Three-Dimensional Distribution of the Electric Field Induced in the Brain by Transcranial Magnetic Stimulation Using Figure-8 and Deep H-Coils

Yiftach Roth, Alon Amir,† Yechiel Levkovitz,‡ and Abraham Zangen†*

Summary: The H-coils are a novel development in transcranial magnetic stimulation (TMS), designed to achieve effective stimulation of deep neuronal regions without inducing unbearable fields cortically, thus broadly expanding the potential feasibility of TMS for research and for treating various neurologic disorders. This study compared the field distribution of two H-coil versions, termed H1 and H2, and of a standard figure-of-eight coil. Three-dimensional electrical field distributions of the H1 and H2-coils, designed for effective stimulation of prefrontal regions, and of a standard figure-8 coil, were measured in a head model filled with physiologic saline solution. With stimulator output at 120% of the hand motor threshold, suprathreshold field is induced by the H1-coil at lateral and medial frontal regions at depths of up to 4 to 5 cm, and by the H2-coil at medial prefrontal regions up to 2 to 3 cm, and at lateral frontal regions up to 5 to 6 cm. The figure-8 coil induced suprathreshold field focally under the coil's central segment, at depths of up to 1.5 cm. The ability of the H-coils to stimulate effectively deeper neuronal structures is obtained at the cost of a wider electrical field distribution in the brain. However, the H-coils enable simultaneous stimulation of several brain regions, whereas the depth penetration in each region can be controlled either by adjusting the stimulator output, and/or by varying the distance between various coil elements and the skull.

Key Words: Transcranial magnetic stimulation, Deep brain stimulation, Electrical field distribution, Motor threshold, Magnetic coil.

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Many studies indicate that medial prefrontal and orbitofrontal cortices and their connections to deeper brain sites are associated with reward processes and motivation (e.g., Breiter and Rosen, 1999; Jentsch and Taylor, 1999; Kalivas and Nakamura, 1999; Kalivas and Volkow, 2005; Parkinson et al., 2000; Tremblay and Schultz, 1999; Volkow and Fowler, 2000). Transcranial magnetic stimulation (TMS) is extensively to study brain function and connectivity and to study and treat various neurobehavioral disorders including depression (Kircaldie et al., 1997; Wassermann and Lisanby, 2001). Several studies suggest some therapeutic efficacy of repetitive TMS over the prefrontal cortex in depressive patients, but a meta-analysis of all studies suggested only a limited efficacy (McNamara et al., 2001). Although standard TMS coils can only stimulate superficial cortical regions of the human brain (the fields induced by these coils decrease rapidly as a function of distance from the coil), there is a reason to assume that activation of deeper prefrontal and limbic regions may increase the antidepressant effect. Yet, effective stimulation of deep brain structures requires the use of nonstandard TMS coils with an appropriate design. Such designs are also necessary for extending basic and clinical TMS research to other applications associated with deeper brain regions.

The construction principles of a new coil design, termed the Hesed coil (H-coil), enabling effective stimulation of deep brain regions without inducing an unbearable field in cortical regions, were presented in a previous study (Roth et al., 2002). The ability of the H-coil to stimulate deep brain regions was demonstrated using mathematical simulations and measurements performed in a phantom brain model (Roth et al., 2002). The efficacy of the H-coil in activating distant brain structures was demonstrated clinically in a recent study, where the motor cortex was activated at a distance of 5 to 6 cm in healthy volunteers, compared with 1.5 cm with a standard figure-8 coil (Zangen et al., 2005). The improved depth penetration and slow rate of electrical field decay presented by the H-coils may have major clinical importance in treatment of a variety of neurologic and psychopathologic disorders.

Two new versions of the H-coil, termed H1 and H2, were developed. Their configurations are designed for achieving efficient stimulation of deep prefrontal and orbitofrontal neuronal structures, while minimizing undesired motor activation and facial muscle contraction. The safety of

