Published in final edited form as:

Clin Neurophysiol. 2009 December ; 120(12): 2071–2081. doi:10.1016/j.clinph.2009.09.007.

Influence of white matter anisotropic conductivity on EEG source localization: Comparison to fMRI in human primary visual cortex

Won Hee Lee^a, Zhongming Liu^a, Bryon A. Mueller^b, Kelvin Lim^b, and Bin He^{a,*}

^aDepartment of Biomedical Engineering, University of Minnesota, 7-105 BSBE, 312 Church Street, Minneapolis, MN 55455, USA

^bCenter for Magnetic Resonance Research, Department of Radiology, University of Minnesota, Minneapolis, MN 55455, USA

Abstract

Objective: The goal of this study was to experimentally investigate the influence of the anisotropy of white matter (WM) conductivity on EEG source localization.

Methods: Visual evoked potentials (VEP) and fMRI data were recorded from three human subjects presented with identical visual stimuli. A finite element method was used to solve the EEG forward problems based on both anisotropic and isotropic head models, and single-dipole source localization was subsequently performed to localize the source underlying the N75 VEP component.

Results: The averaged distances of the localized N75 dipole locations in V1 between the isotropic and anisotropic head models ranged from 0 to 6.22 ± 2.83 mm. The distances between the localized dipole positions and the centers of the fMRI V1 activations were slightly smaller when using an anisotropic model (7.49 ± 1.35 to 15.70 ± 8.60 mm) than when using an isotropic model (7.65 ± 1.30 to 15.31 ± 9.18 mm).

Conclusions: Anisotropic models incorporating realistic WM anisotropic conductivity distributions do not substantially improve the accuracy of EEG dipole localization in the primary visual cortex using experimental data obtained using visual stimulation.

Significance: The present study represents the first attempt using a human experimental approach to assess the effects of WM anisotropy on EEG source analysis.

Keywords

DT-MRI; EEG; fMRI; White matter anisotropy; Source localization; Finite element method

1. Introduction

Electroencephalography (EEG) source localization or imaging may serve as an important tool to investigate sensory and cognitive brain functions (He and Lian, 2005). In order to determine the locations of cerebral current sources generating the signals measured from the scalp surface

using EEG electrodes, numerous approaches have been proposed to solve an ill-posed inverse problem due to the finite surface measurements and the non-uniqueness of the solutions (Michel et al., 2004; He and Lian, 2005). In solving the inverse problem, one critical requirement is an accurate model of the head as a volume conductor, which is utilized to compute the surface potentials from known current sources in the conducting volume (the so-called forward problem). The accuracy of the localization of electrical sources inside the brain (i.e., the inverse solutions associated with the forward solutions) is dependent, in part, on the accuracy of the anatomic description of volume conductor model and on knowledge of electrical properties of the tissues.

In modeling the human head, previous studies have shown that the use of a realistically shaped head model using the boundary element method (BEM) (He et al., 1987; Hamalainen and Sarvas, 1989; Roth et al., 1997) or finite element method (FEM) (Yan et al., 1991) can improve the accuracy of source localization (Buchner et al., 1997). Recently, finite element (FE) head models have become more popular in solving the inverse problem, since the FEM technique is capable of handling individual head geometries with complicated boundaries and allows the incorporation of inhomogeneous and anisotropic tissue properties (Buchner et al., 1997; Awada et al., 1998; Marin et al., 1998; Kim et al., 2002; Lee et al., 2006; Wolters et al., 2006; Zhang et al., 2006, 2008).

Previous investigations of EEG source analysis have often been based on the assumption that the tissues have isotropic electrical conductivity values. However, the skull tissues were considered to be anisotropic due to the different characteristics of its three layers (top and bottom compacta and spongiosum) (Marin et al., 1998; Akhtari et al., 2002). It is also well known that the white matter (WM) of the brain may have an anisotropic conductivity with a ratio of about 1:10, a ten times larger conductivity parallel to the fibers than the normal to the fibers (Nicholson, 1965). A variety of methods have been proposed to estimate WM anisotropic conductivity tensors from diffusion tensor magnetic resonance imaging (DT-MRI), under the assumption that conductivity and diffusion tensors share the same eigenvectors (Basser et al., 1994; Tuch et al., 1999, 2001; Wolters et al., 2006; Hallez et al., 2008; Wang et al., 2008). For instance, the self-consistent effective medium approach asserts a linear relationship between the eigenvalues of the electrical conductivity tensor and the diffusion tensor (Sen et al., 1989; Tuch et al., 1999, 2001). Wolters et al. (2006) proposed a so-called volume constraint algorithm to model the WM conductivity anisotropy under the assumption that the shape of the WM diffusion ellipsoid is prolate (cigar-shaped) rotationally symmetric (Shimony et al., 1999). A technique based on the linear conductivity-to-diffusivity relationship in combination with a constraint on the magnitude of the electrical conductivity tensor (i.e., volume constraint) was also suggested (Hallez et al., 2008). Recently a method to derive the WM anisotropic conductivity from the measured diffusion tensors by incorporating the partial volume effects of the CSF and the intravoxel fiber crossing structure using the volume fraction algorithm was also proposed (Wang et al., 2008).

In order to study the effects of tissue anisotropic conductivity on the EEG forward or inverse solutions, various investigations have been carried out, including phantom and animal experimental study (Baillet et al., 2001; Gullmar et al., 2006; Liehr and Haueisen, 2008) and realistic simulation studies using FE head models (Haueisen et al., 2002; Kim et al., 2003; Wolters et al., 2006; Gullmar et al., 2007; Lee et al., 2008), finite difference method (FDM) (Li et al., 2007; Hallez et al., 2008), or finite volume method (FVM) based models (Cook and Koles, 2008). For instance, various simulation and visualization studies were performed on EEG forward fields and return current computation using different anisotropic conductivity ratios for the WM compartments (Wolters et al., 2006). In addition, the sensitivity of the WM anisotropic conductivities on the source reconstruction was examined (Hallez et al., 2008). They found that in the EEG source location, the dipole estimation error is, on average, 4 mm

with a maximum of 10 mm. These simulation studies tend to suggest that WM tissues have a non-negligible effect on EEG source analysis, thus suggesting modeling WM conductivity anisotropy should be taken into account for accurate source reconstruction.

To the best of our knowledge, there have been no previous reports of experimental results with regard to the influence of WM anisotropic conductivity on EEG source localization. In the present study, we assess the influence of WM anisotropy on the EEG source localization using an experimental protocol. We acquired both visual evoked potential (VEP) and functional magnetic resonance imaging (fMRI) data elicited by the same visual stimuli. The accuracy of EEG source localization was assessed through comparison with the fMRI activation maps, and the retinotopic relationship (Serenó et al., 1995; Grill-Spector and Malach, 2004). It is well known that the activation of an early VEP component (N75) arises from the primary visual cortex (V1) (Di Russo et al., 2001, 2005; Vanni et al., 2004). This correspondence has also been utilized to assess the localization error of EEG source imaging in a previous study (Im et al., 2007). Head volume conductor models were generated with or without incorporating the WM anisotropic conductivity derived from the measured diffusion tensors. A FEM based model was used to solve the EEG forward problems based on both anisotropic and isotropic head models, and single-dipole source localization was subsequently performed based on the early VEP component. The localized dipole positions were quantitatively compared with the locations of the fMRI activation within the primary visual cortex. The distance between the N75 dipole locations and fMRI activations was used to assess the goodness of the forward model and thereby the influence of the WM conductivity anisotropy on the EEG source localization.

2. Materials and methods

2.1. Subjects and stimuli

Three healthy human subjects (males, mean age 29.3, range 24–34 years) participated in this study. All subjects were right-handed and had normal vision. Written informed consent approved by the institutional review board at the University of Minnesota was obtained from the subjects before the experiments.

