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A TMS coil positioning/holding system for MR image-guided TMS interleaved with fMRI☆

Daryl E. Bohning[a,*], S. Denslow[a], P.A. Bohning[b], J.A. Walker[b], M.S. George[a,b,c,d]

[a]Center for Advanced Imaging Research, Department of Radiology, Medical University of South Carolina, 169 Ashley Avenue, Charleston, SC 29425, USA
[b]Center for Advanced Imaging Research, Department of Psychiatry, Medical University of South Carolina, Charleston, SC, USA
[c]Center for Advanced Imaging Research, Department of Neurology, Medical University of South Carolina, Charleston, SC, USA
[d]The Ralph H. Johnson Veterans Hospital, Charleston, SC, USA

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Abstract

Objective: Transcranial magnetic stimulation (TMS) can be interleaved with fMRI to visualize regional brain activity in response to direct, non-invasive, cortical stimulation, making it a promising tool for studying brain function. A major practical difficulty is accurately positioning the TMS coil within the MRI scanner for stimulating a particular area of brain cortex. The objective of this work was to design and build a self-contained hardware/software system for MR-guided TMS coil positioning in interleaved TMS/fMRI studies.

Methods: A compact, manually operated, articulated TMS coil positioner/holder with 6 calibrated degrees of freedom was developed for use inside a cylindrical RF head coil, along with a software package for transforming between MR image coordinates, MR scanner space coordinates, and positioner/holder settings.

Results: Phantom calibration studies gave an accuracy for positioning within setups of $dx = \pm 1.9$ mm, $dy = \pm 1.4$ mm, $dz = \pm 0.8$ mm and a precision for multiple setups of $dx = \pm 0.8$ mm, $dy = \pm 0.1$ mm, $dz = \pm 0.1$ mm.

Conclusions: This self-contained, integrated MR-guided TMS system for interleaved TMS/fMRI studies provides fast, accurate location of motor cortex stimulation sites traditionally located functionally, and a means of consistent, anatomy-based TMS coil positioning for stimulation of brain areas without overt response.

Keywords: Transcranial magnetic stimulation; TMS; MR-guided positioning; Interleaved TMS and fMRI

1. Introduction

Transcranial magnetic stimulation (TMS) is a technique in which a pulsed magnetic field created by a small coil positioned next to the scalp is used to locally depolarize neurons in brain cortex. For example, using TMS over the area of the motor cortex responsible for thumb movement will cause movement of the contra-lateral thumb.

TMS combined with neuro-imaging and used either alone or as a complement to the usual cognitive tasks, can, potentially, be used to study the effective connectivity of brain circuits (Paus et al., 1997). For example, during the presentation of cognitive tasks, which activate well-defined areas of the brain, TMS might be used to modulate or disrupt those areas, one by one, to test if they are essential to the task or only co-activated. Though TMS can be interleaved with fMRI (Bohning et al., 1998; Baudewig et al., 2001) to visualize regional brain activity in response to direct, non-invasive TMS stimulation, a major practical difficulty is the accurate and consistent positioning of the TMS coil so as to stimulate a particular area of an individual's brain cortex.

For locating areas of cortex with an overt response, e.g. motor cortex, TMS coil placement has usually been 'functionally' based. That is, the coil is handheld against the scalp in what is assumed to be the correct place for stimulating the desired area of motor cortex, and then, while the coil is pulsed, its position is adjusted, observing the relative response. This is continued until the operator is satisfied that the optimum position for stimulation of the chosen area/response has been found.

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* Corresponding author. Tel.: +1-843-792-6171; fax: +1-843-792-5067.
E-mail address: bohninde@musc.edu (D.E. Bohning).

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This 'functional' localization method has served reasonably well for motor studies, and, since the focal 'spot' of the coil is relatively broad, some feel that there is little point in pursuing more accurate placement. However, it requires skill, is time consuming, is operator dependent, and in the end, one really did not know exactly where the coil is positioned relative to the subject's brain anatomy. For interleaved TMS/fMRI, though one may have successfully induced motor response using 'functional' localization, the only way to relate the position of the TMS coil to the anatomy of the subject's brain, has been to attach MR visible markers to the TMS coil and work out the 3D relation between the markers and the TMS coil's B-field distribution, a problem comparable to the neuro-navigation problem, and inaccurate unless a special set of high-resolution images is acquired especially for that purpose.

Most important of all, this 'functional' localization method cannot be used for positioning the coil over areas of cortex for which stimulations evoke no overt response. With the exception of the primary motor and visual systems, single pulse TMS over most scalp locations produces no easily observable response. In the past, to stimulate such areas, researchers have used the motor area as a reference, and then consulted probabilistic atlases for relative placement of the coil. For example, for prefrontal cortex stimulation, the motor area for thumb is first located as described above, and the coil is then positioned 5 cm anterior (George et al., 1995) to the motor area reference point. Though this method gives some degree of anatomical localization, it has been shown to be inaccurate (Hervig et al., 2001a), and is certainly not sufficiently accurate for studying brain emotional or cognitive circuitry. In general, such motor-referenced localizations do not provide an accurate and reliable way to reference the coil's position to the actual structural or functional anatomy of the individual's brain.