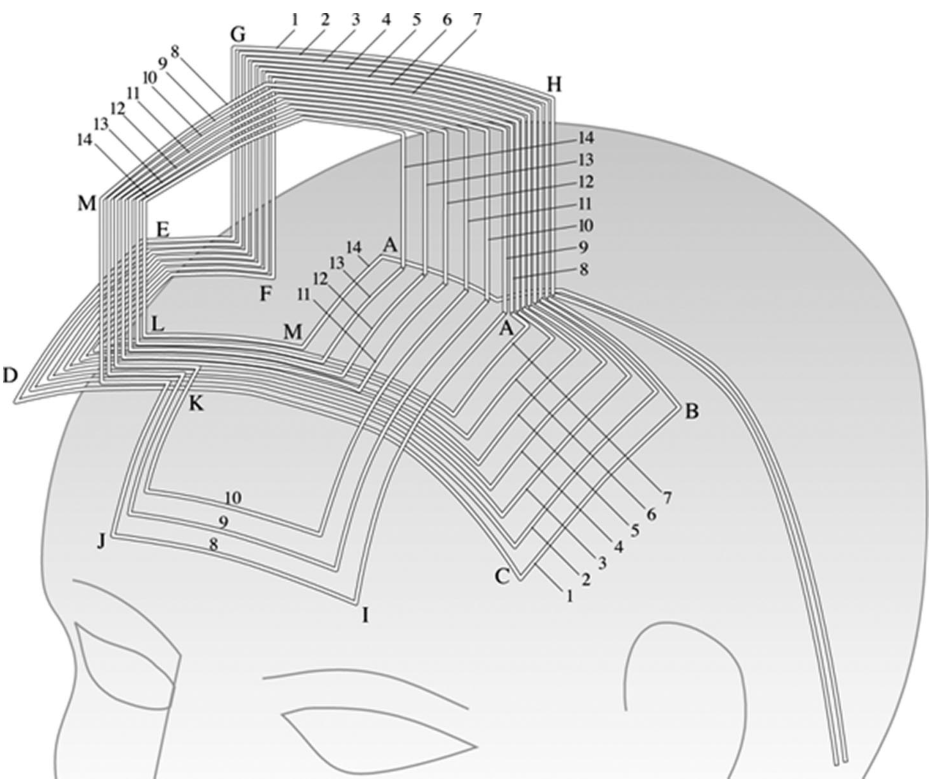

FIGURE 1. Sketch of the H1-coil ("Hesed") near a human head. The coil position and orientation shown in the figure is designated for activation of structures in the prefrontal and orbitofrontal cortical and subcortical regions, with left hemispheric preference.

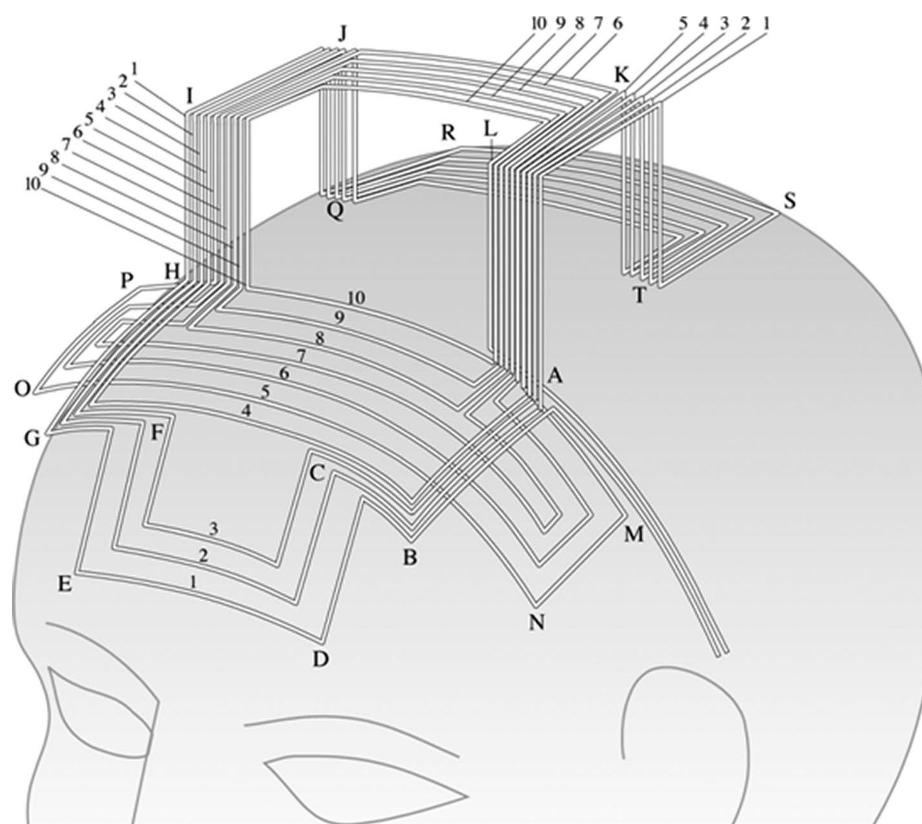

FIGURE 2. Sketch of the H2-coil ("Hesed") near a human head. The coil position and orientation shown in the figure is designated for activation of structures in the prefrontal and orbitofrontal cortical and subcortical regions, with no hemispheric preference.

these coils, along with cognitive and emotional effects, was tested recently in a clinical study (Zangen et al., submitted for publication). Here we describe the design of the H1 and H2-coils, and the three-dimensional distribution of the electrical field induced by these coils and the standard figure-8 coil, as measured in a phantom brain.

METHODS

TMS Coils

The TMS coils used in this study were two versions of the H-coil and a figure-8 coil. The two H-coil versions used were designed for effective activation of cortical and subcortical prefrontal and orbitofrontal neuronal structures. In the H1-coil there is a preference to the left hemisphere, whereas in the H2-coil there is no hemispheric preference.

The H1-coil wiring pattern is illustrated in Fig. 1. The coil has 14 windings. Elements B-C and A-M are oriented along the anterior-posterior axis on the left hemisphere, thus preferably stimulate neuronal pathways along this axis. Elements D-E lead the return currents on the right hemisphere. Elements C-D and I-J produce an electrical field along the lateral-medial axis, in prefrontal and orbitofrontal regions (when placed over the frontal cortex).