Fig. 1 shows the visual stimuli used for the EEG and fMRI experiments. The visual stimuli consisted of circular black-and-white checkerboards within the lower left and right quadrants of the visual field on a homogenous gray background: each visual stimulus had a diameter of 8°, 5°, or 3° visual angle. Each stimulus was placed along a left- or right-facing downward diagonal at different visual angles: 10°, 7°, and 4° as measured from the central fixation point to the center of each stimulus. The stimuli were named with respect to stimulus size and location (LLVF: large left visual field, LRVF: large right visual field, MLVF: middle left visual field, MRVF: middle right visual field, SLVF: small left visual field, and SRVF: small right visual field) as shown in Fig. 1. In the EEG experiment, the pattern-reversal checkerboards were reversed at 2 Hz. The spatial frequency of the visual pattern was 1.0 cycle/degree. Each session for each visual pattern contained two 7 minute runs. The stimulus was presented in one quadrant at a time. In the fMRI experiment, the same visual stimuli were delivered in six 30-second blocks to one quadrant a time separated by seven 30-second resting blocks with only a red fixation point on a neutral gray screen. The stimuli were generated with a DLP projector and back-mirrored to the subjects. Subjects were instructed to gaze at the central fixation point during the EEG recordings and fMRI experiments.

2.2. Data acquisition and preprocessing: MRI, DT-MRI, and fMRI

The MRI data for three subjects were obtained using a 3 Tesla TIM Trio scanner (Siemens, Erlangen, Germany). A three-plane localizer and sagittal scout image were acquired to

determine the location of the anterior commissure (AC) and posterior commissure (PC). Scans with T1, T2 and proton density (PD) contrasts were collected for tissue registration. T1-weighted images were acquired with coronal orientation, using a 3D MP-RAGE sequence (TR=2530 ms; TE=3.65 ms; TI=1100 ms; 240 slices; 1×1×1 mm voxel; flip angle=7 degrees; FOV=256 mm). PD-weighted and T2-weighted images were acquired with AC-PC alignment, using hyper-echo turbo spin echo (TSE) sequences (TR=6500 ms; TE=11 ms and 80 ms; 72 slices; 1×1×2 mm voxel; flip angle=120 degrees; FOV=256 mm).

DT-MRI data were acquired using a dual spin echo, single shot, pulsed gradient, echo planar imaging sequence (TR=10000 ms; TE=90 ms; 72 contiguous slices; 2×2×2 mm voxel; FOV=256 mm; 2 averages; b value=1000 s/mm²) that was co-registered to the PD acquisition. Unique volumes were collected to compute the tensor: six b=0 s/mm² images and 30 images with diffusion gradients applied in non-collinear directions. A dual echo flash field map sequence with voxel parameters common to the DT-MRI was acquired and used to correct the DT-MRI data for geometric distortion caused by magnetic field inhomogeneity (TR=700 ms; TE=4.62 ms/7.08 ms; flip angle=90 degrees; magnitude and phase difference contrasts).

The BOLD-fMRI data was acquired with 18 axial T₂*-weighted images covering both the occipital and parietal lobes using a gradient-echo echo-planar imaging (EPI) sequence (matrix size: 64×64; in-plane resolution: 3×3 mm²; slice thickness: 3 mm; no gap between slices; TR/TE=1000/35 ms).

The image data were preprocessed using software (BET, FLIRT, FUGUE and FDT) from the FMRIB Software Library (<http://www.fmrib.ox.ac.uk/>). FDT was used to correct the diffusion-weighted images for misalignment and distortion caused by the effects of eddy currents and subject motion. The geometric distortion caused by the magnetic field inhomogeneity was determined from the field map image, and FUGUE was then used to correct each of the eddy current corrected diffusion images for this distortion. FDT was then used to compute the diffusion tensor for DT-MRI data, using the eddy current and distortion corrected diffusion images.

2.3. FE volume conductor modeling

In this section, we present FE head modeling approaches to generate the isotropic and anisotropic head models obtained by three different types of anisotropic settings.

2.3.1. FE mesh generation—In FE head modeling, one critical requirement is for the mesh generation to represent the geometric and electrical properties of the head volume conductor. To generate the FE meshes from the co-registered structural MR images, we segmented MR images into five sub-regions: white matter, gray matter, CSF, skull, and scalp. BrainSuite2 (Shattuck and Leahy, 2002) was utilized for the segmentation of the different tissues within the head. The first step was to extract the brain tissues from the MR images exclusively of the skull, scalp, and undesirable structures. Anisotropic diffusion filtering was applied to remove unnecessary image gradients while edges are preserved. The edge detection technique was sequentially applied to create binary edge images with important anatomical boundaries such as that between the brain and skull. Then, morphological processing including erosion and dilation was carried out to identify the brain regions. The preprocessed brain images were classified into each tissue type including white matter, gray matter, and CSF using a maximum *a posteriori* classifier (for the details see Shattuck and Leahy, 2002). Also, the skull and scalp compartments were extracted using the skull extraction technique (Dogdas et al., 2005) based on a combination of thresholding and morphological operations. The FE mesh generation to construct the FE models of the whole head was performed using regular tetrahedral elements with inner-node spacing of 2 mm based on the Delaunay tessellation procedure (Watson, 1981).

2.3.2. FE electrical conductivity—To assign electrical properties to the five tissues segmented, we used the following isotropic electrical conductivities in accordance with each tissue type: WM = 0.14 S/m, gray matter = 0.33 S/m, CSF = 1.79 S/m, skull = 0.0132 S/m, and scalp = 0.35 S/m (Kim et al., 2002; Wolters et al., 2006).

To obtain the anisotropic conductivity tensors in the WM compartments, we first assumed that the conductivity tensors share the eigenvectors with measured diffusion tensors, based on the similarity between the transportation processes of water molecules and electrical charge carriers (Basser et al., 1994). Then, we adopted three existing techniques of estimating the WM anisotropic conductivities derived from the measured diffusion tensors: 1) a linear conductivity-to-diffusivity relationship based on the effective medium approach (Tuch et al., 1999; Haueisen et al., 2002), 2) a fixed anisotropy ratio in each WM voxel (Wolters et al., 2006), and 3) a linear conductivity-to-diffusivity relationship in combination with a volume constraint equation (Hallez et al., 2008). Three different approaches of modeling WM conductivity anisotropy are briefly described as follows.

The effective medium approach defines a linear relationship between the eigenvalues of the conductivity tensors σ and the eigenvalues of the diffusion tensors D in the following way:

$$\sigma = \frac{\sigma_e}{d_e} D \quad (1)$$

where σ_e and d_e denote the extracellular conductivity and diffusivity respectively (Tuch et al., 2001). This approximate linear relationship assumes the intracellular conductivity to be negligible. For the first anisotropic FE model, an empirically determined value of 0.736 S·s/mm³ was used for the scaling factor σ_e/d_e (Tuch et al., 1999; Haueisen et al., 2002). This model will hereafter be referred to as *AnisoLin*.

A second technique, presented by Wolters et al. (2006), proposed the volume constraint algorithm to compute the fixed anisotropic ratio of the WM electrical conductivity tensors as below.

$$\frac{4}{3}\pi\sigma_{iso}^3 = \frac{4}{3}\pi\sigma_1\sigma_2\sigma_3 \quad (2)$$

where σ_1 , σ_2 , and σ_3 denote the eigenvalues of the conductivity tensor, respectively, and σ_{iso} is the isotropic conductivity of the WM tissue. In the present study, we utilized an anisotropic conductivity ratio of 1:10. The conductivity value of the largest eigenvector σ_1 was set as ten times larger than the values of the perpendicular eigenvectors σ_2 and σ_3 . The anisotropic conductivity tensors of the WM compartments were modeled to be prolate (cigar-shaped), rotationally symmetric ellipsoids. This model will be referred to as *AnisoFix*.

The third approach was based on a linear scaling of the diffusion ellipsoids using Eq. (1) in combination with the volume constraint in Eq. (2). In contrast to the first approach, the volume constraint was applied to compute the scaling factor under the assumption that the diffusion tensor and conductivity tensor share the ratio between the respective eigenvalues. This model will be referred to as *AnisoVar*.

