Evaluation of local electric fields generated by transcranial direct current stimulation with an extracephalic reference electrode based on realistic 3D body modeling

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Evaluation of local electric fields generated by transcranial direct current stimulation with an extracephalic reference electrode based on realistic 3D body modeling

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Abstract
In this study, local electric field distributions generated by transcranial direct current stimulation (tDCS) with an extracephalic reference electrode were evaluated to address extracephalic tDCS safety issues. To this aim, we generated a numerical model of an adult male human upper body and applied the 3D finite element method to electric current conduction analysis. In our simulations, the active electrode was placed over the left primary motor cortex (M1) and the reference electrode was placed at six different locations: over the right temporal lobe, on the right supraorbital region, on the right deltoid, on the left deltoid, under the chin, and on the right buccinator muscle. The maximum current density and electric field intensity values in the brainstem generated by the extracephalic reference electrodes were comparable to, or even less than, those generated by the cephalic reference electrodes. These results suggest that extracephalic reference electrodes do not lead to unwanted modulation of the brainstem cardio-respiratory and autonomic centers, as indicated by recent experimental studies. The volume energy density was concentrated at the neck area by the use of deltoid reference electrodes, but was still smaller than that around the active electrode locations. In addition, the distributions of elicited cortical electric fields demonstrated that the use of extracephalic reference electrodes might allow for the robust prediction of cortical modulations with little dependence on the reference electrode locations.

(Some figures may appear in colour only in the online journal)

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1. Introduction

Transcranial direct current stimulation (tDCS) is a noninvasive brain electrical stimulation technique that can modulate cortical excitability by transmitting a small direct current between a pair of scalp electrode pads (Antal et al. 2004, Fregni et al. 2005, Nitsche and Paulus 2000, Nitsche et al. 2007, 2008, Wagner et al. 2007b, Williams et al. 2009). The tDCS technique has been studied in a variety of clinical fields, especially as a potential treatment tool for neuropsychiatric diseases and neurological disorders including depression, epilepsy, electroanalgesia, stroke, Alzheimer’s disease, chronic pain, tinnitus, and Parkinson’s disease (Nitsche et al. 2009, Fregni et al. 2006, 2007, Mignon et al. 1996, Boggio et al. 2007, Ferrucci et al. 2008, Fregni and Pascual-Leone 2007, Schlaug et al. 2008, Williams et al. 2009). Although the effect of tDCS treatment is similar to that of repetitive transcranial magnetic stimulation (rTMS) and is less focal than that of rTMS, tDCS has attracted great attention in neuroscience as it has several advantages over traditional rTMS treatment including ease of implementation, better mobility, good safety profile, and lower cost (Nitsche et al. 2008, Priori 2003, Williams et al. 2009).

Traditionally, tDCS systems use anode and cathode electrodes at empirically determined locations considering the targeted brain area. Extensive clinical studies have shown that anodal and cathodal tDCS facilitate and inhibit cortical excitability, respectively, although the exact underlying mechanisms have not yet been revealed (Antal et al. 2001, Kincses et al. 2004, Nitsche et al. 2008). The most widely used electrode montage is the so-called ‘bi-cephalic’ electrode montage where both of the two electrode pads are attached to specific locations on the scalp surface, e.g. the ‘active’ electrode on M1 and the ‘reference’ electrode on the opposite hemisphere (Nitsche and Paulus 2000). One of the limitations of this electrode montage is that it is difficult to exclude the effect of the reference electrode since the observed tDCS effects could be due to a combination of the modulations of both active and reference electrodes (Nitsche et al. 2007). Moreover, it is generally accepted that for a fixed active electrode position, varying the location of the reference electrode can influence the current distribution formed inside the brain and thereby affect the resultant brain activity modulation (Cogiamanian et al. 2007, Nitsche and Paulus 2000, Mendonca et al. 2011, Priori et al. 2008). The simplest way to address this issue is to use an extracephalic reference electrode montage that places the reference electrode outside the scalp area (Accornero et al. 2007, Galea et al. 2009, Koenigs et al. 2009, Monti et al. 2008, Priori et al. 2008, Vandermeeren et al. 2010, Fertonani et al. 2010, Cogiamanian et al. 2007, Ferrucci et al. 2008, Moliadze et al. 2010, Mahmoud et al. 2010). Nevertheless, the use of an extracephalic reference electrode has been often avoided since the earliest tDCS studies conducted by Lippold and collaborators (Lippold and Redfearn 1964, Redfearn et al. 1964) warned that the use of an extracephalic reference electrode could lead to an unwanted modulation of the brainstem cardio-respiratory and autonomic centers.

