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IMAGING OF CURRENT FLOW IN THE HUMAN HEAD DURING TRANSCRANIAL ELECTRICAL THERAPY

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Abstract

Background—It has been assumed that effects caused by tDCS or tACS neuromodulation are due to electric current flow within brain structures. However, to date, direct current density distributions in the brains of human subjects have not been measured. Instead computational models of tDCS or tACS have been used to predict electric current and field distributions for dosimetry and mechanism analysis purposes.

Objective/Hypothesis—We present the first *in vivo* images of electric current density distributions within the brain in four subjects undergoing transcranial electrical stimulation.

Methods—Magnetic resonance electrical impedance tomography (MREIT) techniques encode current flow in phase images. In four human subjects, we used MREIT to measure magnetic flux density distributions caused by tACS currents, and then calculated current density distributions from these data. Computational models of magnetic flux and current distribution, constructed using contemporaneously collected T₁-weighted structural MRI images, were co-registered to compare predicted and experimental results.

Results—We found consistency between experimental and simulated magnetic flux and current density distributions using transtemporal (T7–T8) and anterior-posterior (Fpz–Oz) electrode montages, and also differences that may indicate a need to improve models to better interpret experimental results. While human subject data agreed with computational model predictions in

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Author contributions

A.K. designed data acquisition methods, acquired and analyzed subject data. A. I. segmented models and performed simulations. M.C. processed subject data and reconstructed projected current density. M. S. designed data acquisition methods. T. M. designed data acquisition methods, analyzed data, and edited manuscript. R.S. designed study and wrote manuscript.

overall scale, differences may result from factors such as effective electrode surface area and conductivities assumed in models.

Conclusions—We believe this method may be useful in improving reproducibility, assessing safety, and ultimately aiding understanding of mechanisms of action in electrical and magnetic neuromodulation modalities.

Keywords

tDCS; tACS; Finite Element Modeling; Current Density; MRI; MREIT

Introduction

Transcranial electrical stimulation (tES) strategies such as tDCS or tACS, have been indicated for stroke rehabilitation, treatment of epilepsy, and improving cognitive, motor or memory performance in healthy subjects [1]. However, the underlying mechanisms of tDCS and tACS remain unclear. It has been assumed tES effects are greatest, and electric fields and current densities are largest, in brain structures near stimulating electrodes. In tDCS at 1 mA intensity, excitatory effects are associated with structures under more positively polarized electrodes and inhibitory effects with those under more negatively polarized electrodes [2]. It is hypothesized that externally applied fields depolarize or hyperpolarize resting membrane voltages in targeted tissue, leading to increased excitability or inhibition respectively. However, there is evidence of increased excitability at 2 mA, regardless of polarity [3]. Effects may also depend on total stimulation time [4]. Further, tACS applied at frequencies up to 80 Hz may entrain neural networks, with excitatory or inhibitory effects that depend on frequency, current intensity and phase of current application relative to underlying activity [5].

High-resolution anatomically-detailed computational models are frequently used to model tES current distributions and inform mechanism theory. Model tissue conductivities are typically derived from measurements on bulk excised tissues [6, 7]. However, while surface field measurements have been made using ECoG arrays [8], systematic model validation has not yet been possible. Knowledge of complete current distributions formed within the brain during tES would clarify study outcomes and allow more detailed explorations of mechanism. Further, effects of different current application protocols, electrode designs, individual neuroanatomy, cerebrospinal volume and many other study factors could easily be resolved.

Recently developed MR electrical impedance tomography (MREIT) [9] methods make it possible to reconstruct conductivity and current density distributions in subjects using only one component (B_z) of magnetic flux density vectors. One MREIT method, DT-MREIT [10], can be used to reconstruct full anisotropic conductivities and current density distributions using MREIT and diffusion tensor image data gathered from the same subject, and has recently been demonstrated in canines [11].

