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Intracranial measurement of current densities induced by transcranial magnetic stimulation in the human brain

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Abstract

Transcranial magnetic stimulation (TMS) is a non-invasive technique that uses the principle of electromagnetic induction to generate currents in the brain via pulsed magnetic fields. The magnitude of such induced currents is unknown. In this study we measured the TMS induced current densities in a patient with implanted depth electrodes for epilepsy monitoring. A maximum current density of 12 $\mu A/cm^2$ was recorded at a depth of 1 cm from scalp surface with the optimum stimulation orientation used in the experiment and an intensity of 7% of the maximal stimulator output. During TMS we recorded relative current variations under different stimulating coil orientations and at different points in the subject's brain. The results were in accordance with current theoretical models. The induced currents decayed with distance form the coil and varied with alterations in coil orientations. These results provide novel insight into the physical and neurophysiological processes of TMS.

Keywords: Transcranial magnetic stimulation; Depth electrode; Induced currents

Transcranial magnetic stimulation (TMS) is a technique that focuses an intense pulsed magnetic field onto the underlying neural tissue to induce currents within the brain capable of neural excitation [1]. However, the magnitude and distribution of the induced currents in the human brain are unknown. To date there have been no human in vivo studies depicting the induced current distributions. The present knowledge is inferred from theoretical models and few phantom and animal experiments. The majority of the phantom model work has centered on either the direct measurement of the magnetic fields from various coil shapes or on the measurement of induced currents in saline baths of various geometries [3,8,13,18]. These measurements were generally conducted with systems that failed to accurately represent tissue inhomogenities, the non-symmetric nature of the human head, and the variable electrical properties of the biological structures. In fact, in one study that incorporated an inhomogeneous conductor to represent the tissue, the results were remarkably different from similar measurements conducted with homogeneous systems [19]. Recently, TMS studies have been completed with animal models to measure either the currents induced due to stimulation, or the secondary currents that arise due to neural excitation. Tay et al. [13] used a loaded probe technique to measure the primary currents in the cerebral tissue of anesthetized cats during surgery. Wang and Wang [15] measured the secondary currents within the auditory cortex of gerbils with implanted electrodes and an active amplifier designed to cancel out the TMS stimulation artifact. Lisanby et al. [5,6] reported the induced voltage changes within the cortex of monkeys with implanted electrodes. Whereas all of these studies provide valuable information, animal models do not completely capture the dynamics of human systems seen in the clinical environment. The induced field is entirely dependent upon the anatomical/geometrical structure and electrical tissue properties of the system and small perturbations can alter the

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field drastically. A human subject with cortically implanted depth electrodes participated in this study with the goal of establishing a safe framework for recording the primary currents in the human cortex during TMS.

The study was approved by the Beth Israel Deaconess Medical Center's Institutional Review Board and the subject gave written informed consent. A protocol emphasizing the safety of TMS in epileptic patients with implanted electrodes was implemented based on preliminary safety studies and the relevant literature [11,16,17,20]. The electrodes used were TMS and magnetic resonance imaging (MRI) compatible and designed to preclude inductive temperature changes [9]. The stimulation intensity was limited to 7% of maximum output. Prior to the in vivo study, we demonstrated that at this stimulation intensity adequate current measurements could be made at a 1.9 cm depth within a phantom model (saline filled 14 cm diameter ball with an implanted electrode). These results were used to guide the choice of stimulation orientations for the human subject.

The subject for this study was a 38 year-old female with a history of partial complex seizures secondary to head trauma at the age of 33 years undergoing presurgical monitoring for medically refractory epilepsy. She was taking the anticonvulsants Phenytoin, Torpiramate, and Levetiracetam at the procedure time. She had eight depth electrodes implanted bilaterally within the cingulum, orbital frontal cortex, amygdala, and hippocampus to localize the epileptic focus. The electrodes were constructed of platinum/iridium contact rings affixed to hollow plastic insulating catheters containing silver wire leads shielded with grounded aluminum. Each catheter had eight contact rings that were 1 mm in diameter, 2 mm in length, and located every 5 mm along the shaft with the first contact site approximately located at the CSF-gray matter interface. The leads were connected to a passive shielded head stage. The differential ground was located on the subject's right shoulder.