2.4. Comparison of FE forward solutions: isotropy vs. anisotropy

To gain insight into the impact of WM anisotropic conductivity on EEG source localization, the effects of WM anisotropic conductivity tensors on the EEG forward solutions were examined by comparing the scalp electrical potentials computed from the anisotropic FE

models to those from the isotropic models. To solve the EEG forward problems, the FE head models, along with electrical conductivity information, were imported into the commercial software ANSYS (ANSYS, Inc., PA, USA). Since previous studies have reported that the EEG sources revealed by early VEP components would appear around the primary visual cortex (Di Russo et al., 2001, 2005; Vanni et al., 2004), we placed over 1500 uniformly distributed current dipoles in the visual cortex for the EEG forward simulation study. An approximately tangentially oriented source (in the posterior-anterior direction) and a radially oriented source (in the inferior-superior direction) were applied to the isotropic and anisotropic FE head models, respectively. For each of these dipole positions, we calculated the EEG forward solutions using the preconditioned conjugate gradients solver within ANSYS (ANSYS, Inc., PA, USA).

The resultant forward potentials were compared using two similarity measures commonly used in previous similar situations (Marin et al., 1998; Wolters et al., 2006; Gullmar et al., 2007). Numerical errors in the topography of the electrical fields were computed using the relative difference measure (RDM) as follows (Meijs et al., 1998):

$$RDM = \sqrt{\sum_{i=1}^n \left(\frac{\Phi_{iso}}{\sqrt{\sum_{i=1}^n (\Phi_{iso})^2}} - \frac{\Phi_{aniso}}{\sqrt{\sum_{i=1}^n (\Phi_{aniso})^2}} \right)^2} \quad (5)$$

The RDM measures the topography error, and the minimum error of RDM is zero.

The second error measure is a magnification factor (MAG) for calculating the potential magnitude errors. The minimum error of MAG is unity. The MAG is defined as (Meijs et al., 1998):

$$MAG = \frac{\sqrt{\sum_{i=1}^n (\Phi_{aniso})^2}}{\sqrt{\sum_{i=1}^n (\Phi_{iso})^2}} \quad (6)$$

where n denotes the number of scalp potential nodes and Φ_{iso} and Φ_{aniso} are the resultant scalp potential values in the isotropic and anisotropic FE head models respectively.

2.5. EEG recording and data analysis

The EEG signals were recorded from a 64-channel system (BrainAmp MR 64 plus, BrainProducts, Germany) with a sampling frequency of 1000 Hz. The EEG electrodes were referenced to FCz and placed according to the extended international 10/20 system. The VEP experiments were conducted over two separate sessions for all subjects. In the preprocessing steps, visible ocular blink and artifact rejection, band-pass filtering (0.3-40 Hz), and segmentation with respect to stimulus onset were conducted within the BrainVision Analyzer (BrainVision, Germany). After segmentation into sweep epochs (−100 to 500 ms temporal range) based on the onsets of triggers recorded during the recording session, pre-stimulus baseline correction and linear trend removal were sequentially applied to the segmented epochs. Bad channels including unexpected distortions or fluctuations were manually discarded based on the examination of the EEG signals from each channel. The processed EEG data in the segmented epochs were averaged to yield the VEP signals. The aforementioned

EEG recording and data processing was carried out for each stimulus pattern. For the determination of the EEG V1 response, an early VEP component (N75) was defined at the earliest peak in the VEP temporal waveform. The N75 component had a peak latency of 73–85 ms following stimulus onset for all subjects. The physical landmarks (nasion, left, and right preauricular points) and EEG electrode positions were digitized using a Polhemus Fastrak digitizer (Polhemus, Colchester, VT) and 3DSpace software from the SCAN software package (Compumedics Inc.).

2.6. EEG source localization: simulation and experimental studies

The ill-posed nature of the inverse problem implies that *a priori* assumptions about the models of both the source and the head volume conductor should be taken into account to estimate neural sources. Numerous previous approaches have been used extensively to localize the neural sources that give rise to the scalp EEG signals (Michel et al., 2004; He and Lian, 2005). In the present study, both simulation and experimental studies were conducted to evaluate the effects of WM anisotropic conductivity on EEG source localization. The volume conductor was represented by the 3-D FE head model. The transfer matrix was calculated using the isotropic and anisotropic FE head models, respectively. The 3-D coordinates of each electrode position measured were fitted to the scalp surface defined by the individual structural MR images by using anatomical landmarks (nasion and two auricular points) with CURRY5 software (Neuroscan, TX, USA).

In modeling the source, a single equivalent dipole model (He et al., 1987) was utilized to approximate brain electrical sources induced by the visual stimuli. Equivalent dipole analysis is used to estimate the dipole parameters (i.e., location and moment) that best account for measured potentials in the least squares sense, thus minimizing the residual error.

$$\Delta^2 = \left\| L_j - \tilde{M} \right\|^2 \quad (7)$$

where L is the lead field matrix, j the dipole moment, and $\tilde{M}$ represents the simulated or measured VEP data. The location of a single focal source was reconstructed by scanning through a grid of dipoles with a spacing of 2 mm defined in the brain volume. At each grid location, the least squares fit was performed to find the best-fitting dipole to the VEP data.

In our simulation, both tangentially and radially oriented dipoles, which were defined with respect to the scalp surface, at one dipole location were considered for each individual subject. The simulated dipole source was placed in the primary visual cortex close to the cluster of inverse dipoles in the experimental study. Gaussian white noise (GWN) of 10 % was added to the scalp forward potentials generated by a single dipole in the anisotropic head model to simulate the noise-contaminated scalp measurements. The noise level was defined as the ratio between the standard deviation of noise and the standard deviation of the simulated scalp potential. Ten trials of randomly generated GWN distributions were applied and EEG inverse estimations were conducted for each of ten sets of noise-contaminated scalp potential data (Wang and He, 1998). The EEG inverse localization was performed using the lead field matrix obtained from the isotropic model and the simulated scalp potentials calculated from the anisotropic model. The EEG dipole location that best fits the simulated electrical potentials with 0 % and 10 % noise levels was determined using Eq. (7).

2.7. fMRI data analysis

The fMRI data were analyzed using BrainVoyager (Brain Innovation, Netherlands). The EPI volumes were motion corrected by aligning all functional volumes to the first collected EPI

volume. Slice scan time correction and linear trend removal procedures were also performed. After preprocessing, the functional volumes were aligned to the subjects' anatomical images for co-registration and visualization. The fMRI activation map from each individual subject was obtained by statistical analysis using a general linear model (GLM) (Friston et al., 1994). In our GLM analysis, the design matrix was defined by convolving the “box-car” stimulus functions with a canonical hemodynamic impulse response function. For the group data analysis, the individual subjects' fMRI images were transformed into a stereotaxic space for normalization (Talairach and Tournoux, 1998). Then a fixed-effects general linear model was employed to compute statistical maps at a group level.

3. Results

3.1. White matter anisotropy

The WM anisotropy information is illustrated in Fig. 2. Fig. 2A shows a transaxial fractional anisotropy (FA) map derived from the measured diffusion tensors (subject #2), indicating that there is strong anisotropy in the corpus callosum and the pyramidal tracts. Fig. 2B displays the color-coded DT ellipsoids where the regions of interest (ROI) are highlighted with a box in red. The enlarged ROI of the diffusion tensor ellipsoids is also illustrated. The directions of the principal tensor eigenvectors are clearly visible according to the RGB sphere (i.e., red: mediolateral, green: anteroposterior, and blue: superoinferior direction). The diameters in any direction of DT ellipsoids reflect the diffusivities in their corresponding directions, and their major principle axes are oriented in the directions of maximum diffusivities.