The H2-coil wiring pattern is illustrated in Fig. 2. The coil has 10 windings. Elements N-O, A-H, and D-E are oriented along the lateral-medial axis, thus preferably stimulate neuronal pathways along this axis. Elements M-N and

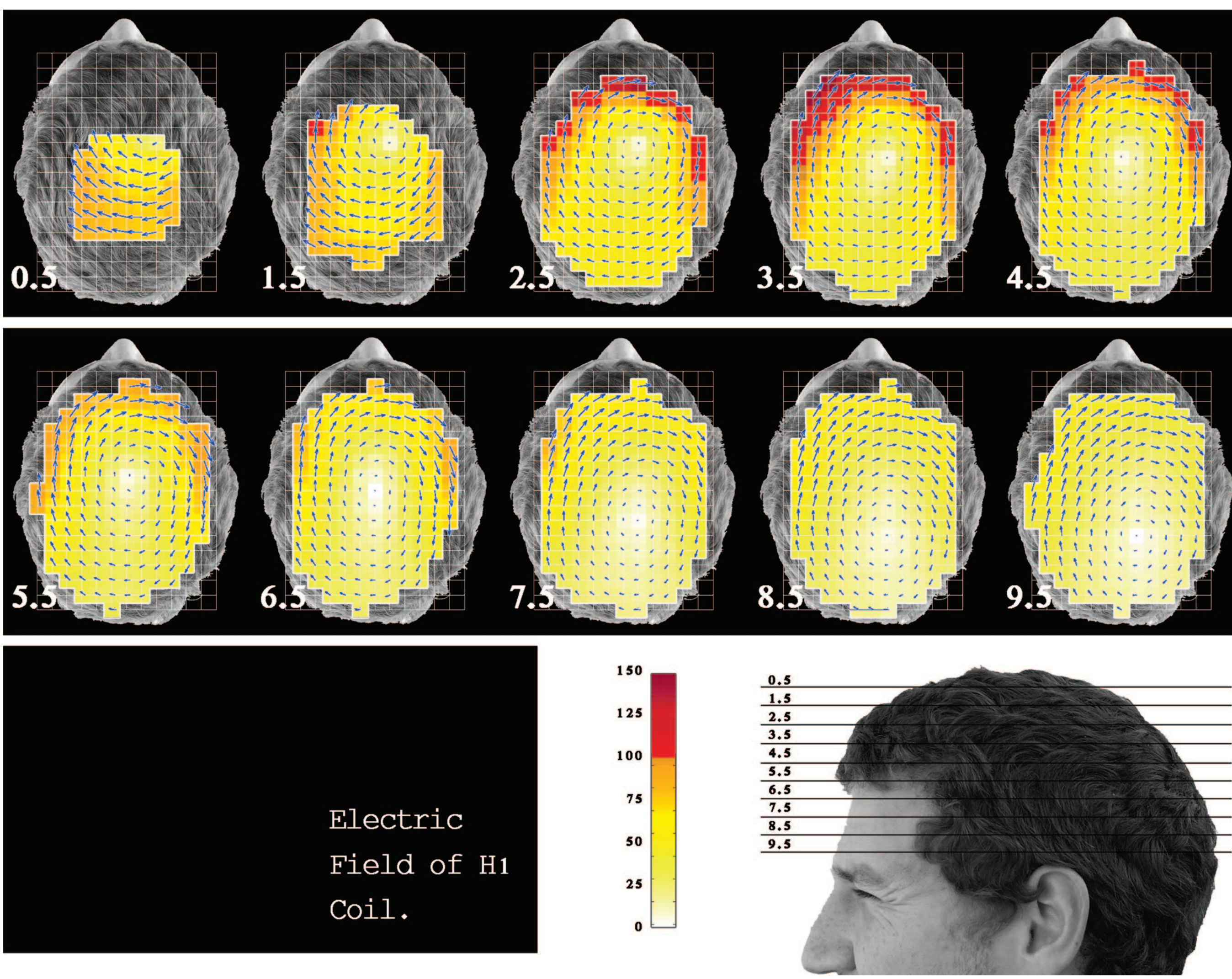

FIGURE 3. Colored field maps for the H1-coil indicating the electrical field absolute magnitude and direction in each pixel, for 10 axial slices 1 cm apart. The colored pixels in each slice indicate the brain conductive tissue. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m. The field maps are adjusted for stimulator power output of 46%, which was the level required to obtain 120% of the threshold, at a depth of 1.5 cm. The orange colors indicate field magnitude above neural threshold, for pulses delivered at 150% of the stimulator output required for hand motor stimulation.

A-B are oriented along the anterior-posterior axis on the left hemisphere, and elements G-H and O-P lead the return currents on the right hemisphere.

The frames of the inner rim of H1 and H2-coil versions are flexible to allow a comfortable attachment to a variety of human skull shapes and to increase depth penetration (Roth et al., 2002).

The field distributions of the two H-coil versions were compared with a standard commercial Magstim figure-8 coil with internal loop diameters of 7 cm.