Functional MRI has been used to characterize responses to tES [12–14] and it has been noted that current administration creates artifacts on MR images [15]. One group used fMRI

methods to identify voxel clusters correlating with current flow [16] and plotted magnetic flux density distributions caused by tDCS during entire MR acquisitions. However, to date, there have been no reports of tES current density imaging in humans.

In this paper, we demonstrate the first MREIT current density images (MREIT-CDI) in human heads. Data was gathered from four human subjects undergoing tACS-like stimulation procedures at frequencies of 10 Hz and 1.5 mA intensity. We used MREIT methods to recover magnetic flux density distributions caused by the current flow, and reconstructed in-plane current density distributions caused by both bilateral (T7–T8) and anterior-posterior (Fpz–Oz) montages. While AC stimulation was employed, electromagnetic field distributions and tissue conductivities at this frequency should be very similar to those found in tDCS [17]. We show correspondences between experimental B_z data and that predicted by computational models constructed using high-resolution T1-weighted MR images obtained in the same imaging session. We then computed measures of current density distribution (projected current density, J^P) within a focus plane for each subject and compared these with model predictions. Because literature conductivity values are almost exclusively derived from excised human or animal tissue samples, and these measurements in the human head are entirely novel, we did not extensively analyze differences between predicted and experimental measurements.

MREIT-CDI techniques may be useful in validating tES models and confirming protocol consistency. These techniques can be used to directly examine the effect of individual neuroanatomic variation, allowing detailed examination of correlations between current distributions and brain structures. Development of this capacity would immediately illuminate mechanism investigations. When current density data is processed further to form conductivity images, the results may have more profound implications in wider fields, such as EEG source imaging, where precise estimations of tissue conductivities are critical to reducing source location uncertainty.

Material and Methods

Subject Selection

All procedures were performed according to protocols approved by the University of Florida (UF) and Arizona State University Institutional Review Boards. Four healthy normal right-handed male volunteers were recruited (mean age 20, range 19–21), screened to exclude metallic implants, agreed to participate, then admitted to the study.

Subjects completed a mini-mental state examination (MMSE) [18], to rule out dementia and neurological deficits (MMSE scores > 24 were required for inclusion), and right-handedness was confirmed (Edinburgh Inventory [19] scores $> +40$ were required for inclusion). Subjects completed brief questionnaires before and after interventions to assess mood, and tACS-related physical sensations. No subject reported any adverse events, either acutely or in follow up meetings approximately 24 hours after interventions.

MR Imaging Setup

All data were measured using a Philips 32-channel head coil in a 3 T MRI Philips Achieva scanner at the Advanced Magnetic Resonance Imaging and Spectroscopy Facility, UF McKnight Brain Institute. We gathered co-registered high resolution T_1 -weighted and diffusion weighted data on all subjects for computational model construction and comparison with MREIT results. MREIT acquisitions employed a Philips *mffe* protocol, modified to produce TTL-logic pulses after each MR excitation pulse, triggering a MR-safe battery-operated constant current source (DC-STIMULATOR MR, neuroConn, Ilmenau, Germany). Figure 1 shows a schematic of the measurement setup. We verified that ‘no current’ (NC) measurements using the MREIT sequence did not affect processed signal phase, and that expected current-induced B_z maps were recovered using an agarose phantom (Figures S1 and S2).

Subject Protocol

Prior to scans, neuroConn carbon-rubber electrodes ($\sim 25 \text{ cm}^2$), enclosed in sponges, were soaked in saline (0.9% NaCl) and squeezed to remove excess solution. Immediately before electrode placement on Fpz, Oz, T7 and T8 locations, a 5-ml volume of saline was applied to both sides of each sponge. Small amounts (ca. 1 ml) of saline were also applied to the scalp under hair at electrode sites. Electrodes were applied approximately 30 minutes before tACS procedures.

Figure 2(i) shows schematic electrode placements for Subject A. Electrodes were secured with elastic bandage (Vetrap, 3M). Stimulator connections were completed after subjects entered the scanner. Stimulation was administered using both an Fpz-Oz and T7–T8 montage. Details of stimulation parameters are described in the sections below.