3.2. White matter anisotropic conductivity tensors: eigenvalue distribution

Fig. 3 displays the distribution of each eigenvalue of the anisotropic conductivity tensors within the WM regions estimated by using three different anisotropic settings (i.e., *AnisoLin*, *AnisoFix*, and *AnisoVar*). In the resultant eigenvalue distributions generated by *AnisoLin* and *AnisoVar*, it is shown that there are various eigenvalues over the transaxial plane, indicating that WM tissue has diverse anisotropic ratios. It is also apparent that there are larger eigenvalues at the corpus callosum, indicating strong anisotropy is present. In comparison to the *AnisoLin* and *AnisoVar* models, three eigenvalue maps derived from the fixed anisotropic conductivity of 1:10 (*AnisoFix*) resulted in homogenous distributions for each eigenvalue. As can be observed in Fig. 3, the distinct characteristics of the WM conductivity tensors are clearly noticeable.

3.3. Comparison of scalp forward potentials: isotropy vs. anisotropy

The numerical differences between the scalp electrical potentials of the isotropic and anisotropic head models for all three subjects are shown in Fig. 4. The statistical measures of RDM and MAG were used to compare the scalp forward potentials. The mean RDM and MAG values in an individual subject are represented for the tangentially oriented sources in Figs. 4A and B respectively. Figs. 4C and D also show the mean RDM and MAG for the radially oriented sources respectively. In the case of the anisotropic models using the tangential source, the *AnisoVar* models resulted in the lowest RDM values for each subject (subject #1: 0.08 ± 0.04 , subject #2: 0.13 ± 0.08 , and subject #3: 0.05 ± 0.03). The mean MAG values indicate that the *AnisoLin* models had the largest differences in the scalp electrical potentials between the isotropic and anisotropic conductivity models (subject #1: 0.87 ± 0.08 , subject #2: 0.87 ± 0.09 , and subject #3: 0.87 ± 0.07). In contrast to the tangentially oriented source, we found slightly larger effects of the WM anisotropy in the mean RDM and MAG errors for the radially oriented source. In the *AnisoLin* models, slightly larger differences were observed in the RDM values in comparison to the other anisotropic models (subject #1: 0.15 ± 0.07 , subject #2: 0.24 ± 0.14 , and subject #3: 0.26 ± 0.12). The quantitative comparison of the scalp electrical potentials in

Fig. 4 indicates that the inclusion of the WM anisotropy leads to the topography and magnitude differences on the EEG forward solutions.

3.4. VEP topographic maps

Fig. 5 illustrates a set of exemplary results from the scalp potential topographic maps elicited by the lower visual field stimuli in each of the six quadrants for subject #2. For the left lower visual fields in the upper row (LLVF, MLVF, and SLVF), the peak latencies were defined at 75 ms, 75 ms, and 78 ms, respectively. Also, the peak latencies of the right lower visual fields in the bottom row (LRVF, MRVF, and SRVF) were determined at 75 ms, 75 ms, and 80 ms, respectively. The N75 component was largest at occipitoparietal sites contralateral to the midline as shown in Fig. 5. Note that in all subjects, the early VEP component varied systematically in amplitude according to each stimulus position. The VEP topographic maps from the N75 components obtained from the lower visual field experiments were examined to better determine the EEG V1 response for each individual subject.

3.5. Source localization from simulations

The EEG dipole localization errors for noise-free and 10% noise level cases in both tangential and radial dipole configurations were determined by the distance between true single dipole locations and estimated dipole locations, and are listed in Table 1. In contrast to the tangential dipoles, relatively larger localization errors were observed for the radial dipoles. We also found that slightly larger errors occurred when using a 10 % noise level in both the tangential and radial dipole cases than when using a 0 % noise level. According to the averaged localization errors across three subjects, the *AnisoFix* model at a 10 % noise level in the radial dipole configuration contained the largest error (5.01 ± 0.72 mm), while there was no localization difference in the *AnisoVar* model at a 0 % noise level for the tangential dipole. The simulation results in Table 1 indicate that neglecting WM anisotropy affects the accuracy of EEG source localization.

3.6. Comparison of EEG source location from measurements: isotropy vs. anisotropy

To investigate the effects of WM anisotropic conductivity tensors on EEG source localization, we evaluated the localization difference of the reconstructed EEG dipole source by determining the distance of the N75 dipole location between the isotropic and anisotropic head models. Table 2 shows the source-to-source distances in individual subjects as well as the averaged distances across three subjects for each stimulus condition. In subject #1, the range of the source-to-source difference was between 0 and 10.68 mm. In comparison to subject #1, there were smaller differences in subject #2 (0–9.43 mm) and subject #3 (0–5.75 mm). The averaged location differences show that *AnisoLin* models had relatively larger differences as compared to the *AnisoFix* and *AnisoVar* models. It can be seen that the largest average distance of the N75 dipoles between the isotropic and anisotropic models was found in the *AnisoFix* model from the SRVF experiments (6.22 ± 2.83 mm). The resultant source-to-source differences in Table 2 indicate that the WM anisotropic conductivity tensors might affect the accuracy of the EEG source localization.

3.7. Comparison between EEG and fMRI

In all three subjects, the visual evoked fMRI activations in response to visual stimuli were observed in multiple visual cortical areas in the contralateral hemisphere. The visual stimuli presented to varied visual fields were used to evoke V1 activations at each cortical visual area with different eccentricities as shown in Fig. 1. Fig. 6 displays the group-averaged fMRI activations on the inflated cortical surface according to each visual stimulus. Significant V1 activations were revealed around the calcarine fissure of the contralateral V1 in the group-averaged data, in accordance with the known retinotopic organization (Sereno et al.,

1995; Deyoe et al., 1996; Engel et al., 1997; Warnking et al., 2002; Grill-Spector and Malach, 2004). The group-averaged fMRI responses in the regions of the calcarine fissure appear to originate primarily from the V1 area, although some contributions from other areas (e.g., V2) are also possible.

As previously mentioned, to study the accuracy of the EEG source localization and thus investigate the effects of the WM anisotropic conductivity tensors, we quantified the localization error between the fMRI activations and EEG sources reconstructed from the isotropic and anisotropic head models by assessing the distance between the fMRI V1 activation centers and N75 dipole locations in response to identical visual stimuli. For fMRI, the center of gravity of the V1 activation was used to define the centers of the fMRI activations (Di Russo et al., 2001; Moradi et al., 2003; Im et al., 2007). For comparison and evaluation, the N75 dipoles were co-registered to the fMRI space in the Talairach coordinate system (Talairach and Tournoux, 1998).

Table 3 shows the spatial location differences between the fMRI centers and N75 dipoles in the individual subjects for all six conditions. The localization errors between the EEG sources determined by the N75 components and fMRI activation centers in V1 varied (range: about 6-26 mm). The largest and smallest differences were observed in subject #2 (MRVF: 26.49 mm) and subject #1 (MLVF: 6.32 mm), respectively. Overall, the results convey that the localization errors between the fMRI centers and N75 dipoles from the anisotropic models are smaller in comparison to the isotropic models, thus indicating that the anisotropic head models have slightly better accuracy in EEG source localization. Also, we found the same localization errors in some visual conditions (e.g., LLVF in subject #2), suggesting that there are no effects of the WM anisotropic conductivity on the EEG inverse solutions. It can be seen that the localization differences in the anisotropic models are relatively larger than in the isotropic models in only two experimental cases (SLVF and SRVF in subject #3). The averaged differences over three subjects are also shown in Table 3 and demonstrate that the N75 dipoles obtained by the anisotropic models are slightly closer to the centers of the fMRI V1 activations in comparison to the isotropic models other than the *AnisoLin* and *AnisoVar* models (SRVF).

We next evaluated the localization errors between the averaged EEG source locations and the centers of the group-averaged fMRI activation maps. Fig. 7 illustrates the centers of the group-averaged fMRI activations and the N75 dipole positions co-registered in the cortical surface for all stimulus conditions. It is clearly visible that the fMRI centers and N75 dipoles are localized in close proximity to the contralateral calcarine fissure or near V1. The detailed quantitative comparison results for all visual patterns are given in Table 4. We found that the largest and smallest localization errors were obtained in the isotropic model (MRVF: 15.78 mm) and the *AnisoLin* and *AnisoVar* models (LLVF: 2.45 mm) respectively. As observed in Table 4, the N75 dipoles obtained by the anisotropic models (range: 2.45 to 15.39 mm) are localized in slightly contiguous sites to the centers of the fMRI activations, indicating that the anisotropic model-driven solution gives slightly better localization results over the isotropic model (3.46 to 15.78 mm).