Experimental Setup

The electrical field distribution of the three TMS coils was measured in a model of the human head (13 × 18 cm, height 15 cm), filled with physiologic saline solution. The phantom was filled up to liquid height of 11 cm, to model the average brain dimension in the superior-inferior axis. This model treats the brain as a homogeneous conductor, and the skull is assumed to be a complete electrical insulator, neglecting the small conductivity differences between the skull and the air. Stimulation was delivered using the Magstim Super Rapid stimulator (Magstim, Whitland, U.K.). The field was measured using a two-wire dipole probe, as described previously (Roth et al., 2002), with 1.7 cm distance between the two tips. The probe was moved in three directions inside the head model using a displacement system with 1 mm resolution, and the field distribution of each coil was measured in the whole head model volume in 1 cm resolution. For the figure-8 coil the field was measured in 0.5 cm resolution, due

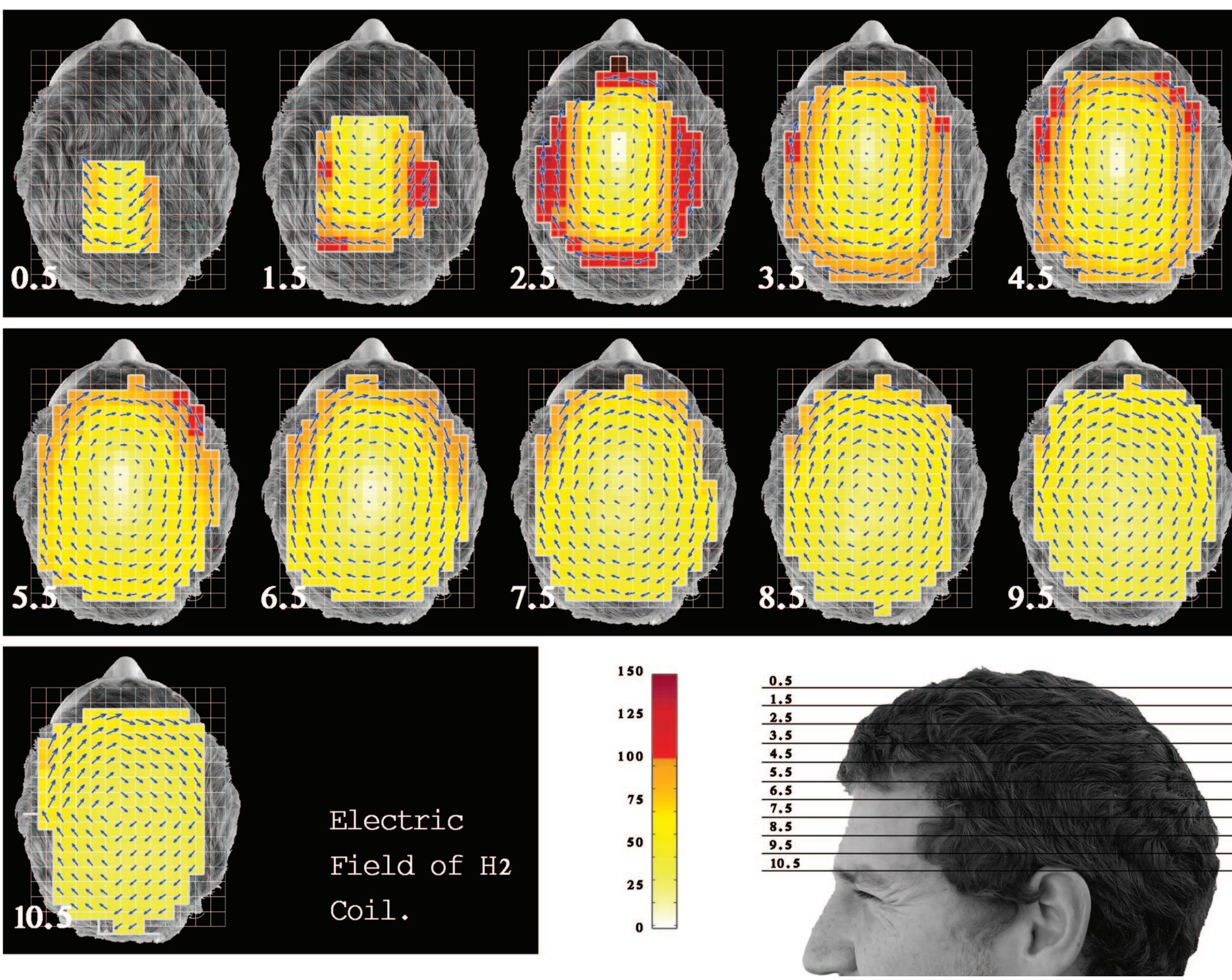

FIGURE 4. Colored field maps for the H2-coil indicating the electrical field absolute magnitude and direction in each pixel, for 11 axial slices 1 cm apart. The colored pixels in each slice indicate the brain conductive tissue. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m. The field maps are adjusted for stimulator power output of 58%, which was the level required to obtain 120% of the threshold, at a depth of 1.5 cm. The orange colors indicate field magnitude above neural threshold, for pulses delivered at 150% of the stimulator output required for hand motor stimulation.

to the fast decay of the electrical field close to coil central segment. In each measurement point the field was measured along two perpendicular directions, along the postero-anterior axis and along the lateral-medial axis. The probe was connected to a high impedance PC-based oscilloscope (Gage Applied Technologies, Inc., Lachine, Quebec, Canada), and the measured maximal voltage divided by the distance between the wire tips gave the electrical field along each axis. The absolute magnitude and the direction of the electrical field were computed for each measurement point. The coils were placed over the theoretic frontal cortex of the head model (i.e., coil centers were placed 5 cm anterior to the theoretic abductor pollicis brevis motor activation point).