Subjects were requested to report stimulation-related side effects while in the scanner. Phosphene perception was rated on a 1–10 scale, with 1 corresponding to ‘no detectable flashing’ and 10 corresponding to ‘white field’. Phosphene fields were recorded as either ‘peripheral’ or ‘central’. Any subject perceptions of cutaneous stimulation were also recorded.

MR Imaging Procedures

After pilot scan acquisition, a 3D FLASH T_1 -weighted structural image was acquired with a 240 mm (FH) $\times$ 240 mm (AP) $\times$ 160 mm (RL) field-of-view (FOV) and 1 mm isotropic resolution, centered laterally on the mid-brain. Figure 1(b) shows the Philips *mffe* sequence modified for MREIT-CDI. MREIT-CDI datasets were acquired in three 5 mm contiguous slices ($NS = 3$) with an in-plane FOV of 224 mm (RL) $\times$ 224 mm (AP) and a data matrix size $100 \times 100 \times 3$ (resolution $2.24 \times 2.24 \times 5 \text{ mm}^3$). MREIT slice positions were aligned to the T_1 -image volumes and chosen to encompass electrodes (Figure 2(i)). MREIT scans were performed for each slice sequentially, and comprised 100 phase encode steps for each slice ($PE = 100$). For each PE step, ten echoes ($NE = 10$) were acquired during a current injection time (T_c) of 32 ms within a TR of 50 ms, then the current polarity was alternated during subsequent TR intervals. This sequence was repeated 12 times ($NAV = 12$) for each PE step. Therefore, the total acquisition time for each MREIT-CDI image was $TR \times 2$ (polarity

switching) $\times$ NAV $\times$ PE $\times$ NS = 6:00 minutes. The entire MREIT-DCI procedure was repeated and results averaged, for a total acquisition time of 12 minutes, to achieve better signal-to-noise ratio (SNR) and to reduce standard deviations in current induced magnetic fields (B_z) [20]. 'Positive' pulses were applied first to the first named electrode in each montage (Fpz or T7). An initial, no current (NC), MREIT scan was performed to verify system stability and produce baseline T_2^* maps. This required only 6 minutes since no polarity switching was used. The entire MREIT-CDI acquisition, comprising stimulation via both Fpz-Oz and T7–T8 electrode pairs and NC scans, lasted approximately 30 minutes.

Electrical Stimulation Protocol

A 1.5 mA current intensity was used in all experiments, for both Fpz-Oz and T7–T8 montages. Figure 3 shows that current was applied for periods of 32 ms of each 50 ms TR. Because current polarity reversed after each TR, the stimulation waveform therefore corresponded to a sequence of rectangular pulses with a duty cycle of approximately 64%. Fourier transformation of the current waveform showed maximum power at around 10 Hz. In summary, the protocol applied was a 10 Hz symmetric biphasic pulse, 50 ms pulse width, 64% duty cycle, 1.5 mA [39].

Experimental Data Optimization and Processing

Phase Processing

MREIT: Positive and negative currents, denoted as I^+ and I^- , respectively, were applied to subjects in alternate TRs. The raw k-space data $S_j^\pm$ corresponding to $I^\pm$ for each echo j , can be described by

$$S_j^\pm(m, n) = \iint \mathcal{M}_j(x, y) e^{i\delta_j(x, y)} e^{\pm i\gamma \hat{B}_z(x, y) T_{c,j}} e^{i(xm\Delta kx + yn\Delta ky)} dx dy \quad (1)$$

where $\mathcal{M}_j$ is the MR signal at position x, y for the j^{th} echo, δ_j represents a systematic background phase, γ is the gyromagnetic ratio of hydrogen, $\hat{B}_z$ is the current induced magnetic flux density and $T_{c,j}$ is the duration of the applied current at echo j . The complex-value image for each echo was obtained by discrete inverse Fourier transform of $S_j^\pm(m, n)$ to obtain

$$M_j^\pm(x, y) = \mathcal{M}_j e^{i\delta_j(x, y)} e^{\pm i\gamma \hat{B}_z(x, y) T_{c,j}} \quad (2)$$

where $M_j^\pm$ corresponded to the image for application of positive or negative currents. Final magnetic flux density ($\hat{B}_{z,j}$) images were determined by complex dividing the images for positive and negative currents [9]

$$\hat{B}_{z,j}(x, y) = \frac{1}{2\gamma T_{c,j}} \arg \frac{\mathcal{M}_j^+(x, y)}{\mathcal{M}_j^-(x, y)}. \quad (3)$$