Image-based anatomy referencing for TMS within a PET scanner or in a TMS lab, has been used by Paus et al. (1998), Krings et al. (1997), Boroojerdi et al. (1999), and Hervig et al. (2001b). Paus et al. (1998) used a Viewing Wand (ISG, Toronto) to mark the location for stimulation over the frontal eye field (FEF) based on the averaged Talairach coordinates of 8 patients from a previous study converted to the individual's own brain coordinates system via a previous MR scan. Krings et al. (1997) used a modified Surgical Arm (Radionics Operating Arm System, OAS, Radionics, Burlington, MA) to hold the coil for stimulation of primary motor cortex, though the position was actually found functionally, i.e. by adjusting the position for consistent motor (thumb twitch) response. However, they were then able to use the system to transform the surgical arms position back to the coordinate system of stored MR images, showing the location of the TMS stimulation on cortical anatomy, and validating the use of TMS relative to electrical brain stimulation (EBS) for pre-operative motor mapping. Boroojerdi et al. (1999) mapped the motor hand area with TMS by stimulating at the intersection points of a grid drawn on an elastic cap worn by the subject. They then acquired a set of MR volume images and used a frameless stereotactic system (Philips EasyGuide™ Neuro, Best, The Netherlands) to record the 3D space positions of those stimulation points by moving the system's infrared (IR) localized pointer to each of the grid points.

Hervig et al. (2001a) review the problems associated with applications of TMS based on external head references rather than cortical anatomy and the importance of individualized anatomical localization, and describe the adaptation of a neuro-navigational system commonly used in neurosurgery (Surgical Tool Navigator™, Zeiss, Oberkochen, Germany) for TMS positioning. Though developed for accurate anatomy-based TMS for clinical applications and neurophysiology rather than PET or fMRI neuroimaging, Ettinger et al. (1998) developed a comparable system. They used a laser scanner to determine subject head position and IR light-emitting diodes (LED) and a 3D tracking system (IGT, Inc., CO) to measure the TMS coil position, and then worked out the association between the 3D positions and orientations of the TMS probe on the scalp and a 3D reconstruction of the brain from MR images.

Basically, these systems all work the same way. A set of MR images is first acquired of the subject's brain, loaded into the neuro-navigational workstation and displayed. Then, the TMS coil or a locating pointer at the end of a moveable arm, of some sort, is moved over the subject's scalp while a marker, displayed on the MR images, tracks the position of the pointer relative to the cortical anatomy displayed in the MR images. Once the anatomical location to be selected as the target for the TMS stimulation is chosen, the pointer's position on the subject's scalp over which the TMS coil is to be placed for stimulating a desired target area is marked. The subject can then be returned to the neuro-imaging scanner or TMS lab, the TMS coil positioned over the mark that has been made on the subject's scalp, and, finally, the coil rigidly fixed, somehow, for the study.

Though these neuro-navigational systems adapted from neurosurgery do perform the required transformations between a target location selected in an MR image volume of the subject's cortex anatomy and a point on the scalp over which to place the coil for the stimulation, and greatly improve localization for clinical or physiology laboratory applications of TMS, they are not ideal for interleaved TMS/fMRI. Since the workstation and locating arm cannot be operated close to an MR scanner, they depend on the crude and problematic method of positioning the TMS coil over a mark on the scalp (usually obscured by the TMS coil), and there is no good way to define the orientation of the coil. In addition, these systems require an independent holder to hold the TMS coil in place for the study.

It should be noted that Narayana et al. (2000) have constructed a TMS coil holder attachment for a surgical robot (NeuroMate, IMMI, Welesley, MA) for use in TMS/PET, and obtained highly accurate and repeatable TMS coil placement with it. Like the other neuro-navigational systems, the robot depends on MR data downloaded into its computer and accurate correlation between the subject's position in the PET scanner compared with that in the MR scanner. However, this system is very expensive (≈US$450,000), and the robot and TMS coil holder could not be used near an MR magnet.

The objective of this work was to develop a self-contained, relatively inexpensive, manually operated, hardware/software system for interleaved TMS/fMRI which would enable the operator to accurately and repeatably position the TMS coil based on anatomical target location selected in an MR volume acquired at the beginning of the TMS/fMRI study, and then, would hold the TMS coil securely in that position during the subsequent fMRI scan.

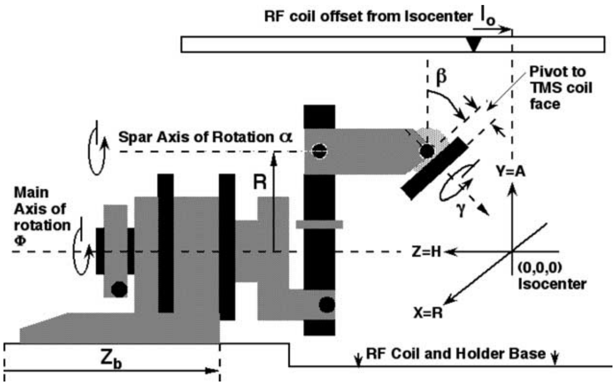

Fig. 1. Schematic of the TMS coil positioner/holder illustrating the 6 scaled degrees of freedom allowing the TMS coil to be moved to any point on the subject's scalp and then oriented so as to stimulate a selected target in the cerebral cortex.

