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Validation of Computational Studies for Electrical Brain Stimulation With Phantom Head Experiments

Donghyeon Kim [a], Jinmo Jeong [c], Sangdo Jeong [b], Sohee Kim [b,c], Sung Chan Jun [a,*], Euiheon Chung [b,c,**]

[a] School of Information and Communications, Gwangju Institute of Science and Technology, 123 Cheomdangwagi-ro, Buk-gu, Gwangju 500-712, South Korea
[b] Department of Medical System Engineering, Gwangju Institute of Science and Technology, Gwangju, South Korea
[c] School of Mechatronics, Gwangju Institute of Science and Technology, Gwangju, South Korea

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ABSTRACT

Background: Although computational studies of electrical brain stimulation (EBS) have received attention as a cost-effective tool, few studies have validated the technique, particularly in invasive cortical stimulation.
Objective: In order to validate such studies, we used EBS to compare electric potential distributions generated by both numerical simulations and empirical measurements in three phantom head models (one-/three-layered spherical heads and MRI-based head).
Methods: We constructed spherical phantom heads that consisted of one or three layers, and an anatomical, MRI-based phantom that consisted of three layers and represented the brain or brain/skull/scalp in order to perform both numerical simulations using the finite element method (FEM) and experimental measurements. Two stimulation electrodes (cathode and anode) were implanted in the phantoms to inject regulated input voltage, and the electric potential distributions induced were measured at various points located either on the surface or deep within the phantoms.
Results: We observed that both the electric potential distributions from the numerical simulations and experiments behaved similarly and resulted in average relative differences of 5.4% (spherical phantom) and 10.3% (MRI-based phantom).
Conclusions: This study demonstrated that numerical simulation is reasonably consistent with actual experimental measurements; thus, because of its cost-effectiveness, EBS computational studies may be an attractive approach for necessary intensive/extensive studies.

Introduction

Electrical brain stimulation (EBS) is a therapy used to modulate or stimulate neural circuits by injecting regulated electrical current/potential into the brain. EBS has long been used to relieve neurological disorders, including essential tremor [1], chronic stroke [2], chronic pain [3], Parkinson's disease [4,5], movement disorders [6], refractory epilepsy [7], depression [8], aphasia [9], and dystonia [10], among others. Thus, EBS has gained more attention recently in treating brain disorders and brain diseases, and various preclinical animal and human studies have been conducted.

However, despite these animal [11–13] and human studies [14,15], a thorough understanding of the fundamental mechanisms of EBS is still lacking; thus, the stimulation parameters for the best medical practices (electrode position, amplitude, waveform, and duration) remain unclear. In order to resolve this issue, a computational approach has been introduced in EBS. The goal of most computational EBS studies has been to reveal the spatial distributions of the current density or electric field within the brain that are induced by injection of electric current or potential in order to provide better insights in the determination of stimulation parameters. One of the simplest methods involves multi-layered spherical head models that have been introduced into the computational EBS domain. For example, a five-layered spherical head model was used to investigate the magnitude and focus of the

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* Corresponding author. Cheomdangwagi-ro 123, Buk-gu, Gwangju, 500-712, South Korea. Tel.: +82 62 715 2216.
** Corresponding author.
E-mail addresses: scjun@gist.ac.kr (S.C. Jun), ogong50@gist.ac.kr (E. Chung).

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electric field in electroconvulsive therapy and magnetic seizure therapy [16], and the effect of electrode configuration on transcranial direct current stimulation (tDCS) has been investigated in a four-layered spherical head model [17]. Such spherical models have low computational costs and are easy to implement; thus, they may further our knowledge of the effects of stimulation parameters. However, studies have been limited to investigations of the effect of neuromodulation in specific, complicated brain areas. Restricting study to a specific area of the brain, and considering anatomical shape to some extent, extruded slab models that represent the motor cortex have also been generated to investigate the effects of motor cortex stimulation [18–20]. These modeling studies may elucidate the neuromodulation effects in more focused target areas; however, the prediction of overall current density in the whole brain may be misinterpreted due to non-negligibly significant mismatches between these models.

Recently, some efforts have been made to reduce model mismatches by using human magnetic resonance imaging (MRI) and considering anatomical connectivity by incorporating diffusion tensor imaging (DTI) into computational EBS. The current density distribution of tDCS on the individualized brain model generated by patients' MRI data has been investigated [21], and the effects of MRI-based brain geometry on the electric field induced by TMS also have been reported [22,23]. In addition, in a recent study [24], the subdural cortical stimulation (SuCS) effect was estimated in the MRI-based full head model as the magnitude of current density or electric field, with the implicit assumption that the excitability of neurons is linearly proportional to the magnitude of the current density (or electric field). Such approaches have advantages in visualizing overall current density or electric fields in the whole brain and estimating the individualized effects of stimulation, although at an increased computational cost. From a clinical perspective, TMS stimulation effects on stroke patients have been estimated in advance with computational human models [25]. For EBS investigations at a neural level, the association between the spatial deviations in current density (that is, activating function) and neuronal responses has been investigated in computational studies [26,27]. Further, the extracellular responses of L3 and L5 pyramidal neurons induced by cortical stimulation have been investigated in the combined neural compartmental model and full head model [28].