Maps of T_2^* distributions were generated for each slice using NC images. Optimal weighting factors (ω_j) for each echo [21] were then generated from these maps. The optimal B_z used for each montage was a weighted sum of the $\hat{B}_{z,j}$ for each echo as

$$B_z = \sum_{j=1}^{NE} \omega_j \hat{B}_{z,j}. \quad (4)$$

Finally, a ramp-preserving denoising preprocessing step [22] was applied to optimized B_z data to improve overall SNR.

Phase and B_z Noise Floor Estimations: Underlying phase noise floor levels were computed using methods described in [20]. Experimental noise levels for each subject were computed inside manually selected white matter regions comprising at least 3000 voxels (Subject A 3196 voxels, B 3127 voxels, C 3334 voxels, D 3456 voxels).

Current density calculations—We used the method of [23] to recover projected current density (J^P) maps as

$$J^P = J^0 + \frac{1}{\mu_0} \left(\frac{\partial(B_z - B_z^0)}{\partial y}, -\frac{\partial(B_z - B_z^0)}{\partial x}, 0 \right) \quad (5)$$

where $\mu_0 = 4\pi \times 10^{-7} \text{ TmA}^{-1}$, J^0 is the current density developed in a homogeneous model of the imaged head, obtained by solving the Laplace equation subject to the same boundary conditions as in the experiment, and B_z^0 is the z -component of the magnetic flux density computed from the model.

B_z data may suffer from poor SNR due to low signal caused by short T_2 values in regions such as the skull, and distortion near air-filled regions. To avoid propagation of noise from these regions, we only reconstructed J^P distributions within a brain region of interest (ROI) free of distortion [24].

Tissue and Electrode Segmentation

For segmentation, de-identified T_1 -weighted axial and sagittal datasets were resampled using FreeSurfer (Cambridge, MA) to 1mm^3 isotropic resolution. Segmentation was completed using resampled sagittal images. Figure 4 outlines segmentation procedures: A combination of automatic and manual steps was used to segment datasets into ten tissue compartments. White and gray matter segmentation was performed using FreeSurfer⁴⁹ (<http://surfer.nmr.mgh.harvard.edu/>) while bone, skin and air segmentations were completed using MATLAB (Mathworks, Natick, MA) and the SPM12 module (Wellcome Trust Centre for Neuroimaging, London, UK). All automated segmented tissue masks were corrected manually in ScanIP v7.0 (Simpleware, Synopsys Inc., Exeter, UK) with reference to an anatomical atlas [25]. The remaining tissue compartments, comprising cerebrospinal fluid (CSF), the eyes, blood, fat and muscle were segmented manually in ScanIP.

Using thresholding in T_1 -weighted axial images, the temporal electrodes (T7, T8) were segmented to an electrode surface area of about 36 cm^2 , in comparison to the 25 cm^2 carbon-rubber core. As a final step, segmented electrodes and tissues were combined into a single ScanIP model for each subject.

Computational Modeling Procedures

ScanIP models were meshed using ScanFE (Simpleware, Synopsys Inc., Exeter, UK) with tissue prioritization assigned as follows: white matter, gray matter, eyes, blood, air, CSF, fat, bone, muscle and skin. Isotropic conductivity values were assigned to each tissue using values conventionally used in the tDCS/tACS modeling literature (Table 1). Electrode conductivity was assumed to be 1 S/m .