To minimize the subject's discomfort and experimental time duration, data from only one electrode was recorded. The electrode was chosen for its planar orientation and proximity to the center-point of the stimulating coil on the scalp; the electrode's insertion point was approximately the same point-to-point distance from the center of the TMS coil for each of the stimulation conditions, making the coil orientation the primary variable modified throughout the experiment. MRI and computed tomography scans of the patient were acquired pre and post electrode implantation in accordance with the surgical protocol for the procedure and used to help determine the relative point-to-point distances between the recording electrode and stimulation positions (circumferential distances were measured directly). Care was taken to avoid any physical contact between the coil and the electrode insertion points; for the free electrode catheters under no tension a minimum circumferential distance of 2 cm was used and for the recording electrode a distance of 9 cm was used between the coil and scalp insertion point. Based on the preliminary phantom experiments four different conditions (position and orientations of the coil) were decided upon for the study and will be referred to as: Inion, 2 cm, Cz, and Cz90 stimulation (see Fig. 1); in addition to similar coil-to-electrode distances the conditions represent coil positions used clinically.

A Magstim Rapid stimulator (Magstim Company, Withland, UK) and a 70 mm figure of eight coil were used for stimulation. A circular pick-up coil was placed on the inferior surface of the TMS stimulation coil to monitor the strength of the stimulating field. The pick up probe signal was used as a reference signal for the machine output, as the terminal voltage of the pickup coil is directly related to the time derivative of its flux linkage and this in turn offers a timing and amplitude reference for the applied field. These measurements were in agreement with data supplied by Magstim Inc. and there was negligible variability in the source during the recording procedure. The stimulating field

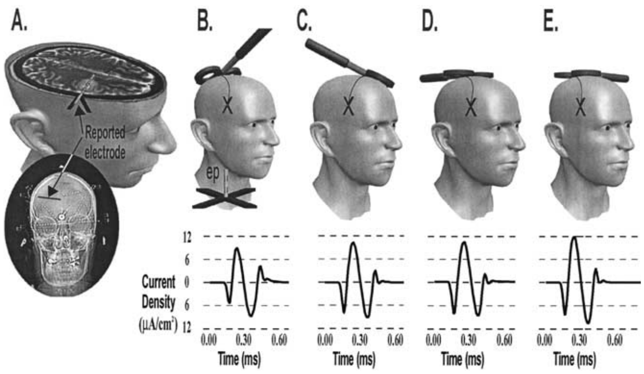

Fig. 1. (A) Electrode placement: The electrode in the right cingulate was chosen for its planar orientation and the comparable proximity of its location to the center of the TMS coil across different stimulation sites. (B) Inion position/contact 1–2: The smallest signal was recorded in the inion position. The coil's hot spot was centered just anterior to the patient's inion with the coil handle vertically oriented (90° out of phase with electrode vertically) and 45° out of phase with the horizontal axis of the electrode. The circumferential distance between the electrode and the center point of the stimulating coil was approximately 9.6 cm, with an approximate point-to-point distance of approximate point-to-point distances of 8.3 cm. The shortest circumferential distance is indicated graphically along the scalp surface. The electrode is marked by an x at the spot of its scalp insertion. In the forefront of the figure it is reconstructed and marked with an 'ep' for electrode placement. (C) 2 cm position/contact 1–2: The recordings from 2 cm position were very similar to the Cz position, seen in D. The 2 cm condition was carried out by centering the coil 2 cm above the complementary electrode on the left side of the patient's head with the handle at a 45° orientation relative to the electrode's vertical and horizontal axis (circumferential distance approximately 10.0 cm, point to point approximately 8.48 cm). (D) Cz position/contact 1–2: The Cz stimulation condition was carried out with the coil's center aimed on the subject's Cz according to the 10–20 electrode system (overlying the vertex) and the coil positioned in phase with the coil's vertical axis and 90° out of phase with the coil's horizontal axis. (circumferential distance approximately 9.6 cm, point to point approximately 8.3 cm). (E) Cz90 position/contact 1–2: The largest signal recorded from the electrodes was in the Cz90 position. This corresponded to the coil axis being parallel vertically and horizontally to the electrode. The peak current density recorded was 12 $\mu A/cm^2$ (circumferential distance approximately 9.6 cm, point to point approximately 8.3 cm).

peak magnitude at the point of stimulation was estimated at 0.14 Tesla with a duration of 0.32 ms for it is typical triphasic waveform as supplied by Magstim. TMS single pulses were delivered every 10 s at 7% of the stimulator output with ten trials for each of the stimulation conditions.

During the experiment, the stimulator power supply, patient, and amplifier/recording equipment were all placed in separate rooms to minimize noise in the measurement. Measurements for each stimulation condition/differential hookup were averaged in order to reduce the possible impact of contamination by random system noise. To account for the deterministic stimulation noise resident in the recording amplifier and not eliminated by the differential stage of the amplifier, a post processing filtering scheme was implemented. This filtering scheme was developed during the preliminary phantom studies and authenticated with pickup probe studies and served to effectively subtract the deterministic noise out of the recorded signal [12].