RESULTS

Colored field maps for the three TMS coils, indicating the model electrical field absolute magnitude and direction in each point, are shown in Figs. 3 to 5. The red colors indicate model field magnitude above the threshold for neuronal activation. The threshold was set to 100 V/m, which is within the accepted range of thresholds required for hand motor activation (Epstein et al., 1990; Tielscher and Kammer, 2002). The intensity of stimulator power output used for drawing the maps representing the distribution of the electrical field for each coil was set to the level required to obtain 120% of the neural motor threshold, at a depth of 1.5 cm, according to the approximate depth of hand motor cortex sites

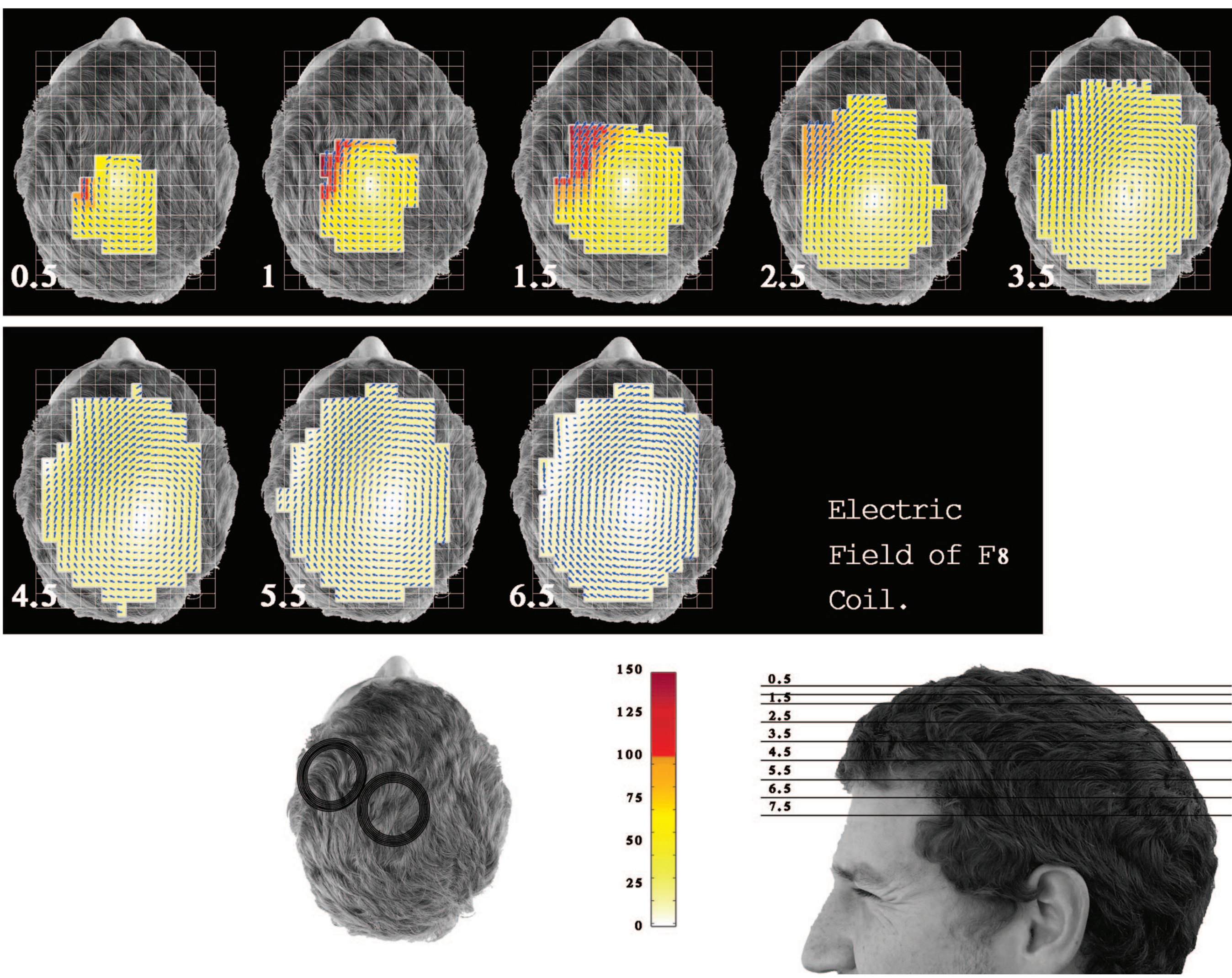

FIGURE 5. Colored field maps for the figure-8 coil indicating the electrical field absolute magnitude and direction in each pixel, for eight axial slices. The three superior slices are 0.5 cm apart, whereas the five inferior slices are 1 cm apart. The colored pixels in each slice indicate the brain conductive tissue. The red colors indicate field magnitude above the threshold for neuronal activation, which was set to 100 V/m. The field maps are adjusted for stimulator power output of 45%, which was the level required to obtain 120% of the threshold, at a depth of 1.5 cm. The orange colors indicate field magnitude above neural threshold, for pulses delivered at 150% of the stimulator output required for hand motor stimulation. The coil location and orientation are presented at the bottom.