Each head model contained approximately 20 million elements. Simpleware meshes were imported into COMSOL (Burlingham, MA, USA). The COMSOL electric currents module was used to predict voltage and current density distributions within the head. Normal current density magnitudes were scaled to be equivalent to current injection of 1.5 mA over the electrode contact area at anodes (T7, Fpz) while cathode potentials (T8, Oz) were set to ground, with the remainder of the skin surface insulated. The resulting simulated current density values, J_x and J_y , were interpolated onto a fine mesh grid with a resolution of 0.25 mm^3 via the MATLAB-COMSOL LiveLink Interface. B_z values at this resolution were then computed from interpolated J_x and J_y values using the Biot-Savart law. Fine-mesh B_z values were integrated over $5 \times 5 \times 5$ stencils overlaid on the data matrix and divided by voxel volume to obtain B_z data at a resolution of 1 mm^3 . Finally, B_z values were resampled to a coarser $2.24 \times 2.24 \times 5 \text{ mm}^3$ resolution to match experimental MREIT B_z data resolution.

Comparison of simulated and experimental data

Prior to comparing simulated and experimental data, we verified the registration of T_1 and MREIT magnitude images. B_z and J^P data profiles were matched manually such that the brain perimeters agreed in the plane of interest. Simulated B_z values were processed to projected current density using the same method used to compute projected current density from experimental B_z data. Differences between J^P values were computed using a relative L^2 error measure

$$\text{err}(J^P) = \frac{\|J_S^P - J_E^P\|}{\|J_S^P\|} \quad (6)$$

where $\|\cdot\|$ denotes the L^2 -norm, J_S^P is the simulated projected current density and J_E^P is the projected current density calculated from experimental B_z data. Error measures were calculated over the entire slice ROI.

Results

Shown in Figure 2(ii–iii) are T_1 -weighted axial magnitude images for Subject A corresponding to the center slice of the MREIT-CDI images, and tissue segmentations based

on these images. Matched MREIT-CDI images and resampled tissue segmentations are shown in Figure 2(iv–v). Note that there was evidence of signal loss, most likely caused by air-related susceptibility artifacts in anterior portions of the upper slice.

Subject Perceptions and Experiences

All subjects reported phosphenes in response to injected currents during imaging procedures. Phosphene perceptions were much larger (mean = 6, range 4–7) for current injection via the anterior-posterior (Fpz-Oz) montage than for left-right (T7–T8) montage (mean = 3.5, range 3–4). Subjects B and C reported discomfort from phosphenes for the Fpz-Oz montage. There was no evidence that electrodes dried appreciably during imaging procedures.

SNR and B_z Noise Levels

SNR values were measured from MREIT magnitude images using the difference method of [26] for both no-current (NC) and current-injection cases. Both magnitude based and experimental calculation methods described in [20] found baseline B_z noise levels of the order of 0.2 nT (Table 2).

Experimental B_z Data

Ranges in B_z data for all subjects were approximately 4 nT (± 2 nT). Qualitative inspection of the data showed that in all cases positive B_z values were observed in the anterior cortex when current flow was from left to right (T7–T8). For anterior-posterior current flow (Fpz-Oz) positive B_z was recovered in the right hemisphere. Both characteristics were consistent with predictions from the right-hand rule convention of Ampere's law, since the magnetic flux density distribution created by the current flow should circulate around current streamlines. In several cases (subjects B and C, Fpz-Oz montage) the distribution was not symmetric, and positive values 'bled' into both hemispheres. Images of raw NC and optimized B_z distributions for each subject are shown in Figures S4–S7. These images confirmed that no phase contrast was developed in images (with the exceptions of artifacts discussed below) when no current was applied.

Both experimental and simulated magnetic field maps showed similar ranges, but values in the experimental maps showed a global offset of 1 nT. This offset was also found in experiments in the MREIT literature [27, 28] but was not appreciable given the high current and magnetic flux density amplitudes used in those studies. Possible offset sources are surface currents in electrode pads or magnetic fields from lead wire currents. Because processing of B_z data to generate current density required differentiation, this offset did not affect J^P computations.