2. Materials and methods

2.1. MR compatible TMS coil

A Dantec B-70 figure-8 TMS coil (Medtronic neuromuscular, Skovlunde, Denmark) specially modified by the factory (Tonica Electronik A/S, Denmark) was used. This particular coil (10.6 cm × 16.5 cm) has a pure copper winding which minimizes artifacts, and was chosen because of its symmetry and rigidity. The modified coil has had most of its handle removed, leaving only enough to accommodate the cable connections. Besides making it easier to maneuver the coil within the confines of an RF head coil, this eliminated the remote switch in the handle containing ferromagnetic materials, which would have caused severe imaging artifacts. The standard 3 m cable was replaced with a 7 m cable to reach from the stimulator power supply outside the scanner room, in through the back of the MR magnet to the subjects' head, while they are lying on the scanner bed outside the scanner. Finally, for attaching the TMS coil to the positioner/holder, a short cylindrical stub, 25.4 mm diameter and 25.4 mm long, was attached to the back of the coil at its center point. The stub has a shallow circumferential groove machined in the middle of its length for a setscrew, so that the TMS coil can be rotated in position.

2.2. TMS/fMRI holder/positioner

For TMS/fMRI, it is desirable to have a TMS coil mounting system, which provides flexible coverage of the scalp to allow stimulation of as many areas of cerebral cortex as possible, yet holds the coil firmly in position over the desired stimulation location during the experiment. It must also be sufficiently compact to operate within the confines of a cylindrical MR imaging RF head coil, with a typical inside diameter of about 28.5–29.5 cm.

Fig. 1 gives a schematic of our design for the device illustrating the 6 scaled degrees of freedom that allow the operator to manually move the TMS coil to a point on the subject's scalp and, at the same time, set its orientation so as to stimulate the selected target in the cerebral cortex. The TMS coil is usually positioned on the scalp so that its plane is tangent to the skull at the point of shortest distance from the stimulation target. As much as possible, the holder's movements were designed to be orthogonal to each other to simplify both the positioning and the computation of the coil's position relative to the isocenter of the MR magnet and the MR image volume.

Fig. 2 shows a photograph of the actual TMS coil positioner/holder as constructed to our specifications by CSI Solutions, Inc., Columbia, SC (copies of the engineering drawings may be obtained by writing to the corresponding author). All of the calibrated scales, except the main axis ϕ-angle scale can be seen in the photograph.

For installation, the holder base rail is mounted so that the holder's main axis is coaxial with the axis of the MR RF coil (Fig. 1) and allows the holder to be moved forward and backward (zb) in the center of the coil. The radial arm (shown with a double offset in the schematic in Fig. 1 and in a single offset version in the photograph of Fig. 2) swings 360° (ϕ-angle) about the main axis. The spar, which holds the TMS coil, slides radially along the radial arm to position the TMS coil pivot at the end of the spar a range of distances (rs = 0.0–11.6 cm) from the main axis. The spar itself is

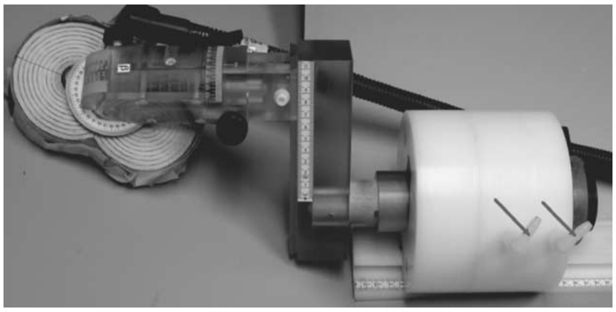

Fig. 2. Photograph of actual TMS coil positioner/holder. Red arrows indicate connections for pneumatic setback operation.

constructed of two pieces, which twist relative to each other (α-angle) about the spar's center axis, parallel to the main axis but offset by the radial position (rs) of the spar. The first piece positions (and locks) the spar on the radial arm at the desired radius, and the second piece allows the TMS coil to be angled (α-angle) relative to the radial arm. Mounted at the end of the spar, there is a short thick cylinder which pivots about an axis perpendicular to the axis of the spar and into which the TMS coil stub sockets. This allows the coil to be tilted with respect to the spar in a range of angles (β-angle) from 0° (coil flat on top of the head) to almost 90° (coil flat on the side or front of the head). Finally, the TMS coil can rotate 360° (γ-angle) about the stub at its center.

At 1.5 T, there is a 10–15% loss of signal due to the susceptibility artifact underneath the TMS coil, depending on the orientations of the coil and the image plane. To minimize this effect, one group has devised a mechanical means of lifting the coil after the TMS pulse and before acquiring the MR images (Josephs et al., 1999). Though a number of interleaved TMS/fMRI studies have been successfully performed at 1.5 T (Bohning et al., 1998, 2000a,b; Baudewig et al., 2001), despite this artifact, it was of concern that the problem will likely be worse at 3–4 T. Consequently, the holder includes a facility for pneumatically shifting the TMS coil away from the subject's head using compressed air (available in most MR scanner rooms). The red arrows (Fig. 2) indicate the air line connectors for the pneumatic setback. The main axle of the holder can shift from its most forward position against the subject's scalp 2 cm backward (z direction) in about 1–2 s depending on the air pressure used. Slower movement is preferred, since it causes less vibration when the cylinder hits the end of its travel. There is no problem with accuracy since the position is controlled by hard stops at either end. A schematic of the pneumatic setback air switches and electronic control is shown in Fig. 3.

