electric field.

METHODS

Motor cortex model

The motor cortex model is the same as used in a previous work [9]. A lateral view of the model is shown in **Fig. 1**. The model consists of three homogeneous and isotropic regions, representing the CSF ($\sigma_{CSF} = 1.79$ S/m), cortical grey matter (GM, $\sigma_{GM} = 0.33$ S/m) and cortical white matter (WM, $\sigma_{WM} = 0.15$ S/m).

The figure-eight coil is placed 3 cm above the upper cortical surface. It is based upon the Magstim Double 70 mm coil, which has 9 windings on each wing. The central element of the coil is placed perpendicularly to the central sulcus. This allows modeling Posterior-Anterior (PA) and Anterior-Posterior (AP) stimulation in the cortex by changing the current's direction in the coil.

The FEM model was created using a commercially available software package (Comsol 3.3a, www.comsol.com). This software calculates the electric scalar potential (ϕ) and the magnetic vector potential ($\vec{A}$), subject to the appropriate boundary conditions. Knowing these potentials the total electric field can be determined from:

$$\vec{E} = -\vec{\nabla}\phi - \partial\vec{A}/\partial t \qquad (1)$$

The total electric field induced by TMS is proportional to the time derivative of the current in the coil [6]. Comsol assumes a sinusoidally varying current waveform; however the pulse delivered by magnetic stimulators is very different [10]. In order to accurately model the effect of the waveform, the electric field calculated by Comsol was scaled (divided by the peak value of the current's time derivative) and then multiplied by waveforms similar to the output of two commercially available magnetic stimulators: the Magstim 200 stimulator (monophasic waveform) and the Magstim Rapid stimulator (biphasic waveform).

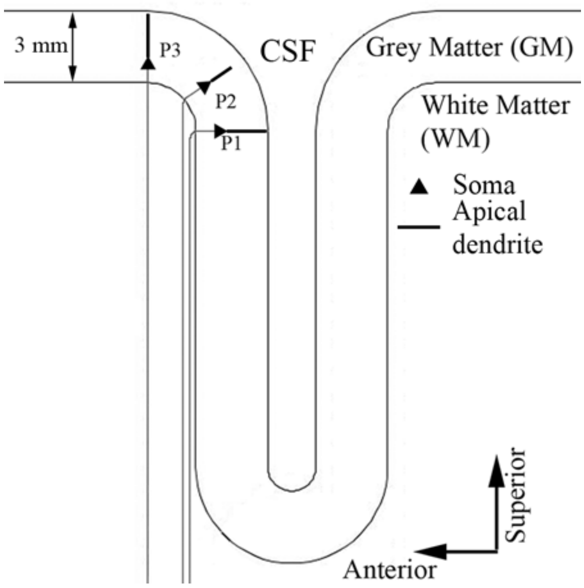

Fig 1. Lateral view of the motor cortex model, showing the position of the three pyramidal tract neurons considered.

Pyramidal tract neuron model

The pyramidal tract neuron model used in this work is based on a previous model proposed by Manola [11]. The model contains active compartments (with sodium, potassium and leakage currents) to model nodes of Ranvier, the initial segment and the axon hillock. The soma, apical dendritic tree and myelinated internodes are modeled as linear RC compartments. The neurons are placed as indicated in **Fig. 1**, entering the WM perpendicularly to the WM-GM interface. Neuron P1 has a radius of curvature of 0.5 mm, whereas P2 has a radius of curvature of 2 mm.

In order to calculate the neuron's response to the field induced by the TMS coil, a spatially discretized version of the cable equation was solved [7]. This was done using the Crank-Nicholson method with a staggered grid approach [12]. All numerical algorithms were implemented in MATLAB (version 7.1 R14 SP3, www.mathworks.com).

RESULTS

Electric field along the PTNs

The total electric field is similar along neurons P1 and P2 (see **Fig. 2**). Starting deep in the white matter, the axon is initially perpendicular to the primary component of the induced field ($-\partial\vec{A}/\partial t$) and, as such, the total field along it is almost negligible. At points on the neuron closer to the coil, charge accumulation at the sulcus wall gives rise to the "hump" in the field, which can be seen in **Fig. 2** just before the neuron's bend. The field changes very rapidly at the bend and when the neuron crosses the WM-GM interface.

Along neuron P3, the field is very different: as this neuron is always perpendicular to the plane containing the coil, the field along it is only due to charge accumulation at the interfaces. Therefore, the magnitude of the field along this neuron is very small (the field's maximum magnitude is about ¼ of the maximum magnitude of the field along P1) and the field is always continuous (even when the neuron crosses the WM-GM interface).