Although classical bi-cephalic electrode montages are most often used, some recent studies have reported the successful application of tDCS with an extracephalic reference electrode without any notable changes in heart rate, blood pressure, body temperature, or respiratory frequency (Accornero et al. 2007, Galea et al. 2009, Koenigs et al. 2009, Monti et al. 2008, Vandermeeren et al. 2010). These experimental studies facilitated the development of a series of experimental conditions in which tDCS with an extracephalic reference electrode could be applied safely. For example, Vandermeeren et al. (2010) confirmed that a 20 min dc stimulation with an active electrode on the midline Fz and a reference electrode over the right tibia did not...
Evaluation of local electric fields generated by transcranial direct current stimulation

2. Methods and materials

2.1. 3D FEM

The 3D FEM was adopted to analyze the current density distribution inside the human body produced by tDCS. Considering direct current conduction, the following electrostatic Laplace equation was used as the governing equation of the FEM:

$$\nabla \cdot (\sigma \nabla V) = 0,$$

(1)

where $\sigma$ and $V$ represent the electrical conductivity and electric potential, respectively. We used a first-order finite element (FE) formulation and incomplete Cholesky conjugate gradient (ICCG) matrix solver (Jin 2002). The convergence criterion of ICCG was $|Ax - b|/|b| < 1.0 \times 10^{-14}$, where $A$, $x$, and $b$ represent a stiffness matrix, unknown vector, and forcing vector, respectively. Two electrode pads were modeled as two sets of surface nodes, each with different Dirichlet-type boundary values, e.g. $-1$ and $1$ V, respectively. The current density was evaluated for every volumetric tetrahedral element using the solution of (1) and then transformed into a node-wise form by interpolation. The total injection current value was computed by integrating the total current density under each surface electrode pad area. The average difference between the total injection currents of two electrodes was less than 6% of the absolute injection current value in our simulations (5.89% ± 1.74%). Based on the linearity between the total injection current and the current density at each node, the current density vectors in the entire analysis domain were scaled by a ratio of the target injection current (1 mA in this study) to the computed total injection current, which consequently led to a result for a constant current injection through a pair of electrode pads (injection current of each pad: 1 and $-1$ mA, respectively). All numerical analyses were performed using an optimized in-house FEM program coded using Fortran 90 (Im et al 2008).
2.2. 3D realistic modeling of an adult male human upper body

For the accurate evaluation of conductive current flow inside a human body, a reasonable resolution model of an adult male upper body was generated from a whole-body CAD model, originating from the Virtual Family project (Christ et al 2010). We used a 1 mm resolution volume pixel (voxel) dataset consisting of more than 80 pre-classified tissue types acquired from whole-body MR images of a healthy European 34 year old male (referred to as Duke), whose height, weight, and BMI were 1.74 m, 70.0 kg, and 23.1 kg m$^{-2}$, respectively.