Differential signals were recorded at the 1–2, 2–3, and 3–7 electrode contact sites for the Cz, Cz90, Inion, and 2 cm configurations. The reversed polarity signals were recorded simultaneously during the recording session. The first contact point was approximately 1 cm from the electrode insertion point in the subject's scalp, right at the CSF/cortical interface, and each subsequent contact point was 5 mm away from the previous contact. The signal was amplified ($\times$ 1000) and filtered (0.3–10 KHz) using Neuroscan Synamps (100 KHz sampling rate). The differential signals were used to estimate the ohmic current densities along the electrode shaft by implementing Ohm's law, $J = \sigma(V_{\text{measured}}/5\ \text{mm})$ where σ of the gray matter was set at 0.276 Siemens/m (calculated from the mean of three studies considered in ref. [2]). The results for the 1–2 recordings are depicted in Fig. 1. The 2–3 differential signal was approximately 1000 times smaller than the 1–2 signal for each of the stimulation configurations and the 3–7 channel provided no measurable signal. The 2–1, 3–2, and 7–3 signals were as above, but of reversed polarity. The current density values that were recorded are higher than those reported earlier in cat cortices, 6–12 μA/cm^2 compared to 0.552 μA/cm^2 for a depth of 1 cm – but the differences may be related to the different stimulating systems, output characteristics, and coils used [13]. It was not possible with the contact size and the output power restrictions to further quantify the degree of signal attenuation or signal characteristics. The current level variations seen with the different stimulating coil orientations were in agreement with our theoretical predictions and phantom model studies. With realistic theoretical models it has been shown that the largest current vector is essentially found in an orientation that is in parallel with the coil's vertical and horizontal axis within continuous tissue (unless great tissue abnormalities are present that alter the tissue conductivities) [10,14]. From these studies it is also apparent that the greatest variations are shown along the coil's horizontal axis. In the Cz90 configuration the figure of eight coil's vertical and horizontal axis was parallel with the electrode and we recorded the largest signal at this orientation. The Inion configuration, where the coil was perpendicular to the horizontal axis and slightly over 45° from the vertical axis, resulted in the smallest recorded signal. The Cz orientation showed similar results as the 2 cm orientation.

This study provides the first measurements of current densities induced by TMS in the human brain in vivo. However, the study has some limitations. First, the electrodes that were used for the study were not designed for the recording of TMS primary currents and had larger than optimal inter-contact distances and contact sizes. In order to get a clearer picture of the current within the cortex, it would be necessary to employ electrodes with smaller contact sites and sub-millimeter inter-electrode distances. Second, the amplifier that was approved for use with the study was not specifically designed for the measurement of TMS-induced currents. It lacked two necessary components: (1) adequate shielding; and (2) an active head stage to cope with the stimulation artifact. While the shielding obstacle was dealt with by wrapping the electrode leads in grounded aluminum and physically separating the amplifier and stimulator in different rooms, the active head stage component was not. Finally, the distance from the stimulating coil to the recording electrode should be minimized to provide a clearer view of the current in the stimulating region where activation threshold would be reached. In our current protocol, safety considerations precluded us from reducing this distance. However, given our results, is seems that this distance could be minimized in future experiments without posing an unacceptable risk to subjects.

The distance between the stimulating coil and the recording electrode is a clear reason why the measured current density values were so low. It should be noted that we recorded at a relative distance where neural stimulation would not be expected even at 100% of the stimulator output power. Nevertheless, the signal decay seen with increasing cortical depth was still greater than what was expected. The signal attenuated beyond measurable levels at a depth greater than 1 cm into the cortex with the 7% power output intensity that was used for this study. The increased attenuation might be the result of the electrode placement procedure. The degree to which the trauma of the surgery altered the region near the electrode tissue interface is difficult to ascertain. All channels were viable prior to the experiment, but signs of inflammation, which has a higher conductivity than the surrounding tissue, was apparent from the acquired scans in the regions surrounding the electrode insertion point (however the electrode contact points were uncompromised). Variations in conductivity of the tissue can perturb the predicted signal and heightened conductivity can provide an alternative less resistive path for the current to flow [4,7,12,14].

Despite the noted limitations, there are important insights that can be derived from this study. The direction of maximum induced current was along the axis of the stimulation coil as predicted by published models [10,14]. The fact that the signal was attenuated beyond measurable levels at depths greater then 1 cm indicates that either cortical surface currents dominated the recorded signal or the signal was altered by the inflammatory induced alterations in conduction. The localized field attenuation could be more easily explored with electrodes with smaller inter-contact distances and contact sizes. Most importantly, it was demonstrated that measurement of the TMS induced currents in the human brain can be done safely if the appropriate methodology and equipment are used. The results of this study provide an initial step in the depiction of the current distributions in the cortex during TMS and future studies will provide a unique opportunity to gain insight into the neurophysiological mechanisms of TMS.

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