4. Discussion

The goal of the present study is to experimentally investigate the influence of WM anisotropic conductivity tensors on EEG source localization using EEG recorded during visual stimulation and fMRI as an independent estimate for true activity location. To the best of our knowledge, this is the first experimental study in humans to examine the effects of WM anisotropy on EEG source localization. The spatial locations of the VEP sources were estimated by an early VEP component (i.e., N75) and compared to the fMRI V1 localization in response to identical visual stimuli by evaluating the distance between the N75 dipole locations and fMRI-determined

activation centers in V1. The present experimental results show that 1) the averaged distances of the localized N75 dipole locations between the anisotropic and isotropic FE head models ranged from 0 to 6.22 ± 2.83 mm; 2) in individual subjects, the averaged distances between the localized dipole positions and the centers of the fMRI V1 activation were slightly smaller when using an anisotropic model (range: 7.49 ± 1.35 to 15.70 ± 8.60 mm) than when using an isotropic model (7.65 ± 1.30 to 15.31 ± 9.18 mm); 3) based on the comparison between the group-averaged fMRI centers and averaged VEP source locations, the N75 dipoles obtained by the anisotropic models were localized in slightly closer sites to the fMRI activation centers with a slightly smaller difference in distance (2.45 to 15.39 mm) than the isotropic models (3.46 to 15.78 mm). This experimental study using visual stimulation demonstrates that anisotropic models incorporating realistic WM anisotropic conductivity distributions do not substantially improve the accuracy of the EEG dipole localization within the human primary visual cortex. The present results suggest that the WM conductivity anisotropy is of less concern for localizing the EEG source within the human primary visual cortex.

Recent studies have shown that neglecting tissue anisotropy influences the accuracy of EEG source localization (Gullmar et al., 2006; Cook and Koles, 2008; Hallez et al., 2008). The inverse simulation study by Gullmar et al. (2006) found differences in source location of up to 1.3 mm with a mean value of 0.3 mm. Cook and Koles (2008) reported that FVM based head models not incorporating the tissue anisotropy resulted in localization errors of a mean value of 2.23 mm and a maximum of 23.02 mm. It was also found that dipole estimation errors of above 5 mm occurred when the dipole was located in the deep regions of the brain and close to the interfaces of the WM and gray matter tissues (Hallez et al., 2008). In the present inverse simulation study, we observed that the average localization errors of three different anisotropic volume conductor models (i.e., *AnisoLin*, *AnisoFix*, and *AnisoVar*) ranged from 0 to 5.01 ± 0.72 mm when WM conductivity anisotropy was neglected. It appears that our inverse simulation results are in agreement with the forward RDM results in both the tangential and radial dipole configuration settings (see Figs. 4A and C). It was also observed that the localization errors were relatively larger for the radial dipoles than those for the tangential dipoles as shown in Table 1. This phenomenon could be explained that the radially oriented dipole source placed in V1 for our inverse simulation was more affected by the WM conductivity anisotropy, thus leading to a larger difference in the topography and magnitude of the EEG potential fields, in comparison to the tangentially oriented source. In our experimental study with real VEP measurements, on the other hand, we found comparable results in the source localization differences, which ranged from 0 to 6.22 ± 2.83 mm between the dipoles using isotropic vs. anisotropic head models (for the details see Table 2). As we used the same forward anisotropic models and the same inverse dipole localization procedures in the simulation and experimental studies, these results indicate the difference in EEG source localization which would occur when using an isotropic or the WM anisotropic models. In other words, the present simulation and experimental results to compare the difference when using the isotropic and anisotropic head model confirm that if the WM anisotropy is well reflected in the modeling, then there will be localization errors associated with it in the range of few mm up to ~6 mm.

In addition to previous studies based on computer simulations, it is of particular interest to assess the effects of WM conductivity anisotropy in EEG source localization in an *in vivo* human brain. To address this question, we have conducted an experimental study to compare the EEG dipole localization results with fMRI activation using an identical visual stimulation.

Characterizing the neuronal generators of major VEP components peaking at several latencies in the VEP temporal waveform is still controversial issue and has been debated (Foxe and Simpson, 2002; Di Russo et al., 2004, 2005). According to many previous studies (e.g., Di Russo et al., 2001, 2005; Vanni et al., 2004; Im et al., 2007) and the results in the present work,

the earliest cortical EEG response elicited by visual stimuli may be assumed to arise predominantly from V1, and thus visually-evoked V1 activation accounts for the early VEP component (N75) at around 75 ms post-stimulus than subsequent waveform components at later latencies. The single dipole model to localize the early VEP activity in V1 has been used in many previous studies (Gratton et al., 1997; Di Russo et al., 2001, 2005; Vanni et al., 2004), since the dipolar field distributions are typically shown on the scalp potential topography at early latencies (Im et al., 2007). The EEG sources elicited by the visual stimuli used in this work were localized near the posterior portion of the calcarine fissure, which is located at the very caudal end of the medial surface of the brain. It is suggested that the source located in the deep regions of the brain is strongly influenced by the anisotropic WM tissues. The significant effects on the forward and inverse solutions in regions surrounded by highly anisotropic WM tissues were well described (Wolters et al., 2006; Hallez et al., 2008). Gullmar et al. (2006) suggested that dipole orientation and strength might be significantly affected by brain anisotropy. Also, it was observed that EEG fields are especially sensitive to the conductivity changes of the brain tissue next to the dipole (Haueisen et al., 1997; Awada et al., 1998; Gencer and Acar, 2004). These simulation studies appear to support the notion that modeling tissue conductivity anisotropies and inhomogeneities for an accurate volume conductor should be taken into account, especially in estimating deep neuronal sources. On the other hand, as we noted above, there is no experimental study, to our knowledge, which assesses the adequacy of the computer models of WM conductivity anisotropy.

In studying the source localization accuracy of EEG inverse methods, fMRI can be a useful approach due to its high spatial resolution. With fMRI, activated brain areas can be localized at millimeter spatial resolution, although the technique has a limited ability to reveal the temporal dynamics of cortical areas. Therefore, the accuracy of EEG source localization has been widely investigated through comparison to cortical activations revealed by fMRI as a reference (Di Russo et al., 2005; Im et al., 2007). Particularly, the EEG estimates of the early V1 activation coincide well with the retinotopically localized activities in the primary visual cortex obtained by fMRI (Di Russo et al., 2001, 2005; Vanni et al., 2004). However, it should be cautioned that there are some mismatches between EEG and fMRI due to the fundamentally different electrophysiological and hemodynamic processes involved (Bonmassar et al., 2001; Disbrow et al., 2005; Liu et al., 2006; He and Liu, 2008). It is worthwhile to mention that the use of fMRI is based on the assumption that the hemodynamic responses revealed by fMRI are colocalized by identical neural activities that produce event-related potentials. In other words, if the hemodynamic BOLD signal does not colocalize with electrical activity, the use of fMRI retinotopic activation as a reference estimate for true V1 activity location may result in distorted error estimates.

Although separate acquisition of fMRI and EEG data, as in the present study, can produce highly reproducible activations (e.g., Di Russo et al., 2001), simultaneous fMRI-EEG recording in a single session maybe desirable to avoid possible discrepancies between the locations of fMRI activations and EEG sources due to different brain responses (i.e., hemodynamics and electrophysiology), particularly for multimodal investigations on human cognitive function or pathology. However, it is not always necessary to concurrently record fMRI and EEG (He and Liu, 2008), since the EEG signals during fMRI scanning are largely contaminated or distorted by the high-frequency gradient and RF pulses inside the MR scanner, and thereby artifact removal techniques should be applied to acquire the reliable EEG data, which is worse than the clear EEG signals recorded through separate sessions.

