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A high-resolution computational localization method for transcranial magnetic stimulation mapping

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ABSTRACT

Background: Transcranial magnetic stimulation (TMS) is used for the mapping of brain motor functions. The complexity of the brain deters determining the exact localization of the stimulation site using simplified methods (e.g., the region below the center of the TMS coil) or conventional computational approaches.
Objective: This study aimed to present a high-precision localization method for a specific motor area by synthesizing computed non-uniform current distributions in the brain for multiple sessions of TMS.
Methods: Peritumoral mapping by TMS was conducted on patients who had intra-axial brain neoplasms located within or close to the motor speech area. The electric field induced by TMS was computed using realistic head models constructed from magnetic resonance images of patients. A post-processing method was implemented to determine a TMS hotspot by combining the computed electric fields for the coil orientations and positions that delivered high motor-evoked potentials during peritumoral mapping. The method was compared to the stimulation site localized via intraoperative direct brain stimulation and navigated TMS.
Results: Four main results were obtained: 1) the dependence of the computed hotspot area on the number of peritumoral measurements was evaluated; 2) the estimated localization of the hand motor area in eight non-affected hemispheres was in good agreement with the position of a so-called "hand-knob"; 3) the estimated hotspot areas were not sensitive to variations in tissue conductivity; and 4) the hand motor areas estimated by this proposal and direct electric stimulation (DES) were in good agreement in the ipsilateral hemisphere of four glioma patients.
Conclusion(s): The TMS localization method was validated by well-known positions of the "hand-knob" in brains for the non-affected hemisphere, and by a hotspot localized via DES during awake craniotomy for the tumor-containing hemisphere.

Introduction

Transcranial magnetic stimulation (TMS) is a technique for non-invasively stimulating a target area of the brain. A current is induced below a stimulation coil, in which a pulsed current is injected through its windings. Single-pulsed and repetitive TMS is used for the diagnoses of diseases, such as stroke and movement disorders, for the treatment of diseases, such as neuropathic pain, and enhancing motor recovery (Leo and Latif, 2007; Hoyer and Celnik, 2011; Stinear et al., 2006). TMS has also been used for the pre-surgical identification of motor and language functions (Takakura et al., 2017).

Different coil configurations can be used for localized stimulation in cortical areas (Deng et al., 2013; Iwahashi et. al., 2017). For the purpose of identification, a figure-eight coil is commonly used to localize a hotspot in clinical practice (Takakura et al., 2017; Picht et al., 2009). Until recently, the stimulation area was considered to be just below the coil center, which could be predicted by Faraday's law (Ueno et al., 1988). However, it is known that the stimulated area of the brain does not always match the desired location (Julkunen et al., 2009; Weiss et al., 2013). One of the main reasons for this mislocalization is the

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non-uniform current flow, especially because of the brain's complexity (Opitz et al., 2011, 2013; Laakso et al., 2015; Miranda et al., 2007; Janssen et al., 2014). Recent studies have adopted electric field-navigated TMS using anatomical head models (Picht et al., 2011; Coburger et al., 2013; Forster et al., 2011; Krieg et al., 2013a). To the best of our knowledge, only two studies have combined the computation of electric fields with motor-evoked potential (MEP) measurements using an "electric field center of gravity" approach (Opitz et al., 2013, 2014). In addition, the TMS performance may be affected by operators' skill, and hence, guidelines have been published (Tarapore et al., 2016).

In clinical applications, the location of the area of interest (particularly for the motor area) must be confirmed by direct electrical stimulation (DES) during awake craniotomy. The operation time for awake craniotomy is substantial, typically lasting between 3 and 8 h per operation according to our experience and other reports (Taylor and Bernstein, 1999); therefore, the indication for awake craniotomy is limited. However, if precise localization by preoperative TMS is achieved, intraoperative cortical mapping to identify the functional localization of the cortex may reduce the time in awake craniotomy (Takahashi et al., 2013), and this can impact the neurosurgical decision-making and lead to modification of the initial treatment strategy (Krieg et al., 2012; Picht et al., 2012). Also, it has been reported improved surgical and oncological outcomes in patients after the adoption of nTMS mapping (Picht et al., 2013, 2016; Krieg et al., 2014; Krieg et al., 2015a).

The purpose of the present study was to propose a high-precision localization method for a specific motor area. In particular, our strategy was to estimate a stimulated area by synthesizing computed non-uniform current distributions in the brain during multiple stimulations considering the measurements of the MEP.

Materials and methods

Subjects and imaging

Eight patients (29–64 years, 4 women) participated in the study. The study subjects had intra-axial brain neoplasms located within or close to the motor eloquent area. Exclusion criteria included the existence of any implanted electrical devices (e.g., cardiac pacemaker or cochlear implant) or intractable seizures (Takakura et al., 2017). Patients provided written informed consent for all medical evaluations and treatments before participating in the study. Eight subjects were examined considering the localization of the hand motor area in their non-affected hemisphere of the brain. Peritumoral mapping was conducted in the tumor-containing hemisphere (affected hemisphere) in only four subjects. The four subjects excluded due to tumor recurrence had metal implanted in the affected hemisphere, which may have altered the distribution of current and disturbed the TMS mapping.