(Epstein et al., 1990; Knecht et al., 2005). The orange colors indicate pixels where model field magnitude would surpass the threshold for neuronal activation, when stimulator output is set to 150% of the neural hand motor threshold. Model field maps for the H1-coil are shown in Fig. 3, for stimulator output set at 46% (i.e., 120% of threshold). It can be seen that when placing the coil over the prefrontal cortex, suprathreshold field is induced at lateral prefrontal and medial prefrontal regions, at depths of up to 4.5 cm. Model field maps for the H2-coil are shown in Fig. 4, for stimulator output set at 58% (i.e., 120% of threshold). Suprathreshold field is induced at lateral cortical regions, posterior regions and medial prefrontal regions at depth of 2 to 3 cm, and in lateral frontal regions at depth of up to 5.5 cm.

Model field maps for the figure-8 coil are shown in Fig. 5, for stimulator output of 45% (i.e., 120% of threshold). Suprathreshold field is induced under the coil central segment at cortical regions up to depth of 1.5 cm.

The field intensity along a lateral-medial axis in the axial slice 3.5 cm below skull upper edge is plotted in Fig. 6 for the H1, H2, and the figure-8 coils. The lateral-medial line is located 4 cm from the surface of the frontal lobe, as illustrated in the MRI coronal image. A clear preference for the left hemisphere is demonstrated for H1, where at any depth the model field is higher in the left relative to the right hemisphere, and the minimal field is 1 cm right to the center. No significant hemispheric difference is seen for the H2-coil. For the figure-8 coil the maximal model field along this line occurs at depth of 4 cm from skull left side, which is 3 cm from the central segment of the coil. The model field intensity at this point is 36% from the maximal field induced by the figure-8 coil in the brain, compared with 63% for the H1-coil and 56% for the H2-coil.

We compared the maximal absolute values of model electrical field intensity, and spatial derivatives of field intensity in the field direction, in the model hand motor cortex region, among the three TMS coils. The maximal model field intensities at stimulator output of 50%, for the H1, H2, and figure-8 coils were 142, 117, and 171 V/m, respectively. The maximal spatial derivatives of model field intensity in the field direction, for the H1, H2, and figure-8 coils were 0.16, 0.10, and 0.35 V/cm^2, respectively.

Model field intensity along left and right lateral anterior-posterior axes in the same axial slice as in Fig. 6 is plotted in Fig. 7 for the H1, H2, and figure-8 coils. The approximate locations of the lateral anterior-posterior axes are illustrated in the coronal MRI image. Again, higher intensity is found in the left relative to the right hemisphere for the H1-coil, but no significant difference between hemispheres is found for the H2-coil. The rate of decay of the model field along the anterior-posterior axis is very slow for

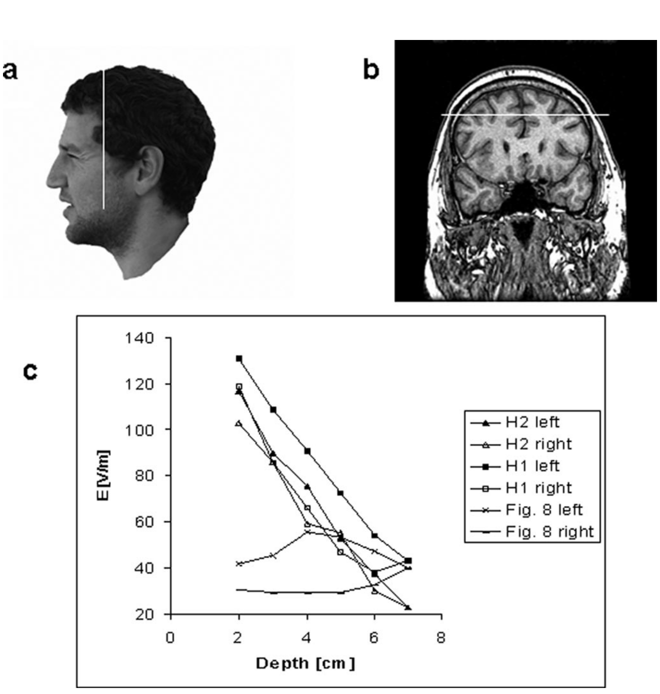

FIGURE 6. The electrical field decay along a lateral-medial line, for the H1, H2, and the figure-8 coil: **a.** Location of the coronal slice. **b.** The lateral-medial line shown on a coronal anatomic T1-weighted MR image. **c.** Electrical field intensity along the lateral-medial line plotted for the H1-coil in the left (full squares) and right (open squares) hemispheres, for the H2-coil in the left (full triangles) and right (open triangles) hemispheres, and for the figure-8 coil in the left (× signs) and right (− signs) hemispheres.