Our experimental results, comparing EEG dipole localization results and fMRI activation in the same human subjects under the same experimental stimulation paradigm, revealed however little difference between the estimated inverse dipoles and the center of gravity in fMRI activation maps when the isotropic and WM anisotropic models were used. Certain deviation

in terms of co-localization was observed between the fMRI activation and EEG dipole locations. Compared with such deviation, the difference due to the use of isotropic model or WM anisotropic models was rather small. In other words, there were no dramatic differences between the isotropic vs. anisotropic models when comparing the equivalent dipole locations to the fMRI activations in the primary visual cortex. Based on our experimental results from three human subjects, our interpretation concerning the use of the isotropic vs. anisotropic models should be cautious in extracting generalized conclusion. However, while the number of human subjects studied was limited (three subjects) in our work, multiple experiments were conducted in each subject, including VEP, structural MRI, DT-MRI, and fMRI. The FE head modeling was performed for each subject based on the individual MRI and DT-MRI. As such, we believe the present experimental results do provide important data with regard to the issue if WM anisotropy would have a significant effect on EEG source localization. While it is beyond the scope of the present study, further experimental investigations are needed in a larger number of subjects to fully address the question if WM conductivity anisotropy will significantly affect EEG inverse source localization.

For our purpose in this study, only WM anisotropic conductivity was incorporated into the FE head models in order to examine its effects on EEG source localization without the consideration of the skull anisotropy and partial volume effects of the CSF in DT-MRIs (Alexander et al., 2001). Regarding the skull anisotropy, although correct representation of the skull anisotropic conductivity is still a challenging problem due to its inhomogeneous and uncertain structure (e.g., compacta and spongiosa), the skull has been treated as an anisotropic conductor (Marin et al., 1998; Wolters et al., 2006). In Marin et al. (1998), it was found that skull anisotropy has an influence on the EEG forward and inverse solutions due to the skull's anisotropic property of having a larger electrical conductivity in the tangential directions than in the radial directions. In addition, the partial volume effects in fiber merging and crossing of the WM are one of the crucial factors to be considered. We have recently proposed an improved method to derive the WM anisotropic conductivity by utilizing the volume fraction of the glia, axons, and partial CSF within each voxel in order to incorporate the partial volume effects of the CSF and the intravoxel fiber crossing structure (Wang et al., 2008). Further studies including these factors should be performed in the movement towards more precise analysis of the bioelectromagnetic phenomena in the human head.

Acknowledgments

This work was supported in part by NIH R01EB007920, R01EB006433, R21EB006070, NSF BES-0602957, a grant from the Institute of Engineering in Medicine of the University of Minnesota, and supported in part by the Supercomputing Institute at the University of Minnesota.

References

- Akhtari M, Bryant HC, Marmelak AN, Flynn ER, Heller L, Mandelkern M, Matlachov A, Ranken DM, Best ED, DiMauro MA, Lee RR, Sutherling WW. Conductivities of three-layer live human skull. *Brain topogr* 2002;14:151–67. [PubMed: 12002346]
- Alexander AL, Hasan KM, Lazar M, Tsuruda JS, Parker DL. Analysis of partial volume effects in diffusion-tensor MRI. *Magn Reson Med* 2001;45:770–80. [PubMed: 11323803]
- Awada KA, Jackson DR, Baumann SB, Williams JT, Wilton DR, Fink PW, Prasky BR. Effect of conductivity uncertainties and modeling errors on EEG source localization using a 2-D model. *IEEE Trans Biomed Eng* 1998;45:1135–45. [PubMed: 9735563]
- Baillet S, Riera JJ, Marin G, Mangin JF, Aubert J, Garnero L. Evaluation of inverse methods and head models for EEG source localization using a human skull phantom. *Phys Med Biol* 2001;46:77–96. [PubMed: 11197680]
- Basser PJ, Mattiello J, Bihan DL. MR diffusion tensor spectroscopy and imaging. *Biophys J* 1994;66:259–67. [PubMed: 8130344]

- Bonmassar G, Schwartz DP, Liu AK, Kwong KK, Dale AM, Belliveau JW. Spatiotemporal brain imaging of visual-evoked activity using interleaved EEG and fMRI recordings. *NeuroImage* 2001;13:1035–43. [PubMed: 11352609]
- Buchner H, Knoll G, Fuchs M, Rienaker A, Beckmann R, Wagner M, Silny J, Pesch J. Inverse localization of electric dipole current sources in finite element models of the human head. *Electroenceph Clin Neurophysiol* 1997;102:267–78. [PubMed: 9146486]
- Cook MJD, Koles ZJ. The effect of tissue anisotropy on the EEG inverse problem. *Proc EMBC'08* 2008:4563–6.
- DeYoe EA, Carman GJ, Bandettini P, Glickman S, Wieser J, Cox R, Miller D, Neitz J. Mapping striate and extrastriate visual areas in human cerebral cortex. *Proc Natl Acad Sci USA* 1996;93:2382–6. [PubMed: 8637882]
- Di Russo F, Martinez A, Sereno MI, Pitzalis S, Hillyard SA. Cortical sources of the early components of the visual evoked potential. *Hum Brain Mapp* 2001;15:95–111. [PubMed: 11835601]
- Di Russo F, Pitzalis S, Spitoni G, Aprile T, Patria F, Spinelli D, Hillyard SA. Identification of the neural sources of the pattern-reversal VEP. *NeuroImage* 2005;24:874–86. [PubMed: 15652322]
- Disbrow EA, Slutsky DA, Roberts TPL, Krubitzer LA. Functional MRI at 1.5 Tesla: a comparison of the blood oxygenation level-dependent signal and electrophysiology. *Proc Natl Acad Sci USA* 2005;97:9718–23. [PubMed: 10931954]
- Dogdas B, Shattuck DW, Leahy RM. Segmentation of skull and scalp in 3-D human MRI using mathematical morphology. *Hum Brain Mapping* 2005;26:273–85.
- Engel SA, Glover GH, Wandell BA. Retinotopic organization in human visual cortex and the spatial precision of functional MRI. *Cereb Cortex* 1997;7:181–92. [PubMed: 9087826]
- Foxe JJ, Simpson GV. Flow of activation from V1 to frontal cortex in human. *Exp Brain Res* 2002;142:139–50. [PubMed: 11797091]
- Friston KJ, Jezzard P, Turner R. Analysis of functional MRI time-series. *Hum Brain Mapp* 1994;1:153–71.
- Gencer NG, Acar CE. Sensitivity of EEG and MEG measurements to tissue conductivity. *Phys Med Biol* 2004;49:701–17. [PubMed: 15070197]
- Gratton G, Fabiani M, Corballis PM, Hood DC, Goodman-Wood MR, Hirsch J, Kim K, Friedman D, Gratton E. Fast and localized event-related optical signals (EROS) in the human occipital cortex: comparisons with the visual evoked potential and fMRI. *NeuroImage* 1997;6:168–80. [PubMed: 9344821]
- Grill-Spector K, Malach R. The human visual cortex. *Annu Rev Neurosci* 2004;27:649–77. [PubMed: 15217346]
- Gullmar D, Haueisen J, Eiselt M, Giessler F, Flemming L, Anwander A, Knosche TR, Wolters CH, Dumpelmann M, Tuch DS, Reichenbach JR. Influence of anisotropic conductivity on EEG source reconstruction: investigations in a rabbit model. *IEEE Trans Biomed Eng* 2006;53(9):1841–50. [PubMed: 16941840]
- Gullmar D, Haueisen J, Reichenbach JR. Influence of anisotropic conductivity measured using DTI on the EEG forward solution: a whole human head sensitivity analysis. *Proc Intl Soc Mag Reson Med* 2007;15:1528.
- Hallez H, Vanrumste B, Hese PV, Delputte S, Lemahieu I. Dipole estimation errors due to differences in modeling anisotropic conductivities in realistic head models for EEG source analysis. *Phys Med Biol* 2008;53:1877–94. [PubMed: 18364544]
- Hamalainen MS, Sarvas J. Realistic conductivity geometry model of the human head for interpretation of neuromagnetic data. *IEEE Trans Biomed Eng* 1989;36:165–71. [PubMed: 2917762]
- Haueisen J, Ramon C, Brauer H, Nowak H. Influence of tissue resistivities on neuromagnetic fields and electric potentials studied with a finite element model of the head. *IEEE Trans Biomed Eng* 1997;44:727–35. [PubMed: 9254986]
- Haueisen J, Tuch DS, Ramon C, Schimpf PH, Wedeen VJ, George JS, Belliveau JW. The influence of brain tissue anisotropy on human EEG and MEG. *NeuroImage* 2002;15:159–66. [PubMed: 11771984]