In general, the computational analysis of EBS is based on such numerical techniques as the finite element method (FEM), the finite difference method (FDM), or the boundary element method (BEM). However, in principle, the computational results may be meaningless without reasonable validation; thus, investigations of whether or not they are consistent with experimental results are required. To the best of our knowledge, there are only a few EBS related studies of validation. A DBS study [29] reported that there was qualitative agreement between phantom experimental and numerical results of electrode impedance. Also, according to a TMS computational study [30], the stimulation effects of the geometrical head model, and the conductivity condition and stimulus position of the electric field were validated with a simplified brain-phantom that described the smooth cortex. Furthermore, experimental validation of computational models has been reported in rats in *in-vivo* trans-spinal DCS studies [31], as well as in tDCS studies of humans [32]. Specifically, the human study attempted a direct comparison of computed and measured scalp potentials (EEG), which showed positive correlations and good agreement.

From the above, one can see that, although it is very important to conduct validation studies of EBS, the subject has been investigated rarely. Particularly, validation studies of such computational cortical stimulation techniques as invasive SuCS or EpCS (epidural cortical stimulation) are lacking. Therefore, for the purposes of validation, we constructed three phantom heads: one-layered and three-layered spherical phantoms, and a human MRI-based phantom. Then, we generated computational head models based on the geometry and properties of these phantom heads, and examined to what degree computational electric potential distributions at designated points on/inside the head models were consistent with distributions measured empirically when regulated input voltage was injected through electrodes implanted on the brain surface of the phantom heads.

Materials and methods

Phantom design

We constructed three phantom heads—a one-layered spherical phantom (representing the brain only), a three-layered spherical phantom, and a human MRI-based three-layered phantom. These were constructed for invasive cortical stimulation with/without skull and scalp, or with simple head/realistic head geometries. To construct the MRI-based phantom, normal human MRI data were obtained, and segmented by *freesurfer* [33] and *fsl* [34] to distinguish the brain, skull, and scalp layers. With these segmented data, a fine mesh consisting of a number of tetrahedrons was generated for FEM analysis. For construction of the MRI-based phantom, several plastic moulds suitable for assembling multi-layer shell structures were built with a 3D printer (Fig. 1A and B). We then made three kinds of Agar/NaCl mixtures with specified electric

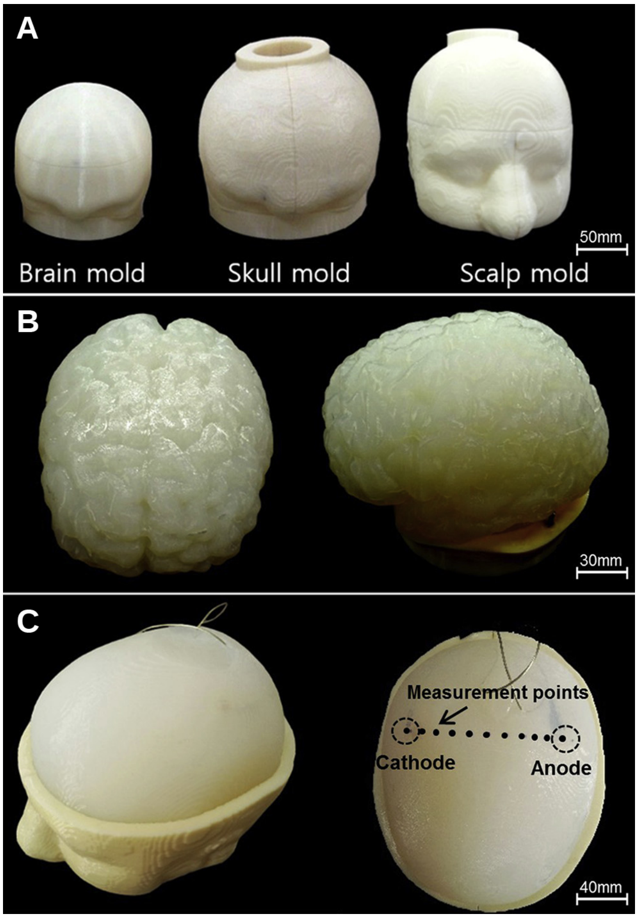

Figure 1. (A) MRI-based phantom head sub-molds representing three layers in the human head. (B) Brain layer generated by brain sub-mold. (C) Assembled phantom with implanted electrodes and measurement (sensing) points.