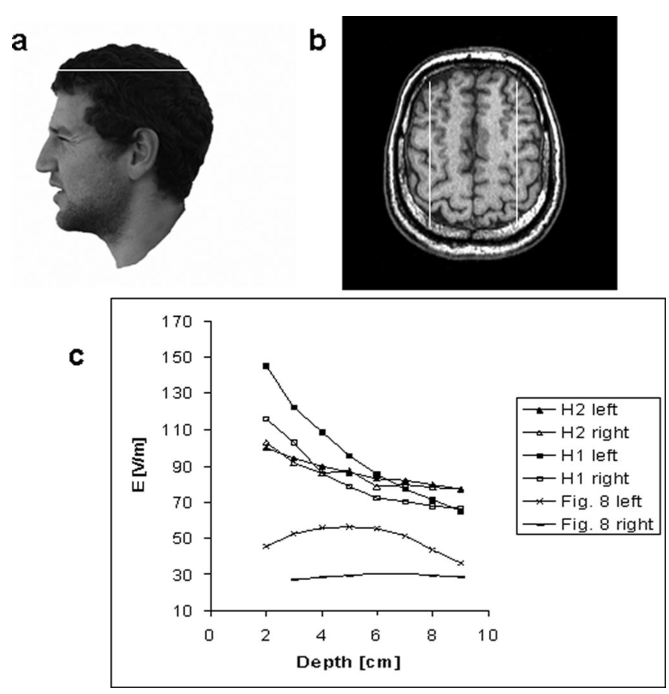

FIGURE 7. The electrical field decay along left and right anterior-posterior lines, for the H1, H2, and figure-8 coils. **a.** Location of the axial slice. **b.** The anterior-posterior lines shown on an axial anatomic T1-weighted MR image. **c.** Electrical field intensity plotted for the H1-coil along the left (full squares) and right (open squares) anterior-posterior lines, for the H2-coil along the left (full triangles) and right (open triangles) anterior-posterior lines, and for the figure-8 coil along the left (× signs) and right (− signs) anterior-posterior lines.

the H2-coil. For the figure-8 coil the maximal model field along the left lateral anterior-posterior line occurs at depth of 4 to 5 cm from the forehead, which is about 3 cm from the central segment of the coil. The model field intensity at this point is 36% from the maximal field induced by the figure-8 coil in the brain model, compared with 66% for the H1-coil and 64% for the H2-coil.

Model field intensity along left and right lateral superior-inferior axes is plotted in Fig. 8 for the H1, H2 and the figure-8 coils. The approximate locations of the lateral superior-inferior axes are illustrated in the coronal MRI image. The prominent slow rate of decay of electrical field with depth is seen for both H-coil versions. For the H1-coil a slower rate of decay is found in the left hemisphere. For the figure-8 coil there is a fast decay in field intensity along the left lateral superior-inferior line which is closer to the coil. At a point at depth of 4.5 cm along this line the model field intensity is only 12% from the maximal field induced by the figure-8 coil in the brain model, compared with 66% for the H1-coil and 81% for the H2-coil.

Model field intensity along a line perpendicular to the coil plane at the coil center is plotted in Fig. 9 for the figure-8 coil. The approximate location of the line is illustrated in the coronal MRI image. The rate of field decay is considerably faster relative to the two H-coil versions.

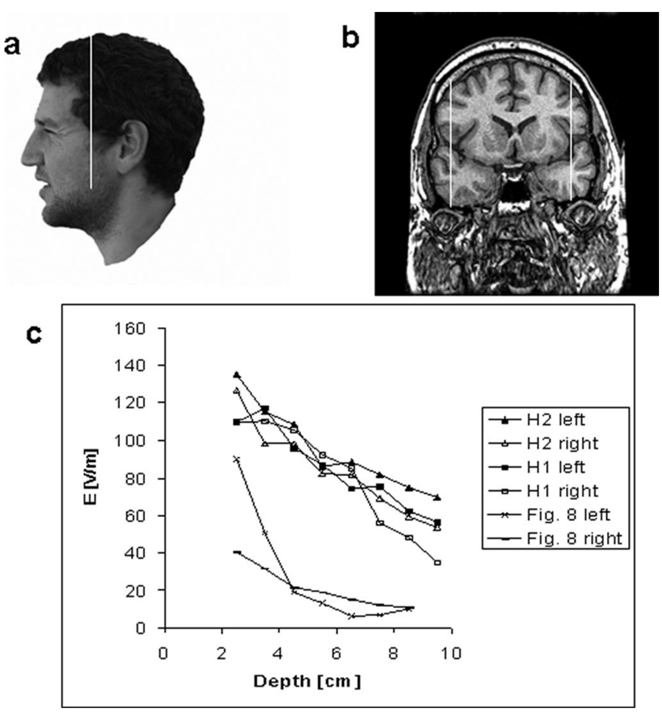

FIGURE 8. The electrical field decay along left and right superior-inferior lines, for the H1, H2, and figure-8 coils. **a.** Location of the coronal slice. **b.** The superior-inferior lines shown on a coronal anatomic T1-weighted MR image. **c.** Electrical field intensity plotted for the H1-coil along the left (full squares) and right (open squares) superior-inferior lines, for the H2-coil along the left (full triangles) and right (open triangles) superior-inferior lines, and for the figure-8 coil along the left (× signs) and right (− signs) superior-inferior lines.