To generate the FE model from the voxel dataset, we first separately extracted voxels included in the 15 different tissue types, which were skin, skull, brain, larynx, pharynx, left lung, right lung, spinal cord, thalamus, hippocampus, cerebellum, midbrain, pons, medulla, and spinal cord. Then, each structure surface was tessellated with surface triangular elements, forming closed surface mesh structures. We used a free software package (MeshLab; http://meshlab.sourceforge.net) to generate surface meshes (Cignoni et al 2008). The initial mesh structures shown in figure 1 (left figure) was generated from the point cloud data of each tissue using the ball-pivoting algorithm (BPA) (Bernardini et al 1999), which forms triangles by repeatedly pivoting a ball around an edge until it touches another point. The BPA variables, such as pivoting ball radius, clustering radius, and angle threshold, were determined independently for each mesh structure after an extensive trial-and-error process. Since the initial mesh structure was generally noisy, it was smoothed using an extended version of Laplacian smoothing (Vollmer et al 1999). Since the extensive geometrical smoothing could eliminate details such as strong curvatures in some structures and thereby affect the solution accuracy, we adjusted the level of smoothing by carefully inspecting the geometrical shape deformation. After removing duplicated points, duplicated surfaces, isolated surfaces, and zero-area elements, the closed surface mesh structure of each tissue was constructed (figure 1, left figure). Then, the independently modeled mesh structures were integrated into a single upper body model as shown in figure 1. The integrated model was tessellated with volumetric tetrahedral elements using an open-source mesh generation software package (TetGen; http://tetgen.belios.de), which was based on the constrained Delaunay tetrahedralization approach (Si 2008). No meshes were generated inside the left lung, right lung, larynx, and pharynx because these structures conduct negligible electric current. The minimum radius–edge ratio was set to 1.8 to generate high quality tetrahedral elements, and the maximum volume of each tetrahedron was set to 50 mm$^3$. The tetrahedralized upper body model consisted of 98 119 nodes and 590 104 elements. The average volume of the generated tetrahedral elements was 20.1 ± 12.9 mm$^3$, corresponding to a 2.7 mm × 2.7 mm × 2.7 mm size voxel. In some complicated structures, relatively smaller elements were generated by controlling the size of initial surface meshes. For example, the average volume of tetrahedral elements in spinal cord was 6.15 ± 3.55 mm$^3$, that of thalamus was 9.22 ± 5.34 mm$^3$, and that of hippocampus was 12.2 ± 7.51 mm$^3$. We then assigned regional attributes for internal air, vertebrae, bone, and fat (which were difficult to generate in closed surface mesh structures) to proper tetrahedral elements in the tessellated body model (see figure 1, right figures) when the minimum distance between each tetrahedral element and adjacent point cloud of the four structures was less than 3 mm. Muscle was not modeled independently since its electrical conductivity value was not significantly different from that of skin (Gabriel et al 1996a, 1996b, Sadleir et al 2010).

Figure 1(a) shows the final upper body model, with the mesh structures other than the brain and nervous system shown in a central figure and those of the brain and nervous systems in a left figure. Figure 1(b) shows the cross-sectional cuts of the volume meshes to demonstrate the level of detail of our body model. The electrical conductivity profiles for each
Figure 1. (a) The FE model of the adult male upper body: (left figure) mesh structures of the brain and nervous system; (middle figure) mesh structures other than the brain and nervous system. Meshes were not generated inside the left lung, right lung, larynx, and pharynx; (right figures) assigned regional attributes of four complex structures (internal air, vertebrae, bone, and fat). Each dot represents a tetrahedral element. (b) Cross-sectional cuts of the volume meshes: four axial cuts (A1–A4) and one coronal cut (C1) are visualized, where different tissue types are coded in color. The positions of the cut planes are illustrated in the upper left figure.
Figure 2. Locations of active and reference electrodes. Reference electrode locations: (a) over the right temporal lobe (Type A), (b) on the right supraorbital region (Type B), (c) on the right deltoid (Type C), (d) on the left deltoid (Type D), (e) under the chin (Type E), (f) on right buccinator muscle (Type F). Each set of clustered dots represents each electrode pad.

Table 1. Electrical conductivities assigned to tissues in the adult male upper body model. Conductivity values were chosen from low frequency (<1 kHz) data in the literature.

<table>
<thead>
<tr>
<th>Tissue types</th>
<th>Conductivity (S m$^{-1}$)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>$4.3 \times 10^{-1}$</td>
<td>Haueisen et al (1997), Sadleir et al (2010)</td>
</tr>
<tr>
<td>CSF</td>
<td>$1.5 \times 10^{0}$</td>
<td>Haueisen et al (1997)</td>
</tr>
<tr>
<td>Bone (incl. vertebrae and skull)</td>
<td>$1.5 \times 10^{-2}$</td>
<td>Oostendorp et al (2000)</td>
</tr>
<tr>
<td>Fat</td>
<td>$2.5 \times 10^{-2}$</td>
<td>Gabriel et al (1996a, 1996b)</td>
</tr>
<tr>
<td>Brain (cerebrum)</td>
<td>$2.0 \times 10^{-1}$</td>
<td>Mean of Haueisen et al (1997)</td>
</tr>
<tr>
<td>Spinal cord and cerebellum</td>
<td>$1.5 \times 10^{-1}$</td>
<td>Haueisen et al (1997)</td>
</tr>
<tr>
<td>Brainstem (medulla, pons, and midbrain)</td>
<td>$4.7 \times 10^{-1}$</td>
<td>Gabriel et al (1996a, 1996b)</td>
</tr>
<tr>
<td>Hippocampus and thalamus</td>
<td>$1.0 \times 10^{0}$</td>
<td>Holsheimer (1987), Gabriel et al (1996a, 1996b)</td>
</tr>
</tbody>
</table>

