Approximating Transcranial Magnetic Stimulation with Electric Stimulation in Mouse: A Simulation Study

Walter L. Barnes*, Won Hee Lee*, *Student Member, IEEE*, and Angel V. Peterchev, *Member, IEEE*

Abstract— **Rodent models are valuable for preclinical examination of novel therapeutic techniques, including transcranial magnetic stimulation (TMS). However, comparison of TMS effects in rodents and humans is confounded by inaccurate scaling of the spatial extent of the induced electric field in rodents. The electric field is substantially less focal in rodent models of TMS due to the technical restrictions of making very small coils that can handle the currents required for TMS. We examine the electric field distributions generated by various electrode configurations of electric stimulation in an inhomogeneous high-resolution finite element mouse model, and show that the electric field distributions produced by human TMS can be approximated by electric stimulation in mouse. Based on these results and the limits of magnetic stimulation in mice, we argue that the most practical and accurate way to model focal TMS in mice is electric stimulation through either cortical surface electrodes or electrodes implanted halfway through the mouse cranium. This approach could allow much more accurate approximation of the human TMS electric field focality and strength than that offered by TMS in mouse, enabling, for example, focal targeting of specific cortical regions, which is common in human TMS paradigms.**

I. Introduction

Transcranial magnetic stimulation (TMS) is a useful tool for brain mapping, and has an increasing number of potential therapeutic applications, including as an FDA-approved intervention for depression [1, 2]. Mouse models of TMS can be a valuable platform for exploring the mechanisms and optimizing the dosing of TMS. Applying TMS in mice, however, is extremely technologically challenging and may even be impossible, due to the need to focus an enormous amount of electrical energy in a tiny coil to-scale with the mouse head [3].

For example, a conventional TMS coil is an 87 mm outer diameter (OD), 56 mm inner diameter (ID) figure-8 coil (Magstim, 70 mm figure-8 coil). Considering relative head and brain size, approximate scaling for stimulation of a mouse would demand a coil with an OD of less than 1 millimeter. However, due to constraints in fabrication techniques, the smallest currently reported TMS coil sizes are ~27 mm OD, which elicited movement in a cynomolgus macaque [4]. Based on the ability to empirically confirm and/or compare their results, the majority of current computational investigations model commercially available human TMS coil configurations for mouse brain stimulation [5]. However, such models indicate that large regions of the mouse brain – and often the whole brain – are being activated (i.e. at potentials >1 V/cm) [6, 7]. This nonfocal neural activation is substantially different than the focal approaches utilized in human TMS investigations, and it may not be necessary.

The physics of TMS can be broken down to three steps: current is passed through a magnetic coil, thereby generating a magnetic field which, in turn, induces an electric field in the brain. The neurostimulation effects of TMS are mediated by this electric field [8]. Therefore, it is valid to seek a way to approximate the focality and strength of human TMS with electric stimulation in mice, which requires dramatically less energy than magnetic stimulation. Such approximations can be designed and evaluated using models of the induced electric field distributions by electric stimulation in the mouse, to those produced by TMS in the human. Such a comparison, powered by metrics of focality and specific brain region targeting, could be a powerful tool in preclinical mouse model investigations of various pathologies, acting to guide potential clinical investigations in humans.

In this work, we examine electric field distributions produced in the mouse brain by various electric stimulation configurations, namely: electrodes placed on the surface of the mouse skull, midway through the skull (termed intracranial stimulation), and on the cortical surface of the brain. We offer visual representations of the distributions arising from different electrode depths, and provide data relating percent of total mouse brain volume at or above threshold with similar data from previous studies investigating TMS in homogeneous human spherical head models. This establishes a relationship across the two stimulation paradigms, electric in the mouse and magnetic in the human, and provides a framework for future preclinical investigation of such models.

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*These authors contributed equally to this work.

W. L. Barnes is with the Department of Biomedical Engineering, Duke University, Durham, NC 27710, USA (e-mail: walter.barnes@duke.edu).

W. H. Lee is with the Department of Biomedical Engineering, Columbia University, New York, NY 10027 and with the Department of Psychiatry and Behavioral Sciences, Duke University, Durham, NC 27710, USA (e-mail: wl2324@columbia.edu).

A. V. Peterchev is with Departments of Psychiatry and Behavioral Sciences, Biomedical Engineering, and Electrical and Computer Engineering, Duke University, Durham, NC 27710, USA (phone: 919-684-0383; fax: 919-681-9962; e-mail: angel.peterchev@duke.edu).