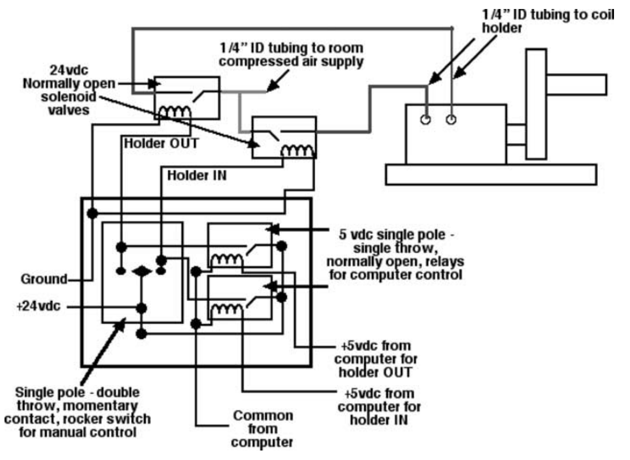

Fig. 3. Schematic for pneumatic setback air switch operation and control.

2.3. MR-guided TMS software

A small software package was developed to perform the transformations required for the MR-guided positioning (see interface palettes in Figs. 4 and 5). The software can display a set of MR images of the subject's brain and then relate the coordinates of a point in the brain identified on the MR images to the settings of the TMS coil holder in either of two modes. In the first mode, the operator places markers on target and scalp locations in the MR images and the software computes the holder settings needed to position the coil over that area for stimulation. Conversely, in the second mode, the operator enters a set of TMS coil holder settings and the software performs the required computations and places markers on the MR images, one for the TMS coil's position on the subject's scalp and, a second one, for the area of the cortex targeted for stimulation. To account for holder mounting offsets relative to the origin of the MR scanner coordinate system, site-specific holder calibration parameter values are entered in the palette shown in Fig. 4a.

At the beginning of the study, after the subject has been placed in the scanner for imaging and the head has been stabilized, the MR volume to be used for the image guidance is acquired. The images are then transferred to the MR-guided TMS system and the image parameters for the image set are entered manually. Fig. 4b shows the image parameter palette, which allows the investigator to enter the parameters: field-of-view (FOV), slice thickness, offsets, etc.,

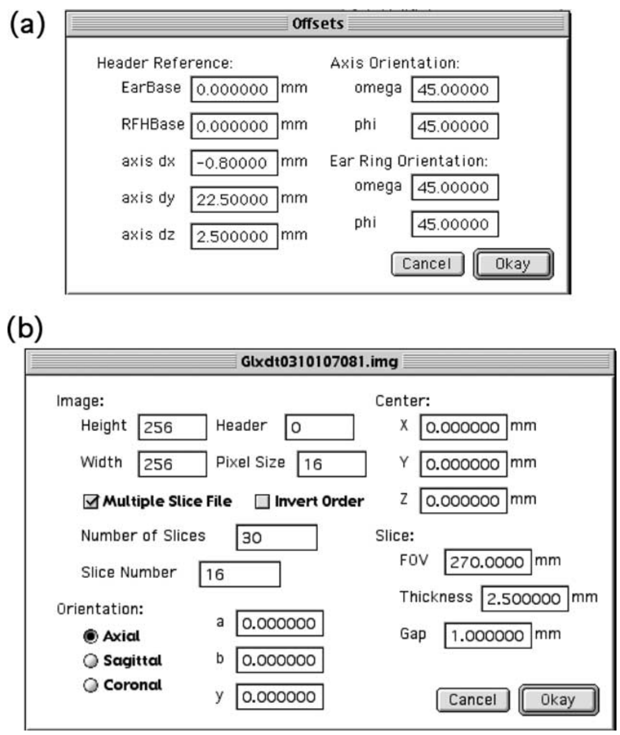

Fig. 4. (a) Calibration settings and (b) image parameter palettes for MR-guided TMS software.

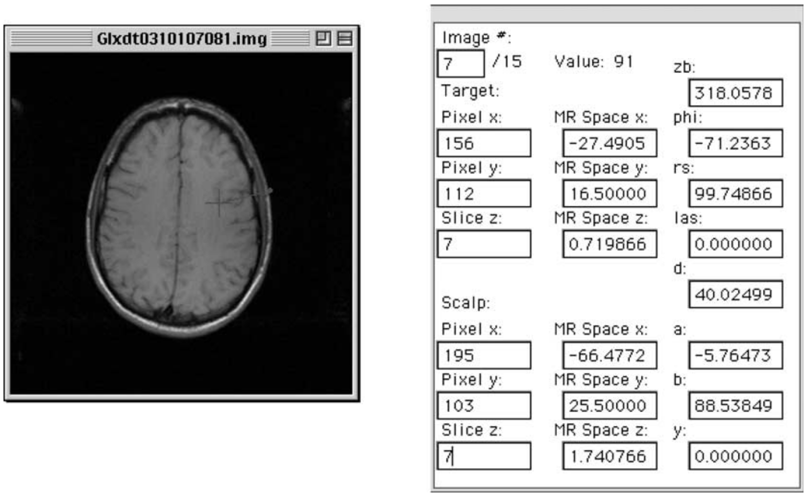

Fig. 5. (a) Image indicating positions of TMS coil against scalp (dot) and TMS stimulation target (cross) and (b) display of: image coordinates, MR space coordinates, and holder settings.

for the MRI volume and then load it for display. Though the position information must be transferred manually, this makes the standalone personal computer-based software system relatively self-contained and eliminates the problem of obtaining access to the proprietary software of the different MR scanner manufacturers.