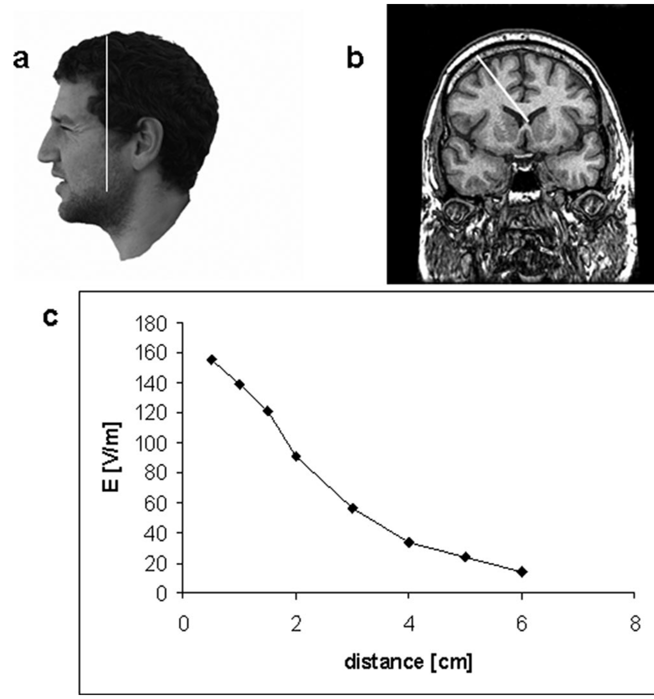

FIGURE 9. The electrical field decay for the figure-8 coil, along a line perpendicular to the central segment of the coil. **a.** Location of the coronal slice. **b.** The line perpendicular to the central segment of the coil shown on a coronal anatomic T1-weighted MR image. **c.** Electrical field intensity along the line, plotted as a function of distance.

DISCUSSION

The model electrical field distribution maps of the H1 and H2 coils, when placed over the prefrontal cortex, demonstrate their ability to surpass the neuronal activation threshold in deep prefrontal brain structures. The safety of these coils, when placed over the prefrontal cortex, along with cognitive and emotional effects, was tested in a clinical study with 32 healthy volunteers (Zangen et al., submitted for publication). For both coil versions the produced electrical field in lateral prefrontal regions is mainly along the postero-anterior axis, whereas in orbitofrontal and medial prefrontal regions the produced field is mainly along the lateral-medial axis. The red colored pixels in Fig. 3 demonstrate that on delivering of pulses at 120% of the stimulator output required for hand motor stimulation, the H1-coil enables effective activation of both the dorsolateral and the ventrolateral prefrontal regions up to depth of 4 to 5 cm below skull upper edge, and of medial prefrontal regions up to depth of 3 to 4 cm below skull upper edge. The H2-coil enables effective activation of lateral prefrontal and subcortical frontal regions up to depth of 5 to 6 cm below skull upper edge, and of medial prefrontal regions up to depth of 2 to 3 cm below skull upper edge (Fig. 4). The figure-8 coil induces suprathreshold field only at a superficial region up to 1.5 cm under the central segment of the coil (Fig. 5).

The depth penetration depends on the stimulator output intensity used relative to the motor threshold. The orange pixels in Fig. 3 demonstrate that if pulses are delivered at 150% of the stimulator output required for hand motor stimulation, the H1-coil enables effective activation of medial prefrontal and subcortical frontal regions up to depth of 5 to 6 cm below skull upper edge, and of lateral prefrontal and subcortical frontal regions, especially in the left hemisphere, up to depth of 7 to 8 cm below skull upper edge.

The H2-coil enables, on delivering of pulses at 150% of the stimulator output required for hand motor stimulation, effective activation of lateral prefrontal and subcortical frontal regions in both hemispheres, and of medial prefrontal and subcortical frontal regions, up to depth of 7 to 8 cm below skull upper edge (Fig. 4).

Activating the figure-8 coil at 150% of hand motor threshold will induce suprathreshold field at a cortical region up to only 2.5 cm under the central segment of the coil (Fig. 5).

In principle, two related parameters may be relevant for neuronal activation: electrical field strength, and the spatial derivative of the electrical field. Although the activation of peripheral nerves depends mainly on the derivative of the electrical field along the nerve fiber (Maccabee et al., 1993), when we deal with neuronal tissue having relatively short axons with bents and branches, such as the brain, it was predicted theoretically (Amassian et al., 1992; Ilmoniemi et al., 1999) and demonstrated experimentally (Kammer et al., 2001; Stewart et al., 2001; Tielscher and Kammer, 2002) that the absolute magnitude of the electrical field is the biologically relevant parameter for neuronal stimulation. In this study, whereas the maximal field intensities of the figure-8 and the H-coils are comparable, the maximal spatial derivative of the figure-8 coil along the field direction is about twofold to threefold larger, due to the faster decay of field intensity with distance for this coil. In a recent clinical study with 32 healthy volunteers, using the same three TMS coils, the abductor pollicis brevis motor thresholds were comparable among the three coils (Zangen et al., submitted for publication). The combination of these findings clearly supports the conclusion that the absolute magnitude of the electrical field is the biologically relevant parameter for neuronal stimulation.

The ability of the H-coil versions to stimulate deep brain structures, and to obtain simultaneous activation of several brain regions, may have important clinical implications. For example, a recent rTMS study conducted in parkinsonian patients indicated a significant improvement in gait and reduction in upper limb bradykinesia, where the rTMS stimulation was given at four distinct cortical targets (left and right motor and dorsolateral prefrontal cortex), using a standard figure-8 coil (Lomarev et al., 2005). Treatment with the H1 or H2 coils may enable simultaneous stimulation of several brain regions, whereas the depth penetration can be varied in a controlled manner either by adjusting the stimulator output and/or by varying the distance between various coil elements and the skull.

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