tissue were obtained from the literature (Haueisen et al 1997, Sadleir et al 2010, Oostendorp et al 2000, Gabriel et al 1996a, 1996b, Holsheimer 1987) and are summarized in table 1. The active electrode (anode) and reference electrode (cathode) were modeled as two rectangular pads ($7 \times 5$ cm$^2$ each). Figure 2 shows the locations of the active and reference electrodes. The active electrode was attached over the left primary hand motor cortex (M1), while the reference electrode was placed at six different locations (figure 2), over the contralateral temporal lobe (Hummel et al 2010), on the contralateral supraorbital region (Datta et al 2009), on the right deltoid (Cogiamanian et al 2007), on the left deltoid, under the chin (Priori et al 1997), and on the right buccinator muscle (Galea et al 2009). Based on previous studies, either the contralateral shoulder, deltoid, or upper arm is most frequently
selected when the extracephalic reference electrode was attached to the upper body of a subject (Monti et al 2008, Fertonani et al 2010, Priori et al 2008, Cogiamanian et al 2007, Koenigs et al 2009, Ferrucci et al 2008, Moliadze et al 2010, Mahmoud et al 2010). Attaching a reference electrode to the face (e.g. under the chin, on the inferior cheek, on the anterior neck) is not usual, but was occasionally done in a few experimental studies (Galea et al 2009, Koenigs et al 2010, Priori et al 1998, Berryhill et al 2010, Accornero et al 2007). One of the popular extracephalic reference electrode locations was the contralateral leg, either at the tibia, thigh, or knee (Lippold and Redfearn 1964, Redfearn et al 1964, Vandermeeren et al 2010, Carney 1969, Arfai et al 1970), but we did not consider those locations in this study due to the significantly increased complexity in modeling and computation. For the six different electrode montages, the maximum current density and maximum electric field intensity values at the skin, cerebral cortex, spinal cord, midbrain, pons, medulla, hippocampus, and thalamus were evaluated.

3. Results

We first compared the maximum current density and maximum electric field intensity values from various brain tissues among the six different electrode montages (table 2). The examples of electric field distributions in the brainstem and the spinal cord are shown in figure 3. The