Once the image volumes are loaded, the TMS stimulation target and scalp locations can be located graphically. Fig. 5a shows the display of a structural MR image for interactive target and scalp location, and Fig. 5b shows the window in which the transformations between MR coordinates and holder settings are computed and displayed. The red dot and cross in Fig. 5a, respectively, indicate the TMS coil's scalp placement and the TMS stimulation target position, which have been selected by the user. The software displays the scalp and target voxel coordinates in both image and real space, and then translates these coordinates into coil holder settings for placement of the TMS coil over the scalp location, with the correct orientation for stimulation of the target location (Fig. 5b). Contrariwise, if the operator has positioned the TMS coil 'functionally', the resulting settings of the holder can be fed into the MR-guided TMS software to obtain the coordinates of the coil in the MR scanner's imaging frame of reference and display the corresponding scalp and target (given a depth, d) locations on the MR images. Entries can be made for any of the MR image coordinates, MR scanner space coordinates or holder settings, and the other coordinates will immediately be recomputed and displayed.

2.4. Procedure for MR-guided TMS system validation and calibration

Simultaneous validation and calibration of the system were performed with the TMS coil replaced by a special small cylindrical phantom with a mounting stub similar to that on the TMS coil (Fig. 7f, here the holder is shown installed inside the head coil from a Picker MR scanner). The phantom moves with the positioner/holder's spar in exactly the same way as the TMS coil, and provides sufficient signal for imaging. At each end of the phantom, in the center of the circular end plate, there are small nylon screws that create a signal void that can easily and accurately be located within the image of the phantom. These two signal voids effectively form two MR visible 'point sources' at 29 and 100 mm, respectively, from the holder pivot (β-angle) along the line through the center of the TMS coil (when in place) and perpendicular to it.

To calibrate the holder, calibration scans (3D gradient echo, 256 × 256 matrix, slice thickness = 2 mm, no gap) were acquired with the holder in 4 positions, carefully noting the exact holder settings in each position: (1) holder base set forward ($z \approx 10$ mm) with spar at about 3 o'clock, (2) holder base in same position as in first scan, but spar set to about 10 o'clock, (3) holder base pushed back ($z \approx 70$ mm), spar again about 3 o'clock, and, finally, (4) holder base left in the same position as the 3rd scan and the spar set to about 10 o'clock again. The 4 sets of holder setting and the corresponding coordinates of the proximal and distal 'point sources' read from the scans, 8 measured points in all, are entered in a small program which then computes the calibration constants needed to correct for errors in holder mounting: dx, dy, dz, da1, da2, da3.

3. Results

The criterion for the success of this MR-guided TMS system is that it accurately positions the TMS coil over, and points the coil at, the anatomy chosen in the MR images, and that is a question of geometry completely answered using the phantom (Fig. 7f) and the system validation and

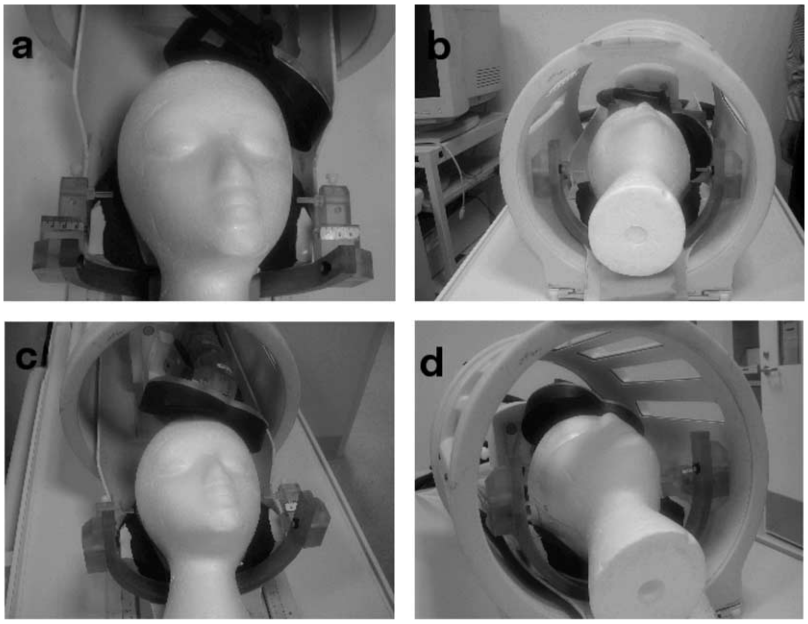

Fig. 6. Photographs of device with TMS coil in place in different positions on a manikin head inside 29.5 cm ID MR RF head coil: (a) motor area and earplug referencing system, (b) motor area, (c) prefrontal area, and (d) prefrontal area.

calibration procedure described above. In this section, we present the results of that validation/calibration along with some practical 'results' related to the design/construction/application of the system.

3.1. Results of MR-guided TMS system validation and calibration

Phantom calibration studies were performed with the calibration phantom described above in a variety of positions; first, to validate the transformation algorithms and, secondly, to obtain the installation-dependent constants, and determine the accuracy of the system. These studies showed that the accuracy for TMS targeting within setups, i.e. without removing the holder base assembly from the magnet, can be performed with an accuracy of $dx = \pm 1.9$ mm, $dy = \pm 1.4$ mm, $dz = \pm 0.8$ mm. The precision for multiple setups, i.e. the error for holder placement from setup to setup, taking the entire system out of the magnet and reinstalling it, was $dx = \pm 0.8$ mm, $dy = \pm 0.1$ mm, $dz = \pm 0.1$ mm. This implies that most of the error is due to holder scale reading and image partial volume.