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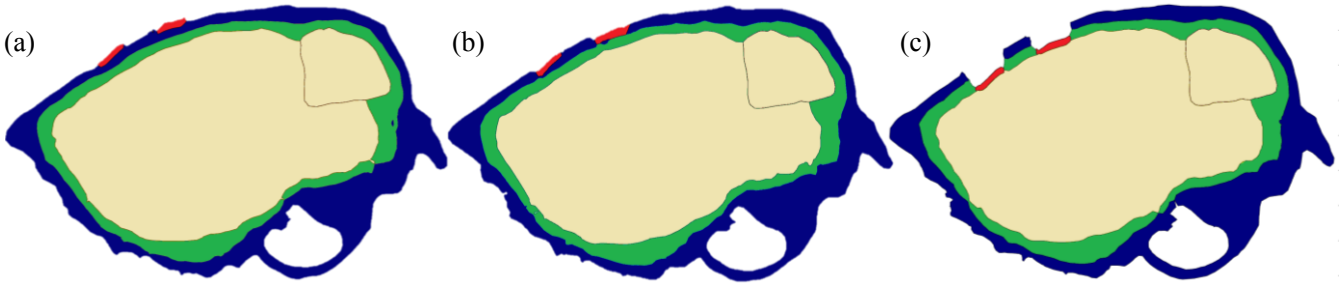

Fig. 1. Sagittal view of electrode locations shown in red for the (a) transcranial, (b) intracranial, and (c) cortical surface stimulation configurations. Skull is illustrated in blue, CSF in green, and brain regions in tan.

II. Methods

A. Image Segmentation

Whole-body computed tomography (CT) data of a 28 g nude normal male mouse was acquired from the Biomedical Imaging Group at the University of Southern California (http://neuroimage.usc.edu/neuro/Digimouse) [9, 10]. This data included 21 segmented structures with cubic voxel size of 0.1mm and a matrix dimension of 380x992x208. The Digimouse segmentation data was further refined using manual segmentation editing tools in the ITK-SNAP software [11], which allowed addition of ears and a layer of highly conductive CSF to the mouse atlas, as guided by Digimouse CT and cryosection data, and the Golgi atlas of the postnatal mouse brain [12].

B. Electrodes and Finite Element Meshing

The two round electrodes with a diameter of 1 mm and 0.2 mm thickness were added to the mouse head representation within the ITK-SNAP software. In each configuration, the electrodes are 1 mm apart (i.e. electrode center-to-center distance = 2 mm). Adding the electrodes as separate labels at the level of segmentation allowed accurate placement at desired locations: on the surface of the skull, midway through the skull, and on the surface of the brain (see Fig. 1). The placement of these electrodes was intended to target the left dorsolateral prefrontal cortex, as in human TMS for depression. To better model future experimental setups, regions above the electrodes were re-labeled, which allowed conductivity assignment to that of air, or any insulating material that may house the electrodes. The composite mouse whole body models incorporating the stimulation electrodes were meshed by means of the restricted Delaunay tessellation algorithm [13, 14], each consisting of ~1.7 million tetrahedral elements.

C. Electric Field Simulation

For each electrode configuration, the corresponding finite element mesh model was imported into COMSOL Multiphysics (COMSOL Inc., Burlington, MA, USA) for the electric field simulation. Isotropic conductivities were assigned as outlined in Table I [15]. The electric field distributions were acquired by solving the quasi-static Laplace equation with appropriate boundary conditions:

$$\nabla \cdot (\sigma \nabla V) = 0 \qquad (1)$$

where σ and V are electrical conductivity and electric potential, respectively. For our analysis, the distal surface of the posterior electrode was allowed to vary in voltage, and the distal surface of the anterior electrode was assigned as ground. The Multifrontal Massively Parallel sparse direct Solver (MUMPS) successfully solved each linear equation system involving ~2.5 million degrees of freedom, with a runtime of approximately 20 minutes on a computer with a 4 core 3.4 GHz processor and 16 GB of RAM. To determine equivalent current injected for each configuration, the normal component of electric current density (A/m^2) was integrated over a coronal plane bisecting the two electrodes. This allowed scaling of input voltage based on a range of desired input current.

TABLE I
Tissue Electrical Conductivities (S/m)

Tissue	Conductivity
Soft tissue	0.33
Bone	0.0083
Cerebrospinal fluid	1.79
Brain	0.33
Eye	0.5
Electrodes	9.8×10^5

D. Stimulation Target and Calculation of Activated Brain Volume

A point ~0.5 mm below the cortical surface, in the region between the two electrodes, was identified as the stimulation target. For each electrode configuration, the same point was selected, and the electric field magnitude, E_{tar}, was determined at this point. Using the volume integration feature in COMSOL, total brain volume and brain volume representing electric field magnitude $\geq 0.5E_{tar}$ (termed $V_{1/2}$) was determined.