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Quantity</th>
<th>Type A</th>
<th>Type B</th>
<th>Type C</th>
<th>Type D</th>
<th>Type E</th>
<th>Type F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>$E$</td>
<td>1.7499</td>
<td>2.6010</td>
<td>1.5665</td>
<td>1.8018</td>
<td>2.0719</td>
<td>2.1711</td>
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<tr>
<td></td>
<td>$J$</td>
<td>0.7992</td>
<td>1.1509</td>
<td>0.7707</td>
<td>0.8407</td>
<td>0.8288</td>
<td>0.8684</td>
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<tr>
<td></td>
<td>$\sigma E^2$</td>
<td>1.31</td>
<td>2.76</td>
<td>1.02</td>
<td>1.12</td>
<td>1.80</td>
<td>1.94</td>
</tr>
<tr>
<td>Cerebral cortex</td>
<td>$E$</td>
<td>0.9970</td>
<td>0.9927</td>
<td>0.8852</td>
<td>0.9047</td>
<td>0.9309</td>
<td>0.8961</td>
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<tr>
<td></td>
<td>$\sigma E^2$</td>
<td>1.50 $\times$ 10$^{-2}$</td>
<td>1.50 $\times$ 10$^{-2}$</td>
<td>1.18 $\times$ 10$^{-2}$</td>
<td>1.24 $\times$ 10$^{-2}$</td>
<td>1.3 $\times$ 10$^{-2}$</td>
<td>1.22 $\times$ 10$^{-2}$</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>$E$</td>
<td>0.1612</td>
<td>0.0700</td>
<td>0.7534</td>
<td>0.7535</td>
<td>0.3824</td>
<td>0.1769</td>
</tr>
<tr>
<td></td>
<td>$\sigma E^2$</td>
<td>2.05 $\times$ 10$^{-2}$</td>
<td>4.32 $\times$ 10$^{-3}$</td>
<td>0.12</td>
<td>0.11</td>
<td>2.41 $\times$ 10$^{-2}$</td>
<td>2.40 $\times$ 10$^{-2}$</td>
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<tr>
<td>Midbrain</td>
<td>$E$</td>
<td>0.4726</td>
<td>0.2431</td>
<td>0.4118</td>
<td>0.4255</td>
<td>0.5093</td>
<td>0.3864</td>
</tr>
<tr>
<td></td>
<td>$\sigma E^2$</td>
<td>3.35 $\times$ 10$^{-2}$</td>
<td>8.89 $\times$ 10$^{-4}$</td>
<td>2.54 $\times$ 10$^{-3}$</td>
<td>2.72 $\times$ 10$^{-3}$</td>
<td>3.90 $\times$ 10$^{-3}$</td>
<td>2.24 $\times$ 10$^{-3}$</td>
</tr>
<tr>
<td>Pons</td>
<td>$E$</td>
<td>0.3776</td>
<td>0.1760</td>
<td>0.4361</td>
<td>0.4551</td>
<td>0.4684</td>
<td>0.3626</td>
</tr>
<tr>
<td></td>
<td>$\sigma E^2$</td>
<td>0.0057</td>
<td>0.0026</td>
<td>0.0071</td>
<td>0.0073</td>
<td>0.0070</td>
<td>0.0054</td>
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<tr>
<td>Medulla</td>
<td>$E$</td>
<td>0.2355</td>
<td>0.1064</td>
<td>0.3361</td>
<td>0.3551</td>
<td>0.3496</td>
<td>0.3020</td>
</tr>
<tr>
<td></td>
<td>$\sigma E^2$</td>
<td>1.89 $\times$ 10$^{-2}$</td>
<td>4.05 $\times$ 10$^{-3}$</td>
<td>2.94 $\times$ 10$^{-3}$</td>
<td>3.05 $\times$ 10$^{-3}$</td>
<td>2.77 $\times$ 10$^{-2}$</td>
<td>2.25 $\times$ 10$^{-2}$</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>$E$</td>
<td>0.5638</td>
<td>0.2336</td>
<td>0.4271</td>
<td>0.4439</td>
<td>0.5544</td>
<td>0.4187</td>
</tr>
<tr>
<td></td>
<td>$\sigma E^2$</td>
<td>0.0085</td>
<td>0.0035</td>
<td>0.0064</td>
<td>0.0067</td>
<td>0.0083</td>
<td>0.0063</td>
</tr>
<tr>
<td>Thalamus</td>
<td>$E$</td>
<td>0.5141</td>
<td>0.2974</td>
<td>0.4191</td>
<td>0.4310</td>
<td>0.4607</td>
<td>0.4129</td>
</tr>
<tr>
<td></td>
<td>$\sigma E^2$</td>
<td>0.0077</td>
<td>0.0045</td>
<td>0.0063</td>
<td>0.0065</td>
<td>0.0069</td>
<td>0.0062</td>
</tr>
</tbody>
</table>

Type A: left M1–right temporal lobe; Type B: left M1–right supraorbital region; Type C: left M1–right deltoid; Type D: left M1–left deltoid; Type E: left M1–chin; Type F: left M1–right buccinator muscle.