- He B, Musha T, Okamoto Y, Homma S, Nakajima Y, Sato T. Electric dipole tracing in the brain by means of the boundary element method and its accuracy. *IEEE Trans Biomed Eng* 1987;34:406–14. [PubMed: 3610187]
- He, B.; Lian, J. Electrophysiological neuroimaging. In: He, B., editor. *Neural Engineering*. Kluwer Academic/Plenum Publishers; 2005. p. 221–62.
- He B, Liu Z. Multimodal functional neuroimaging: integrating functional MRI and EEG/MEG. *IEEE Reviews Biomed Eng* 2008;1:23–40.
- Im CH, Gururajan A, Zhang N, Chen W, He B. Spatial resolution of EEG cortical source imaging revealed by localization of retinotopic organization in human primary visual cortex. *J Neurosci Meth* 2007;161:142–54.
- Kim S, Kim TS, Zhou Y, Singh M. Influence of conductivity tensors on the scalp electrical potential: study with 2-D finite element models. *IEEE Trans Nucl Sci* 2003;50:133–8.
- Kim TS, Zhou Y, Kim S, Singh M. EEG distributed source imaging with a realistic finite-element head model. *IEEE Trans Nucl Sci* 2002;49:745–52.
- Lee WH, Kim TS, Cho MH, Ahn YB, Lee SY. Methods and evaluations of MRI content-adaptive finite element mesh generation for bioelectromagnetic problems. *Phys Med Biol* 2006;51:6173–86. [PubMed: 17110778]
- Lee WH, Kim TS, Kim AT, Lee SY. 3-D diffusion tensor MRI anisotropy content-adaptive finite element head model generation for bioelectromagnetic imaging. *Proc EMBC'08* 2008:4003–6.
- Li J, Wang K, Zhu S, Mueller B, Lim K, Liu Z, He B. A study of white matter anisotropic conductivity on EEG forward solutions. *Proc. NFSI&ICFBI'07* 2007:130–2.
- Liehr M, Haueisen J. Influence of anisotropic compartment on magnetic field and electric potential distributions generated by artificial current dipoles inside a torso phantom. *Phys Med Biol* 2008;53:245–54. [PubMed: 18182700]
- Liu Z, Kecman F, He B. Effects of fMRI-EEG mismatches in cortical current density estimation integrating fMRI and EEG: A simulation study. *Clin NeuroPhysiol* 2006;117:1610–22. [PubMed: 16765085]
- Marin G, Guerin C, Baillet S, Garnero L, Meunier G. Influence of skull anisotropy for the forward and inverse problem in EEG: simulation studies using FEM on realistic head models. *Hum Brain Mapp* 1998;6:250–69. [PubMed: 9704264]
- Meijs JWH, Weier OW, Peters MJ, Oosterom AV. On the numerical accuracy of the boundary element method. *IEEE Trans Biomed Eng* 1989;36:1038–49. [PubMed: 2793196]
- Michel CM, Murray MM, Lantz G, Gonzalez S, Spinelli L, Peralta RG. EEG source imaging. *Clin Neurophysiol* 2004;115:2195–222. [PubMed: 15351361]
- Moradi F, Liu LC, Cheng K, Waggoner RA, Tanaka K, Ioannides AA. Consistent and precise localization of brain activity in human primary visual cortex by MEG and fMRI. *NeuroImage* 2003;18:595–609. [PubMed: 12667837]
- Nicholson PW. Specific impedance of cerebral white matter. *Exp Neurol* 1965;13:386–401. [PubMed: 5847284]
- Roth BJ, Ko D, von Albertini-Carletti IR, Scaffidi D, Sato S. Dipole localization in patients with epilepsy using the realistically shaped head model. *Electroencephalogr Clin Neurophysiol* 1997;102:159–66. [PubMed: 9129570]
- Sarvas J. Basic mathematical and electromagnetic concepts of the biomagnetic inverse problem. *Phys Med Biol* 1987;32:11–22. [PubMed: 3823129]
- Schimpf PH, Ramon CR, Haueisen. Dipole models for the EEG and MEG. *IEEE Trans Biomed Eng* 2002;49(50):409–18. [PubMed: 12002172]
- Sen AK, Torquato S. Effective electrical conductivity of two-phase disordered anisotropic composite media. *Phys Rev B Condens Matter* 1989;39(7):4504–15. [PubMed: 9948799]
- Sereno MI, Dale AM, Reppas JB, Kwong KK, Belliveau JW, Brady TJ, Rosen BR, Tootell RB. Borders of multiple visual areas in humans revealed by functional resonance imaging. *Science* 1995;268:889–93. [PubMed: 7754376]
- Shattuck DW, Leahy RM. BrainSuite: an automated cortical surface identification tool. *Med Image Anal* 2002;8:129–42. [PubMed: 12045000]

- Shimony JS, Mckinstry R, Akbudak E, Aronovitz JA, Snyder AZ, Lori NF, Cull TS, Conturo TE. Quantitative diffusion-tensor anisotropy brain MRI imaging: normative human data and anatomic analysis. *Radiology* 1999;212:770–84. [PubMed: 10478246]
- Talairach, J.; Tournoux, P. Thieme. New York, NY: 1988. Co-planar stereotaxic atlas of the human brain.
- Tuch DS, Wedeen VJ, Dale AM, George JS, Belliveau JW. Conductivity mapping of biological tissue using the diffusion MRI. *Ann N Y Acad Sci* 1999;888:314–16. [PubMed: 10842642]
- Tuch DS, Wedeen VJ, Dale AM, George JS, Belliveau JW. Conductivity tensor mapping of the human brain using diffusion tensor MRI. *Proc Natl Acad Sci USA* 2001;98:11697–701. [PubMed: 11573005]
- Vanni S, Warnking J, Dojat M, Delon-Martin C, Bullier J, Segebarth C. Sequence of pattern onset responses in the human visual areas: an fMRI constrained VEP source analysis. *NeuroImage* 2004;91:1282–96.
- Wang K, Zhu S, Mueller AB, Lim K, Liu Z, He B. A new method to derive white matter conductivity from diffusion tensor MRI. *IEEE Trans Biomed Eng* 2008;55:2481–6. [PubMed: 18838374]
- Wang Y, He B. A computer simulation study of cortical imaging from scalp potentials. *IEEE Trans Biomed Eng* 1998;45:724–35. [PubMed: 9609937]
- Warnking J, Dojat M, Guerin-Dugue A, Delon-Martin C, Olympeff S, Richard N, Chehikian A, Segebarth C. fMRI retinotopic mapping-step by step. *NeuroImage* 2002;17:1666–83.
- Watson DF. Computing the n-dimensional Delaunay tessellation with application to Voronoi polytypes. *The Comp Jour* 1981;24:167–72.
- Wolters CH, Anwander A, Tricoche X, Weinstein D, Koch MA, MacLeod RS. Influence of tissue conductivity anisotropy on EEG/MEG field and return current computation in a realistic head model: a simulation and visualization study using high-resolution finite element modeling. *NeuroImage* 2006;30:813–26. [PubMed: 16364662]
- Yan Y, Nunez PL, Hart RT. Finite-element model of the human head: scalp potentials due to dipole sources. *Med Biol Eng Comput* 1991;29:475–81. [PubMed: 1817208]
- Zhang YC, Ding L, van Drongelen W, Hecox K, Frim DM, He B. A cortical potential imaging study from simultaneous extra- and intracranial electrical recordings by means of the finite element method. *NeuroImage* 2006;31:1513–24. [PubMed: 16631381]
- Zhang YC, van Drongelen W, Kohrman M, He B. Three-dimensional brain current source reconstruction from intra-cranial ECoG recordings. *NeuroImage* 2008;42:683–95. [PubMed: 18579412]

Fig. 1.