III. Results

Fig. 2 displays the electric field distributions that arise from injecting 1mA of current in the electrodes. The planes chosen for coronal and sagittal slices (Figs. 2(b)-(c)) each bisect the electrodes. The color scale is normalized for each configuration (i.e. 100% represents E_{tar} for each configuration). Fig. 2 illustrates increase in focality with proximity of the electrodes to the brain surface.

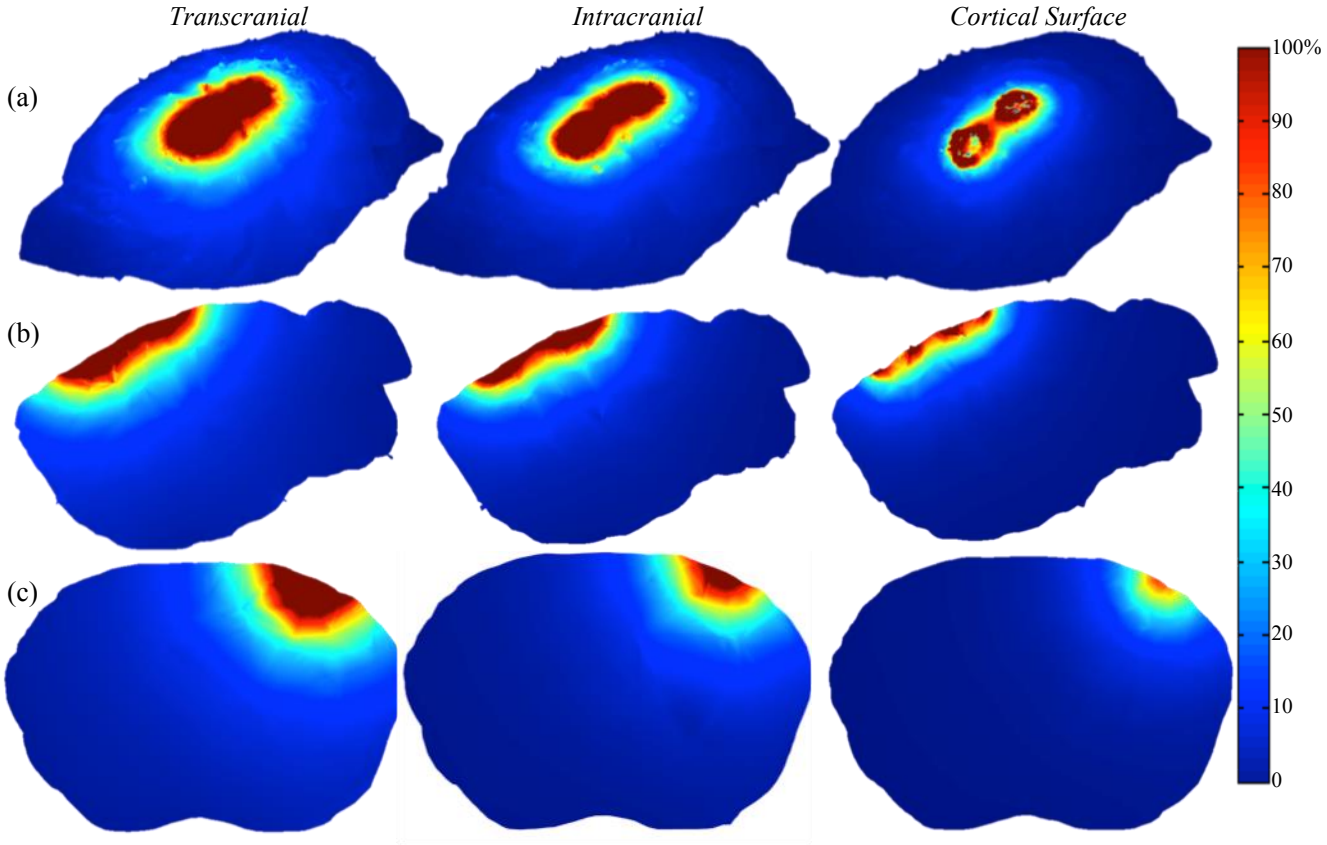

Fig. 2. Electric field distributions throughout (a) the cortical surface as observed on a 3-dimensional rendering of the brain, (b) a sagittal slice bisecting the electrodes, and (c) a coronal slice bisecting the electrodes. The scale located on the right side of the figure represents percent of the electric field magnitude value at the cortical target, E_{tar}.