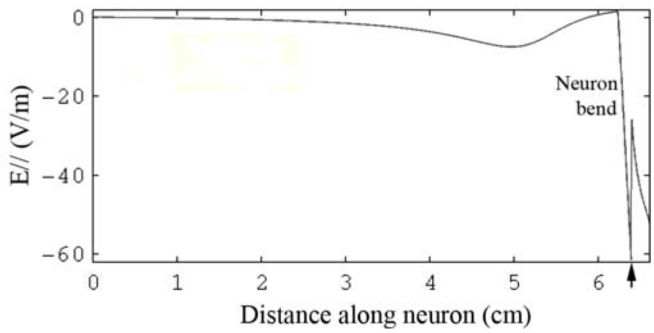

Fig 2. Total electric field along neuron P2 (field calculated for a charging voltage of 1000V, $di/dt|_{Max}$ = 61.2 A/μs, and for PA current direction in the tissue). The distance is measured from the last point of the discretized neuron, in the WM, to the last point of the apical dendrite. The arrow, on the x-axis, indicates the white matter - grey matter interface.

Activation site and thresholds

Activation thresholds were calculated for several different fiber diameters, ranging from 6 μm to 20 μm (medium to large sized pyramidal fibers, according to [13]).

Regarding neurons P1 and P2, their sites of activation were always at the nodes of Ranvier where the axons bend. For monophasic pulses, the lowest thresholds were obtained for PA stimulation. Thresholds for AP current direction were 2.7 – 2.8 times higher. Biphasic pulses had the opposite behavior, with lowest thresholds being obtained for AP – PA pulses (thresholds for PA – AP were always 1.4 to 1.5 times higher). Overall, biphasic stimulation was achieved at lower thresholds than monophasic stimulation (PA thresholds were 1.3 times higher than AP – PA thresholds). This is summarized in **Fig. 3**. From the analysis of the figure we also conclude that the lowest threshold for neuron P1 is smaller than the one for neuron P2.

Stimulation thresholds tend to decrease with increasing fiber diameter. For neurons P1 and P2, thresholds below 100 A/μs were obtained for diameters ranging from 16 – 20 μm (monophasic PA pulse) and 10 – 20 μm (biphasic AP – PA pulse).

The thresholds for neuron P3 were always much higher than the thresholds for the other two neurons. This neuron is not likely to be stimulated, regardless of the waveform or current direction used.

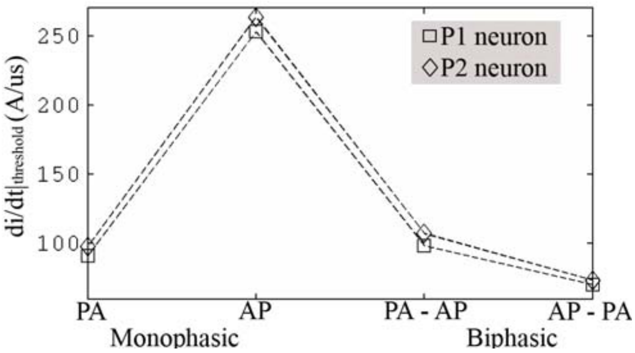

Fig 3. Lowest thresholds (fiber diameter of 20 μm) for neurons P1 and P2 as a function of pulse waveform and current direction.

DISCUSSION

Stimulation mechanisms

The modeling results presented in this work suggest that PTN direct activation occurs at the region where the axon bends, after it enters the WM. Despite the fact that the field's discontinuity, at the WM – GM interface, produced a higher spatial derivative, this stimulation mechanism is not the dominant one. This can be explained perhaps by the fact that the field jump is highly localized as compared to the more widespread influence caused by the neuron's bend.

Stimulus waveform

Regarding the waveform of the TMS stimulus, we found that, with monophasic pulses, PA stimulation was more efficient. This is consistent with the fact that the axon's bend is the relevant stimulation mechanism. Indeed, the spatial derivative caused by the axon's bend is negative for PA current direction and positive for AP stimulation. Therefore, in PA stimulation it is the first phase of the current pulse that causes stimulation. AP stimulation is only achieved at the second phase of the waveform which, for a monophasic pulse, is much smaller than the first one.

For biphasic waveforms, AP – PA stimulation was more efficient than PA – AP stimulation, and even more efficient than monophasic PA stimulation. This is caused by the fact that the first phase of the AP – PA current pulse causes a hyperpolarization which diminishes the sodium channels' inactivation. This makes the second phase of the TMS stimulus more efficient in stimulating the neuron. This effect has also been reported in other experimental works [4].

Stimulation thresholds

The stimulation thresholds decreased with increasing fiber diameter, as expected. The values obtained for higher fiber diameters (10 – 20 μm) are close to the values reported in the literature for thresholds required to obtain D-waves (180% to 200% of active motor threshold - AMT - [4] or about 92 – 102 A/μs using AMT values given by [14]). A more accurate prediction requires knowledge of electrophysiological parameters of pyramidal cells' membranes, which is still limited.

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