3.1.1. Practical limitations of scalp coverage

In theory, flexible access to all areas of the scalp is inherent in the positioner's design. It provides 360° of movement of the main axis, 15 cm of foot-to-head movement, and 11.6 cm of radial movement. The TMS coil face to pivot distance is 3.1 cm and the coil spar extends 3.2 cm beyond the pivot, hence, the coil can cover a cylinder 15.9 cm in diameter by 15 cm long inside

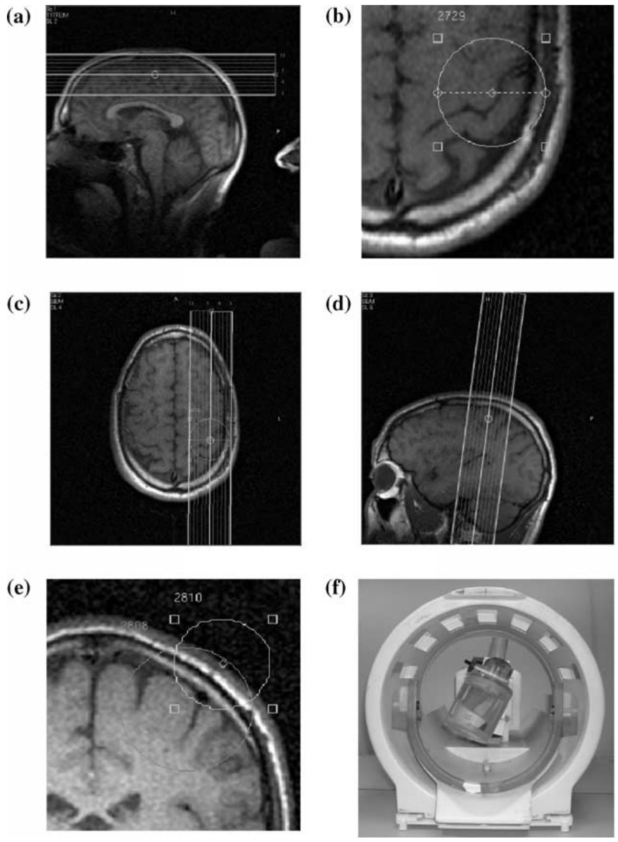

Fig. 7. MR image series for determination of target and scalp locations: (a) axial setup, (b) target location, (c) sagittal setup, (d) coronal setup, and (e) scalp location, and (f) calibration phantom in position for calibration scans.

of an RF coil with a clear internal diameter (ID) of $15.9 + 2(3.1 + 3.2) = 28.5$ cm, the ID of our GE RF head coil. The ID of our Picker RF head coil is 29.5 cm, so this gave us some extra room to accommodate the wings of the coil when oriented perpendicular to the RF coil axis. Hence this enables the holder to accommodate a range of head sizes and shapes. Fig. 6a–d shows the positioner holding the Dantec TMS coil against a life-size manikin head in realistic motor and prefrontal area positions inside the 29.5 cm ID Picker RF head coil.

In practice, scalp coverage is usually limited by paraphernalia related to the support and stabilization of the subject's head, and this has to be worked out for the desired placement of the TMS coil. We use a combination of foam pads and elastic velcro straps placed so as not to interfere with the coil, but some placements are, obviously, more difficult than others to work out. In addition, there might be rotation angles (γ-angle) of the figure-8 coil, which might cause it to interfere with the MR RF coil. In that case, it might be necessary to support the subject's head off-center to give more working room.

3.1.2. Repeatable subject positioning

Though not normally required, since TMS target location is usually found based on anatomical location in a set of MR images newly acquired at the beginning of each study, a provision for positioning the subject's head at the same place with respect to the TMS coil holder has also been incorporated. The scaled, adjustable mounts for pins which are referenced to molded earplugs can be seen in Fig. 6 on either side of the manikin's head.

3.1.3. Pneumatic retraction

A complete experiment was run with the pneumatic setback in the Picker scanner. The slight jarring as the pneumatic piston hits the end of its travel created a significant movement artifact. However, the Picker RF head coil assembly is not rigidly fixed to the scanner bed, so can shift forward and backward a small amount. At 1.5 T, we preferred to accept the modest signal loss rather than have any additional movement artifacts. Once we move to our new 3 T system, we will try to determine if we can use the pneumatic setback, by building a more rigid base to see if this artifact can be eliminated.

An important consideration to keep in mind when using the pneumatic setback is that the subject's head must be securely restrained. Though the coil is positioned against the subject's scalp with the pneumatic cylinder in its most forward position, so it can only move away from the subject's head, one must be certain that the subject cannot move back far enough to be struck when the coil returns after retraction.

3.1.4. MR-guided TMS using MR scanner MR space coordinate readouts

In practice, if the scanner has facilities for displaying the coordinates of points selected in images, the images need not even be transferred to the MR-guided TMS system; one only need enter the MR space coordinates provided by the MR scanner. This eliminates the need to extract the MR images from the scanner database, transfer them to the MR-guided TMS system, and load them for display and target/scalp location selection, saving considerable time. This method of operation is described in Section A.3 of Appendix A.

4. Discussion

MR guidance is essential for accurate positioning of the TMS coil relative to the area of the brain to be stimulated in TMS/fMRI studies. This integrated system for MR-guided positioning of the TMS coil and then holding it for the study is more accurate, less expensive, and more convenient than systems that involve exporting MR images to expensive, neuro-navigation workstations, marking the scalp, and then fixing the TMS coil over the place to be stimulated with some other device.