Blue bars in Fig. 3 show percentage of total brain volume at or above one-half electric field magnitude at target, allowing comparison of stimulation focality across electrode configurations. As expected, focality increases as electrodes become closer to the cortical surface.

Red bars in Fig. 3 display input current required to reach threshold in each electrode configuration, where threshold is defined as 100 V/m, as outlined in previous work [16]. The values for current that comprise the red bars of Fig. 3 were calculated by scaling the E values achieved with 1 mA of current in each configuration. We see that with increasing electrode proximity, the input current required to activate the target decreases.

IV. Discussion

We characterized electric field generated by electric stimulation with electrodes at various depths in a mouse head, which is intended to approximate the focality and strength of stimulation in human TMS. A comparison with human TMS can be made, for example, with results from our previous study, which examined electric field distributions resulting from a range of TMS coils used to stimulate a homogeneous human spherical head model [17]. In that work, we reported that a standard 70 mm figure-8 coil activated 0.69% of brain volume, where activation is defined in a manner similar to the $V_{1/2}$ metric we employed in this work. Based on the data presented in Fig. 3, this activated brain volume could likely be achieved in our mouse model by using electrodes embedded into the skull or placed intracranially. For electrodes within the cranium, both epidural and subdural placements would be options, although we did not model these two separate entities. Though not presented here, a quantitative comparison of the results presented in Fig. 2(a), illustrating activation on the cortical surface, can be made with analogous results for TMS in realistic human head models [18]. Tuning our model of electric stimulation in mouse to approach results achieved in such models of human TMS is an important direction for our future work. Furthermore, we could compare results achieved through the wide range of TMS coil designs explored in our previous work [17], seeking to approximate the focality of coils of interest with electric stimulation configurations in our mouse model.

The model we presented for examining electric stimulation in mouse as an approximation of TMS in a human is especially significant when considering its implications in preclinical examinations of laboratory mice. Lower costs (as compared with investigation in other mammals) associated with preclinical mouse models have made such models attractive for biomedical researchers. As well, there are a wide range of TMS

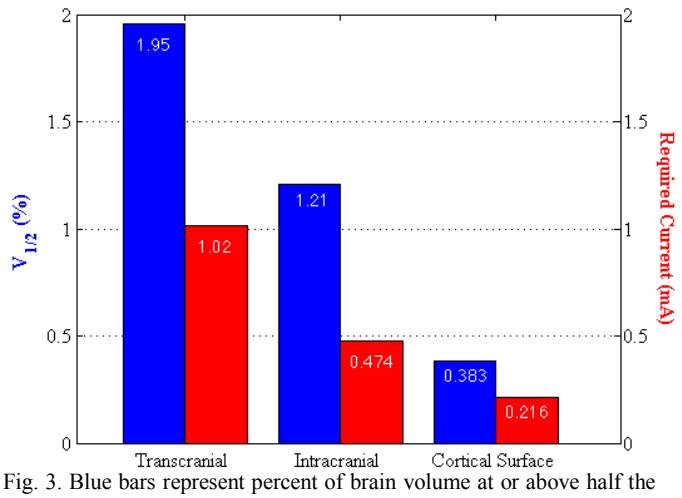

Fig. 3. Blue bars represent percent of brain volume at or above half the electric field magnitude at target, E_{tar}. Red bars represent input current required to reach neural activation threshold at the cortical target, E_{tar} = 100 V/m.

applications currently under investigation for potential human use [1], making our model an attractive option for such explorations in mouse.

Limitations of our mouse model stem from the nature of the mouse anatomy, specifically the thickness of the skull and CSF layers (each < 0.5mm). This made electrode placement within the cranium, for example, challenging, and resulted in imperfect volumetric meshing. Potential improvements and future work on this model include more refined electrode placement and model meshing, and placing insulation around the electrodes, which could act to focus the path of the current flow and increase the distinction between resulting electric field distributions.

V. Conclusion

Due to the technical limitations of realizing TMS in small animals such as mice, it is compelling to approximate human TMS with focal electric stimulation in these animals. This approach is appropriate since both TMS and electric stimulation affect neural activity by inducing an electric field pulses in the tissue. We created a finite element model of the electric field induced by electric stimulation at various depths in a mouse's head. The model showed that a pair of closely spaced cortical surface electrodes or electrodes implanted halfway through the mouse cranium could be used to approximate the electric field focality and strength of human TMS with currents of only 0.2–0.5 mA.

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