Comparison of Predicted and Measured data

Comparisons of optimized MREIT B_z data and values predicted from isotropic computational models are shown in Figure 5 for each electrode montage in a central MREIT-CDI image plane. Profile plots comparing distributions are shown in the right of each sub-figure. Qualitatively, simulated and experimental data followed the same patterns. However, ranges observed in experimental data were consistently larger than that predicted

from computational models. Qualitative agreement between model and experiment was closer for subjects A and D than B and C.

Projected Current Density

Projected current density (J^P) distributions measure current flow transverse to the main MR magnetic field [29]. Because electrode pairs were approximately co-planar and transverse to the main field, we expected the majority of current flow to be captured in B_z , and that reconstructed J^P images would produce a good representation of actual current flow.

Reconstructed and predicted projected J^P images are shown for each montage in Figure 6. Maximal J^P values near electrodes and in CSF compartments for both montages were on the order of 0.5 A/m². This value is below that estimated to be necessary to cause direct stimulation in peripheral nerves [30]. Overall, L^2 errors between reconstructed and predicted J^P values were found to be around 30% for all cases, similar to errors found in animal MREIT-CDI studies [11].

Discussion

In sections below, we discuss individual elements of the study and their implications for tES practice, computational model validation, and mechanism exploration.

B_z Data Quality, Subject Experience and Possible Motion Artifact

We expected subjects to experience phosphenes, because the current waveform of about 10 Hz corresponds to a maximum in phosphene sensitivity³⁴. Phosphenes were most severe for Fpz-Oz montages, probably because these electrodes were proximal to occipital cortex and retina, and either or both of which may have been involved in phosphene origination [31–33].

Experimental and simulated magnetic flux density maps were in good qualitative agreement for subjects A and D. However, the comparison for subjects B and C did not agree as well, which may be due to phase image artifacts caused by subject motion during electrical stimulation, especially with the Fpz-Oz montage. Subjects B and C reported discomfort during Fpz-Oz stimulation, reflected in their high perception ratings (6 and 7) for this montage. Subject A did not strongly perceive current applied by either electrode pair, but subjects B, C and D reported perceiving phosphenes strongly. Subjects B and C described moving their head during imaging to reduce discomfort from the electrical stimulation. Motion artifacts would easily distort measured MREIT signals. The good comparisons obtained for subject D may be due to instructing this participant not to move during imaging and rigorously securing that subject in the head coil. Other possible artifact sources are cardiac pulsations and respiration-related changes in thoracic cavity size. We believe that results for subjects B and C show that future experiments should involve appropriate attention to head immobilization, particularly if stimulation is likely to cause phosphenes.

J^P Characteristics

Experimental and computed J^P values were qualitatively similar to predictions for all four subjects. We expected that experimental J^P values would correspond well with predictions because of the approximately transverse nature of current flows, since J^P error is smallest when most current flow is within the imaged plane [23]. Further, because J^P calculations involved gradients of experimental B_z values offset from values derived from a uniform model of the subject head developed from T₁ data (5), offsets observed in experimental B_z distributions were deemphasized by the J^P calculation. Interestingly, J^P distributions did indicate that there may have been some extension of electrode areas beyond sponges, most likely because the saline may have soaked into elastic bandages used to secure electrodes to the head. This indicates a need for precise control of saline volume, a need to use more viscous contact media [34], or scalp hair removal before electrode placement.

An intriguing observation was the high current density localized in the ventricles in the projected current density maps during Fpz-Oz stimulation for subjects A and C. This should be expected since CSF has higher conductivity than other tissues. However, this high current density was not observed in projected current density maps for T7–T8 stimulation, indicating that current flow in the central sagittal sinus region was larger for the Fpz-Oz montage. This indicates that, depending on electrode position, current may potentially penetrate to subcortical regions via the sagittal sinus.