Alternatively, in cases where the application is motor cortex, and the TMS stimulation site has been determined by manually moving the TMS coil until the associated motor response is observed, the investigator can enter the resulting settings of the holder, and the software will compute the point of scalp contact, and the point of maximum TMS coil magnetic field intensity at the approximate depth of cerebral cortex. This makes it possible to determine the relation of the TMS coil's field pattern to that individual's brain anatomy, and the areas showing fMRI activation.

It is not surprising that the MR-guided TMS system can place the TMS coil accurately with respect to brain anatomy. This is implied by simple geometry and the phantom calibration data. What is interesting is that it seems to do better than the functional method for achieving consistent, strong stimulation, even with a skilled clinical practitioner performing the functional localization (Denslow et al., 2003). In that study, for all 11 scans, in 7 different subjects, motor movement was obtained without having to move from the TMS coil setting determined by the image-guidance procedure described above. Only the coil's angle (γ) about the mounting stub—not determined in the current version of the software—was changed to optimize response. This implies that the accuracy of the system is significantly greater than the stimulation pattern of the coil and/or the variability of the motor area, and that, as we hypothesized, functional localization is variable and may place the coil to one side or another of the optimum spot.

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Appendix A

A.1. Function for determining the MR space position of the TMS coil stimulation target from the positioner/holder settings (Mathematica format)

```
(* Module to get position of tms from holder settings! *)
Arguments:
zb = ?; (* Holder zb scale reading *)
ϕ = ?; (* Holder main axis f angle reading *)
rs = ?; (* Radial position of spar reading *)
α = ?; (* Holder spar axis a angle reading *)
β = ?; (* Spar coil pivot b angle reading *)
γ = ?; (* coil rotation f angle reading *)
las = ?; (* Additional z-direction laser position offset for Picker MR scanner. *)
d = ?; (* Target depth *)
Constants:
dtr = Pi/180.0 (* angle to radian conversion factor. *)
colthk = 31.0; (* coil pivot to coil face thickness *)
rfrefbasz0 = (* z - position of holder base z = 0 relative to RF coil isocenter reference mark. *)
hldpvtz = (* (* z - distance from holder front measurement face to center of coil pivot. *)*)
r0 = 0.0; (* Correction for zero point of radial scale *)
x0=0.0; (* Installation dependent offset in x direction. *)
y0=0.0; (* Installation dependent offset in y direction. *)
z0=0.0; (* Installation dependent offset in z direction. *)
tmsfrmhldmod[zb_,ϕ_,rs_,α_,β_,γ_,las_,d_]: =
Module[{},
(* Computes position of tms from holder settings. *)
   tms = {
      x0 + Sin[ϕ*dtr]*(rs + r0)-(d + colthk)*Sin[(ϕ +
α)*dtr]*Sin[β*dtr],
      y0 + Cos[ϕ*dtr]*(rs + r0)-(d + colthk)*Cos[(ϕ +
α])*dtr]*Sin[β*dtr],
      z0 + rfrefbasz0-zb-hldpvtz-(d +
colthk)*Cos[β*dtr] + las
      };
   tms
];
```