The subjects' T1-and T2-weighted magnetic resonance (MR) images were acquired using a 3-T MR scanner (Achieva; Philips Medical Systems, Amsterdam, Netherlands) with the following parameters: T1 MPRAGE sequence with TR/TE/FA/FOV/voxel size/slice number = 6.85 ms/4.61 ms/8/240 mm/1 mm × 1 mm × 1 mm/200, and T2 with TR/TE/FOV/voxel size/slice number = 2500 ms/236 ms/240 mm// 1 mm × 1 mm × 1 mm/200. MR scanning was performed no more than 3 months prior to surgery.

Image segmentation

In-house software (Laakso et al., 2015) that used FreeSurfer (Fischl, 2012) was implemented for brain segmentation using the MR images. First, the scalp, outer skull, inner skull, gray matter, white matter, cerebellar gray matter, cerebellar white matter, brainstem, nuclei, ventricles, and eyes were reconstructed.

The tissue compartments were further segmented on the basis of both T1 and T2 image intensities and geometric information as follows: the scalp compartment was segmented into fat (bright T1), muscle (darker T1), the average of the two (voxels that could not be reliably identified), and skin (non-fat voxels close to the outer surface); the skull into compact (dark T2) and spongy bone (bright T2); and the space between the skull and gray matter into CSF (bright T2), blood (voxels with T1 and T2 close to the mean T1 and T2 of large venous sinuses), and dura (non-blood non-CSF voxels close to the inner skull surface or interhemispheric fissure). The final volume conductor models were represented in a grid of cubical 0.5 mm × 0.5 mm × 0.5 mm voxels.

Computer simulation

A volume conductor model was used to compute the induced electric field in the head models. The electric displacement current was ignored because the magnetoquasistatic approximation is applicable in the 10-kHz frequency band, i.e., the displacement current is negligible when compared to the conduction current. The induced current in biological tissues was assumed to not perturb the external magnetic field. The induced scalar potential ϕ is given by the following equation:

$$\nabla \bullet [\sigma(-\nabla\phi - j\omega A_0)] = 0 \quad (1)$$

where A_0 and σ denote the magnetic vector potential of the applied magnetic field and tissue conductivity, respectively.

The magnetic field and magnetic vector potential distributions, generated by the induction coils for TMS, were obtained using the commercial software FEKO (EMSS-SA, Stellenbosch, South Africa), which utilizes a method of moments. A figure-eight coil was modeled as a single loop of thin wire with a radius for each wing of 70 mm in diameter and an input current of 1 A. This approximation is appropriate for the coil-to-cortex distance in humans (Salinas et al., 2007). Eq. (1) was discretized using the scalar potential finite difference method (Dawson and Stuchly, 1996), producing a sparse matrix equation with approximately 30 million unknowns. The matrix equation was solved iteratively using the geometric multigrid method with successive over-relaxation (Laakso and Hirata, 2012a). By defining scalar potentials (unknowns) at each node of a cubic voxel, a branch current flowing from one node to a neighboring node along the side of the voxels was derived. This branch current included a scalar potential owing to the applied electric charge and the impedance between nodes. The electric field along the edge of the voxel was obtained by dividing the difference in potential between the nodes of the voxel by the distance across the nodes, then adding the vector potential. There were 6 multigrid levels, and the iterations continued until the relative residual was less than 10^{-6} (Laakso and Hirata, 2012a). For this residual, the error relative to the maximum internal electric field was less than 0.5%. Based on the results, a 0.5 mm voxel size was chosen because it yielded good agreement in the finer resolutions, and provided an average computational time of 60 s for 3×10^7 voxel elements on a computer with Intel Xeon E5-2 637 v3 @ 3.50 GHz running Windows 7 and MATLAB R2015b (MathWorks, Inc., Japan). The validity of the computational code has been confirmed in our previous study (Gomez-Tames et al., 2017; Laakso and Hirata, 2012b).

Tissue electrical properties

The head model consisted of 14 tissues/body fluids, whose electrical conductivities were determined using the fourth order Cole-Cole model (Gabriel et al., 1996) at 10 kHz (Nieminen et al., 2015) and other typical values in TMS computational models (Opitz et al., 2014; Thielscher et al., 2011; Janssen and Oostendorp, 2015), as presented in Table 1. Tissue conductivity was assumed to be linear and isotropic. The tumor conductivity (σ_{tumor}) was considered to be between 0.2 S/m and 1.25 S/m as an exact conductivity value for tumors is difficult to determine owing to location and cancerization degree (Song et al., 2016). The tumor conductivity values were based on measurements at frequencies between 50 kHz and 5 MHz *in vivo* (Latikka et al., 2001; Lu, Li, Xu, Yu), and 64 MHz using MR conductivity imaging (Huhndorf et al., 2013; Voigt et