Table 2. Maximum electric field intensity ($E$, unit: V m$^{-1}$), current density ($J$, unit: A m$^{-2}$), and volume energy density ($\sigma E^2$, unit: J m$^{-3}$) values at various brain tissues generated by six different electrode montages.
maximum current density values in the brainstem (midbrain, pons, and medulla) generated by the reference electrodes on the right or left deltoid were not significantly different from, or was less than, those generated by the conventional cephalic reference electrodes (table 2). The maximum current densities of the other brain structures generated by the extracephalic reference on the right or left deltoid were also comparable to those of the cephalic references. The only distinct difference was observed at the spinal cord (table 2 and figure 3), where the maximum current density generated by tDCS with deltoid references was approximately twice that of the tDCS with cephalic references. Although twice as high, the value for the tDCS with a deltoid reference might not be significant because the current density level was still far under the threshold current density used for spinal cord stimulation (23 A m$^{-2}$, Wesselink et al 1998) and to the best of our knowledge, no research has addressed any risks regarding potential spinal cord modulation by tDCS with an extracephalic reference electrode. In tDCS with an extracephalic reference under the chin or on the right buccinator muscle, no significant field concentrations in specific brain structures were observed compared to conventional tDCS results. The maximum electric field intensity and volume energy density values in the brainstem were also mildly influenced by the use of extracephalic reference electrodes.

To further evaluate the influence of the extracephalic reference electrode on tDCS current flows, we investigated the volume energy density distribution on the skin surface when the right and left deltoid references were used (figure 4). We evaluated the volume energy density ($\sigma E^2$) because it is the critical parameter associated with the safety aspects due to ohmic heating. Interestingly, the energy density was concentrated at the right neck with the right deltoid reference and at the left neck with the left deltoid reference, because the dispersed currents starting from the active electrode came together while passing through the narrow portion of the neck. However, the maximum energy density amplitudes at the right and left necks were less than half of those under the electrode pads, indicating that the use of a deltoid reference electrode would not provoke any side effects on the body surface such as skin burns.

Figure 3. Distributions of electric fields in the brainstem and the spinal cord. Figure indices A–F represent different electrode configurations, respectively corresponding to Types A–F (please refer to the caption of figure 2).
Figure 4. Volume energy density distributions on the skin surface from different viewpoints (3D view, right view, and cross-sectional view) when (a) the M1–right deltoid electrode montage and (b) the M1–left deltoid electrode montage were used.

and muscle spasms. Since no other electrode montages generated any distinct current density concentrations outside the electrode area, their distributions were not shown.

Figure 5 shows the electric field distributions on the cerebral cortex when the six different electrode montages were used. In all cases, the maximum electric fields were generated at locations slightly outside of the target area (originally under the active electrode) toward the direction of the reference electrode. This phenomenon is extensively reported in many computer simulation-based tDCS studies (Mendonca et al 2011, Datta et al 2009, Wagner et al 2007a). In particular, in the case of Type B (M1–contralateral supraorbital area), the generated electric field was mostly distributed around the anterior part of the brain, which was also reported in a study by Datta et al (figure 2.A.5 in Datta et al (2009)). However, it is noteworthy that the four different extracephalic reference electrode locations did not make any significant difference in the cortical field distribution due to longer current conduction paths relative to the cephalic tDCS. Our results demonstrate that the elicited cortical electric field distributions may not be significantly affected by variations in the reference electrode location in extracephalic tDCS, suggesting that the use of extracephalic reference electrodes could allow for a robust and intuitive estimation of cortical modulations even without the aid of complex field simulations.

4. Discussion

Safety is regarded as one of the key issues in the field of noninvasive brain stimulation. A number of studies have provided guidelines for the safe use of noninvasive electromagnetic
Figure 5. Electric field distributions in the cerebral cortex when six different electrode montages were used. Reference electrode locations: (a) over the right temporal lobe (Type A), (b) on the right supraorbital region (Type B), (c) on the right deltoid (Type C), (d) on the left deltoid (Type D), (e) under the chin (Type E), (f) on right buccinator muscle (Type F).

stimulation in various clinical applications and a recent review article summarized the safety guidelines in a well-organized manner (Poreisz et al. 2007). Although the necessity of using tDCS with an extracephalic reference electrode has been raised by many researchers, whether the use of an extracephalic reference electrode could lead to an unwanted modulation of brainstem autonomic functions was still controversial. Also, though studies by Lippold and collaborators (Lippold and Redfearn 1964, Redfearn et al. 1964) reported the possibility of the influence of an extracephalic reference electrode upon brainstem cardio-respiratory functions, a series of recent tDCS studies utilizing an extracephalic reference electrode did not report any significant changes in heart rate, blood pressure, body temperature, and respiratory frequency (Accornero et al. 2007, Galea et al. 2009, Koenigs et al. 2009, Monti et al. 2008, Vandermeeren et al. 2010). Despite this abundant experimental evidence, no previous studies quantitatively evaluated electric fields in the brainstem generated by tDCS with an extracephalic reference electrode. To investigate the safety of extracephalic tDCS, we evaluated the current density and electric field distributions inside a simulated human upper body based on 3D FE analysis. We compared the maximum current density and electric field intensity values generated by six different electrode montages with reference electrodes over the right temporal lobe, on the right supraorbital area, on the right deltoid, on the left deltoid, under the chin, and on the right buccinator muscle, respectively. Our simulation results did not support hypotheses that the use of extracephalic reference electrodes increased electric fields in the brainstem and other sub-cortical nuclei, suggesting that the use of extracephalic reference electrodes does not lead to unwanted modulation of brainstem autonomic centers.