Image Artifacts

Susceptibility affected peripheral anterior regions of some slices (notably Subject A, see Figure S3). Unexpected high values in reconstructed J^P maps, in both anterior and posterior regions, were also noted (again in Subject A) and corresponded to regions containing large blood vessels [35]. Therefore, both anterior and posterior artifacts may result from blood flow in large vessels near the sagittal sinus (anterior) and calcarine fissure (posterior). Note that for these artifacts to become apparent there had to be differential blood flow at alternating current polarity. We found a similar artifact in the posterior region of NC B_z data for subject A (Figure S4). Therefore this artifact may result from pulsatile blood flow at a period related to the imaging sequence TR. Future studies specifically evaluating blood flow and perfusion (e.g., arterial spin labeling) in these regions in relation to stimulation will help clarify the impact of blood flow on artifacts found in the present study.

Model Integrity

In finite element simulations, electrode models were based on boundaries of saline sponges detected in T₁-weighted images. However, saline may have soaked into bandages securing the electrodes and caused effective electrode areas to be larger than modeled. This would account for peak J^P values appearing over a larger region of the brain perimeter than expected. Therefore, MREIT-CDI may be useful for the detection of inconsistencies in tDCS electrode application or for the study of different electrode geometries.

Scales of experimental B_z values and reconstructed J^P values were consistently higher than predicted by simulations. This scaling issue may be reconciled if conductivities in simulated tissues were increased. Conductivities used in simulations were typical of many tES studies

[6, 7]. Model conductivities are typically derived from cadaver or excised specimens, measured at room temperatures (conductivities typically decrease approximately 2% per degree C [17]), and may not represent those *in vivo*, since tissue properties degrade rapidly after death. Therefore, it is likely that modeled conductivity values were lower than those *in vivo*. Further model validation should also include sensitivity studies to explore effects of varying model skull and scalp conductivity distributions on the correspondence of model-experimental results, since these tissues are critical determinants of current delivered to the brain compartment [8].

Future Work in MREIT-CDI

In this work, three images of 5-mm slice thickness centered on electrode regions were acquired in a time that depended linearly on the number of slices. However, more brain coverage is essential to perform group level field-distribution analyses across subjects. In addition, SNR was limited, but can be improved by averaging more data sets. Both enhancements generally require increased scan time. Fast techniques like EPI/RARE encoding or parallel imaging techniques [36, 37] coupled with appropriate hardware development [38] should greatly accelerate image acquisition with minimal cost in SNR, facilitating greater slice coverage. Furthermore, the gradient echo based imaging used here was very susceptible to motion artifact, which can severely distort the phase data required for calculation of magnetic flux density distributions. These faster MRI pulse sequences should be less affected by motion, which may be of particular significance when applying current to subjects perceiving stimulation. Using faster sequences, any remaining subject motion-induced artifacts may be removed, or at least minimized, during data post-processing if the motion is not too severe. If the motion is a straightforward rigid body displacement or rotation, time-series images may be corrected to align with a reference image from the series using a method such as that described in [40].

Implications for Mechanism Investigation

The study purpose was to demonstrate a new instrumental tool for investigating the practice of tES and for the study of the underlying mechanisms of tES therapies. We anticipate that future studies, combining MREIT-CDI and fMRI techniques, will allow exploration of relationships between current density, electric fields, and other possible technique parameters, and functional tES outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- First in-vivo images showing current flow in human heads during tES.
- Images were acquired using MR current density imaging techniques
- Technique can be used to investigate tDCS or tACS mechanisms.
- Technique can be used to explore dose-response relationships.

Figure 1.

Experimental setup showing the components used for collecting MREIT data. The subject was placed inside the MRI room in the bore of a 3T Philips Achieva magnet system and data was collected using a SENSE 32 channel head coil. An RF filter box was placed in the bore that attached to electrode leads used to deliver stimulation using a battery operated constant current stimulator. A custom switch box was used to deliver electrical stimulation in synchrony with RF excitation and control the duration of stimulation. TTL trigger and input stimulation waveforms were monitored on an oscilloscope.

Figure 2.