Visual stimuli used for both EEG and fMRI experiments. Circular checkerboards placed in the left and right quadrants of the visual field were flashed one at a time at six different locations. The visual stimuli were named with respect to stimulus size and location (LLVF: large left visual field, MLVF: middle left visual field, SLVF: small left visual field, LRVF: large right visual field, MRVF: middle right visual field, and SRVF: small right visual field).

Fig. 2.

(A) A transaxial fractional anisotropy (FA) map derived from the measured diffusion tensors (subject #2). (B) Corresponding color-coded diffusion tensor ellipsoids according to the red-green-blue sphere (red: mediolateral, green: anteroposterior, and blue: superoinferior direction). The regions of interest in the red box are also illustrated (right).

Fig. 3. The eigenvalue distributions of the anisotropic conductivity tensors within the WM regions generated by three different anisotropic algorithms (*AnisoLin*, *AnisoFix*, and *AnisoVar* models). Three rows indicate three different anisotropic settings. Three columns refer to three sorted eigenvalue maps of the anisotropic conductivity tensors.

Fig. 4.

Quantitative comparison between the scalp electrical potentials of the isotropic and three different anisotropic models for each subject. Mean RDM values and mean MAG values are plotted for the tangentially oriented sources (A and B) and radially oriented sources (C and D), respectively. Black bars: standard deviations. (Different anisotropic models are represented by different colors in the plots).

Fig. 5.

Topographic maps of an early VEP component elicited by the lower visual field stimuli in each of six different quadrants (subject #2). VEP topographic potential maps for (A) LLVF (75 ms after the visual onset), (B) MLVF (75 ms), (C) SLVF (78 ms), (D) LRVF (75 ms), (E) MRVF (75 ms), and (F) SRVF (80 ms) are illustrated in 3-D (the plots are scaled individually according to the color bars on the right).

Fig. 6.

Group-averaged fMRI activations on the inflated cortical surface for all six visual field stimuli with a threshold $p < 0.001$ uncorrected (the color bar indicates the statistical significance of the response).

Fig. 7.

Locations of the group-averaged fMRI centers and averaged N75 dipole sources co-registered in the cortical surface. Middle left and right figures show the enlarged images around the primary visual cortex from the left and right visual fields, respectively. The different types of markers are also shown for the representation of the fMRI center and each N75 dipole (red circle: fMRI, green pentagram: isotropic, yellow diamond: *AnisoVar*, blue square: *AnisoLin*, and magenta triangle: *AnisoFix*).

Table 1
Localization errors in millimeters for noise-free and 10 % noise level cases in the tangential and radial dipole configurations

Subject #	Models	Tangential		Radial	
		0% noise	10% noise	0% noise	10% noise
1	AnisoLin	2.45	4.12	4.24	4.83
	AnisoFix	2.45	4.35	4.12	4.35
	AnisoVar	0	1.70	4.00	4.12
2	AnisoLin	0	2.04	2.45	4.00
	AnisoFix	4.00	4.10	5.66	5.78
	AnisoVar	0	1.20	0	1.27
3	AnisoLin	2.45	4.00	4.00	4.33
	AnisoFix	2.45	4.35	4.00	4.90
	AnisoVar	0	1.26	3.16	4.00
Average	AnisoLin	1.63 ± 1.41	3.39 ± 1.17	3.56 ± 0.97	4.39 ± 0.42
	AnisoFix	2.96 ± 0.89	4.27 ± 0.14	4.59 ± 0.93	5.01 ± 0.72
	AnisoVar	0	1.38 ± 0.27	2.39 ± 2.11	3.13 ± 1.61

Table 2

Localization differences of the N75 dipole locations in millimeters between the isotropic and anisotropic models for all stimulus conditions

Subject #	Models	LLVF	LRVF	MLVF	MRVF	SLVF	SRVF
1	AnisoLin	4.12	10.68	8.31	2.45	4.24	3.16
	AnisoFix	0	8.60	8.31	2.45	4.12	4.12
	AnisoVar	4.12	10.68	8.31	0	4.24	3.16
2	AnisoLin	0	6.78	4.00	0	4.12	0
	AnisoFix	0	0	4.00	0	4.12	9.43
	AnisoVar	0	0	4.00	0	4.12	0
3	AnisoLin	4.00	0	5.75	0	5.39	5.10
	AnisoFix	4.00	4.12	4.12	0	5.39	5.10
	AnisoVar	4.00	0	0	0	5.39	5.10
Average	AnisoLin	2.71 ± 2.35	5.82 ± 5.40	6.02 ± 2.17	0.82 ± 1.41	4.58 ± 0.70	2.75 ± 2.57
	AnisoFix	1.33 ± 2.31	4.24 ± 4.30	5.48 ± 2.46	0.82 ± 1.41	4.58 ± 0.70	6.22 ± 2.83
	AnisoVar	2.71 ± 2.35	3.56 ± 6.16	4.10 ± 4.16	0	4.58 ± 0.70	2.75 ± 2.57

Table 3

Localization errors in millimeters between the fMRI centers and N75 dipole locations in individual subjects for all stimulus conditions

Subject #	Models	LLVF	LRVF	MLVF	MRVF	SLVF	SRVF
1	Isotropic	7.55	10.63	7.55	8.66	12.00	13.04
	AnisoLin	7.07	6.56	6.32	7.00	8.12	12.65
	AnisoFix	7.55	9.11	6.32	7.00	8.12	12.69
	AnisoVar	7.07	6.56	6.32	8.66	8.12	12.65
2	Isotropic	9.00	25.71	16.16	26.49	19.31	25.41
	AnisoLin	9.00	22.56	14.87	26.49	17.26	25.41
	AnisoFix	9.00	25.71	14.87	26.49	17.26	23.38
	AnisoVar	9.00	25.71	14.87	26.49	17.26	25.41
3	Isotropic	6.40	7.34	9.00	6.78	9.27	7.48
	AnisoLin	6.40	7.34	9.00	6.78	14.24	9.05
	AnisoFix	6.40	7.34	7.61	6.78	14.24	9.05
	AnisoVar	6.40	7.34	8.60	6.78	14.24	9.05
Average	Isotropic	7.65 ± 1.30	14.56 ± 9.80	10.90 ± 4.61	13.98 ± 10.88	13.53 ± 5.19	15.31 ± 9.18
	AnisoLin	7.49 ± 1.35	12.15 ± 9.02	10.06 ± 4.37	13.42 ± 11.32	13.21 ± 4.66	15.70 ± 8.60
	AnisoFix	7.65 ± 1.30	14.05 ± 10.13	9.60 ± 4.61	13.42 ± 11.32	13.21 ± 4.66	15.04 ± 7.45
	AnisoVar	7.49 ± 1.35	13.20 ± 10.84	9.93 ± 4.43	13.98 ± 10.88	13.21 ± 4.66	15.70 ± 8.60

Table 4

Localization errors in millimeters between the group-averaged fMRI centers and averaged N75 dipole locations for all stimulus conditions

Models	LLVF	LRVF	MLVF	MRVF	SLVF	SRVF
Isotropic	3.46	8.60	5.39	15.78	10.00	15.56
AnisoLin	2.45	5.48	4.24	15.36	7.21	15.39
AnisoFix	3.30	7.35	4.24	15.36	7.21	15.13
AnisoVar	2.45	7.55	3.16	15.78	7.21	15.39