According to our simulation results, tDCS with an extracephalic reference electrode did not elicit more current density and electric field intensity in the brainstem than tDCS with
a cephalic reference electrode while tDCS with an extracephalic reference electrode evoked a two-fold increase in current density in the spinal cord, the location of which is not very distant from that of the brainstem, relative to the tDCS with a cephalic reference electrode. The main reason for this difference is that the brainstem is located inside the skull, which has much lower electrical conductivity than the skin. Previous simulation studies have shown that most current is conducted via the skin, and only a little penetrates through the skull for brain stimulation (Miranda et al. 2006, Holdefer et al. 2006, Im et al. 2008). Our result suggests that the use of an extracephalic reference electrode does not significantly increase the amount of current penetration through the skull. Interestingly, the current density in the spinal cord was much stronger than that in the cerebral cortex in all simulations. These results indirectly support the above explanations because the spinal cord is surrounded by vertebrae that have many holes through which electric currents can flow, whereas the cerebral cortex is enclosed by the skull. We also illustrated the energy density distribution on the skin surface when the deltoid references were used (figure 4). Our simulation led to an interesting result showing concentrated energy density on the neck surface, but fortunately the maximum energy density around the neck was still lower than that around the active and reference electrode locations, demonstrating that the increased energy density around the neck would not provoke any side effects on the skin. Summarizing our simulation results, we did not detect any evidence suggesting that tDCS with an extracephalic reference electrode would be less safe than tDCS with a cephalic reference electrode.

Our FE body model had a resolution corresponding to 2.7 mm × 2.7 mm × 2.7 mm voxel size, which was relatively lower compared to a recent study (Sadleir et al. 2010) where 1.1 mm × 1.1 mm × 1.4 mm regular voxels were used. Although our model was constructed from 1 mm × 1 mm × 1 mm resolution MRI data, it was necessary for us to find the compromise between the solution accuracy and the computational load. Considering that our model included a large portion of the body, it was difficult to use a higher resolution model for the practical field analyses. In addition, we did not consider some complex tissue structures including muscles and eyes due to the difficulty in modeling. Although the electrical conductivities of those structures were not significantly different from the surrounding tissues compared to that of fat or bone, such simplification might affect the accuracy of the field simulations to some extent, especially for the cases when extracephalic reference electrodes are attached on the facial muscles. Therefore, it will be an interesting future topic to investigate the influences of modeling accuracy, model simplification, element shapes, and model resolution on the solution accuracy of the electric field analyses. Indeed, such studies have been extensively carried out in the field of electroencephalography (EEG) source imaging (e.g. Ferguson and Stroink 1997).

In this study, we determined electrical conductivity values for each tissue based on previously published results (Haueisen et al. 1997, Sadleir et al. 2010, Oostendorp et al. 2000, Gabriel et al. 1996a, 1996b, Holsheimer 1987). Since electric current flow is influenced by electrical conductivity values, it is obvious that an accurate estimation of tissue electrical conductivity would enhance overall accuracy of the analysis results. Indeed, some researchers even attempted to take tissue anisotropy into account for enhanced current density estimation (Suh et al. 2009). Despite progress in medical imaging technology, the estimation of individual conductivity profiles has not yet reached to a practical level (Woo and Seo 2008). Nevertheless, considering that some EEG studies assumed large variations of individual conductivity values, up to ± 50% of the mean value (Haueisen et al. 1997), it would be interesting to investigate the influences of individual tissue conductivity variations on the accuracy of 3D field analysis results.
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