Illustration of electrode placements on the head and example T₁ and MREIT magnitude data. Shown from left to right are (i) cartoon of electrode placement on Subject A including 5 mm MREIT image slices; (ii) T₁-weighted FLASH images of all three slices for Subject A. FLASH images were 1mm thick and slices shown correspond to the center of MREIT image slice locations; (iii) segmented T₁ slice based on (ii); (iv) MREIT $m_{f f e}$ magnitude image co registered to the FLASH image shown in (ii); (v) resampled segmented volume based on (iv). AP and LR directions are illustrated in the central slice of (ii).

Figure 3.

2D spoiled multi-multigradient echo sequence used for data acquisition. The repetition time (TR) was 50 ms. Current was injected after a delay (T_d) of 4 ms following RF excitation, which allowed time to switch current polarities. The first echo time of the sequence (TE_1) was 7 ms and subsequent echoes were collected with an echo spacing (ESP) of 3 ms. Current amplitudes of 1.5 mA and -1.5 mA were injected for 32 ms (T_c) at each phase encoding step. $T_{c,j=1,2,\dots,10}$ represent current injection times for each echo. The data acquisition bandwidth was 550 Hz/voxel and the total time to acquire one slice was 2:00 min.

Figure 4.

Modeling simulation workflow. Outlined here is the general procedure used to process raw T_1 datasets (top) into synthetic B_z (bottom). Raw T_1 datasets were resampled prior to segmentation, and a combination of manual and automatic steps were used for the segmentation process. The segmented model was meshed in Simpleware ScanFE. All finite element simulation was performed using MLI and simulation results were processed and analyzed in MATLAB.

Figure 5.

Comparison of simulated and experimental magnetic flux density (B_z) slice data for each subject and montage. Shown from left to right for each montage are (i) Magnitude image of focus slice; (ii) simulated B_z pattern within the brain ROI based on isotropic conductivity distribution and tissue segmentations from T₁-weighted FLASH data volume; (iii) experimentally measured B_z distribution within the brain ROI and (iv) comparison of B_z values along the profiles plotted as black lines in (ii) and (iii).

Figure 6.

Comparison of simulated and experimental projected current density J^P distributions for all subjects and both montages. Shown from left to right for each montage are (i) Magnitude image of focus slice; (ii) reconstructed J^P distribution within brain ROI overlaid on focus slice (60% opacity); (iii) reconstructed J^P distribution within brain ROI overlaid on focus slice (100% opacity) and (iv) J^P distribution computed from simulated B_z data within the brain ROI.

Table 1

Conductivity Values used in computational models, with literature sources.

Tissue	σ (S/m)	Source
Air	0	-
Blood	6.7×10^{-1}	[1]
Bone	10.9×10^{-3}	[2]
Cerebrospinal fluid	1.8	[3]
Fat	2.5×10^{-2}	[4]
Gray matter	1.0×10^{-1}	[4]
Muscle	1.6×10^{-1}	[1]
Sclera, lens	5.0×10^{-1}	[4]
Skin	4.3×10^{-1}	[5]
White matter	3.8×10^{-1}	[1]

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Table 2

SNR in magnitude images and baseline B_z noise levels measured in mff e magnitude images of central MREIT-CDI slices for each subject using no current, and Fpz-Oz and T7–T8 electrode montages. Values of magnitude-based noise floors were derived from magnitude SNR of MREIT images, and experimental noise floor values from Laplacians of measured B_z distributions within a uniform conductivity region, as described in [20]. Experimental B_z baseline noise levels were calculated within white matter ROIs.

	SNR in magnitude data			Magnitude-Based		Experimental (WM ROI)	
	No Current	T3–T4	Fpz–Oz	T3–T4	Fpz–Oz	T3–T4	Fpz–Oz
A	348	330	395	0.26 nT	0.22 nT	0.22 nT	0.18 nT
B	432	406	307	0.21 nT	0.29 nT	0.21 nT	0.19 nT
C	380	388	436	0.22 nT	0.20 nT	0.21 nT	0.16 nT
D	521	525	495	0.17 nT	0.18 nT	0.23 nT	0.21nT