A.2. Function for determining the positioner/holder settings from the MR space position of the TMS coil stimulation target (Mathematica format)

```
(* Module to get holder settings from positions of scalp and tms points! *)
Arguments:
sx = ?; (* Scalp point MR scanner space x coordinate*)
sy = ?; (* Scalp point MR scanner space y coordinate*)
sz = ?; (* Scalp point MR scanner space z coordinate*)
tx = ?; (* Target point MR scanner space x coordinate*)
ty = ?; (* Target point MR scanner space y coordinate*)
tz = ?; (* Target point MR scanner space z coordinate*)
las = ?; (* Additional z-direction laser position offset for Picker MR scanner. *)
Constants:
dtr = Pi/180.0 (* angle to radian conversion factor. *)
colthk = 31.0; (* coil pivot to coil face thickness *)
rfrefbasz0 = (* z-position of holder base z = 0 relative to RF coil isocenter reference mark. *)
hldpvtz = (* (* z - distance from holder front measurement face to center of coil pivot. *)*)
r0 = 0.0; (* Correction for zero point of radial scale *)
x0 = 0.0; (* Installation dependent offset in x direction. *)
y0 = 0.0; (* Installation dependent offset in y direction. *)
z0 = 0.0; (* Installation dependent offset in z direction. *)
hldfrmtmsmodx[sx_ , sy_ , sz_, tx_, ty_, tz_, las_,
mrztbasz_, sparz_, ]: = Module[{d,},
(* Computes holder settings from scalp and tms positions. *)
(* Scalp and tms positions in DEB coordinates, +y = up, +x = operator left, +z = into magnet bore. *)
d = Sqrt[({tx,ty,tz}-{sx,sy,sz}).({tx,ty,tz}-{sx,sy,sz})];
(* depth! *)
β = ArcCos[(tz-sz)/(-d)]/dtr;
zb = z0 + rfrefbasz0-sz-hldpvtz-(colthk)*Cos[β*dtr] +
las;
(* Position of pivot in MR space. *)
px = tx + ((d + colthk)/d)*(sx-tx);
py = ty + ((d + colthk)/d)*(sy-ty);
pm = Sqrt[px*px + py*py];
(* Position of pivot relative to holder main axis. *)
px1 = px-x0;
py1 = py-y0;
(*ϕ angle. *)
If[Abs[py-y0] > 0.0001,
   If[(px-x0 > 0.0),
      If[(py-y0 > 0.0),
         ϕ = ArcTan[( px-x0)/(py-y0)]/dtr;,
         ϕ = 180.0-ArcTan[( px-x0)/(py-y0)]/dtr;
         ];,
      If[(py-y0 > 0.0),
         ϕ = ArcTan[( px-x0)/(py-y0)]/dtr;,
         ϕ = -180.0 + ArcTan[( px-x0)/(py-y0)]/dtr;
         ];
      ];
   If[px-x0 > 0.0,
      ϕ = 90.0;,
      \ϕ = -90.0;
      ];
];
If[ϕ > 180.0,ϕ = ϕ-360.0];
If[ϕ < -180.0,ϕ = ϕ + 360.0];
```

```
(* rs = ra + rb *)
rs = Sqrt[({px,py}-{x0,y0}).({px,py}-{x0,y0})]-r0;
tpx = px-tx;
tpy = py-ty;
tpm = Sqrt[tpx*tpx + tpy*tpy];
tsta = ArcCos[{px,py}.{tpx,tpy}/(pm*tpm)];
(* Position of target if alpha = 0 - in MR space. *)
a0x = x0 + (rs-(d + colthk)*Sin[(β*dtr])*Sin[ϕ*dtr];
a0y = y0 + (rs-(d + colthk)*Sin[(β*dtr])*Cos[ϕ*dtr];
(* alpha is the angle between the a0-p vector and the t-p
vector. *)
(* Note: These are all in MR space, not relative to
{x0,y0} *)
tstb = Abs[ArcCos[({a0x,a0y}-{px,py}).({tx,ty}-
{px,py})/
    (Sqrt[({a0x,a0y}-{px,py}).({a0x,a0y}-{px,py})]*
    Sqrt[({tx,ty}-{px,py}).({tx,ty}-{px,py})])]]/dtr;
(* Sign of alpha depends on quadrant and a0-p vector
versus t-p vector. *)
    If[Abs[ϕ] < = 45.0,
        If[tx < a0x,
            tstc = tstb,
            tstc = -tstb;
        ];,
        If[Abs[ϕ] > = 135.0,
            If[tx < a0x,
tstc = -tstb,
tstc = tstb;
];,
        If[ϕ > 0.0,
            If[ty > a0y,
tstc = tstb,
tstc = -tstb;
];,
            If[ty > a0y,
tstc = -tstb,
tstc = tstb;
];
            ];
        ];
];
(* Position of target relative to spar pivot. *)
tdph = (d + colthk)*Sin[(β*dtr];
trad = rs-tdph;
trpx = (tx-x0-Sin[ϕ*dtr]*(rs + r0));
trph = (-(d + colthk)*Sin[(β*dtr]);
If[Abs[(-(d + colthk)*Sin[(β*dtr])] > 0.0001,
0.1. α = ArcSin[(tx-x0-Sin[ϕ*dtr]*(rs + r0))/(-(d +
colthk)*Sin[(β*dtr])]/dtr-ϕ;
0.2. α = ?;
0.3. ];
α = tstc;
hld = {zb,ϕ,rs,d,α,β,tsta,tstb,tstc};
hld
];
```

A.3. MR-guided TMS using MR scanner MR space coordinate readouts

The subject first lies on the scanner bed and places his/her head in the head cradle of the device. The subject's head is then centered and restrained with foam padding, and they are moved into the scanner.

A series of high-resolution structural MR scans (TR = 600 ms, TE = 20, 256 × 256, 3 mm thick, no gap, 11 slices) is taken for selection of the scalp and target positions. The MR scanner bed is then slid out of the scanner without disturbing the subject, the TMS coil is positioned according to the settings computed by the software, and, finally, the MR scanner bed is put back into scan position in the scanner for the interleaved TMS/fMRI study.

The procedure for determining TMS target and scalp positions for stimulation of thumb is as follows:

1. A 3-plane scout is acquired.
2. Using the scout images for reference, a T1-weighted axial scan is set up covering approximately the superior 3rd of the brain as shown in Fig. 7a. These slices should cover the hand knob of the motor strip.
3. On the axial scan, find the highest slice in which the motor knob for the left side of the brain is well defined. Center the region-of-interest about 2/3 of the way to the lateral edge of the motor knob in line with the sulcus (Fig. 7b). This is the target point; record its MR space coordinates (for Philips Intera, Philips Medical Systems, The Netherlands: X = LR mm, Y = AP mm, Z = FH mm).
4. Set up sagittal slices centered on the coordinates of the just-determined **target** point and parallel to the brain midline (Fig. 7c).
5. Set up coronal slices on the center sagittal slice. The slice set is centered at the target. Tilt the slice package so that the center slice is perpendicular to the scalp (Fig. 7d).
6. On the center coronal slice, set up a circular ROI centered at the target point coordinates (Fig. 7e). Once the center of the ROI is at the target position, adjust the size of the ROI (keeping it circular) so that the circumference is tangent to the scalp. This will be the scalp point where the center of the TMS coil should be positioned. Use a second ROI to determine and record the 3D coordinates of the tangent point (for Philips Intera: X = LR mm, Y = AP mm, Z = FH mm).
7. Enter the target and scalp position coordinates into the MR-guided TMS program to obtain the settings for the holder (TMS coil Holder Settings: zb in mm, rs in mm, and $\phi°$, $\alpha°$, $\beta°$, all in degrees) (note: the depth, d, is automatically computed as the distance between the scalp and target points and displayed).
8. Slide the MR scanner bed out of the scanner to set the TMS coil positioner to the computed settings (note: the subject's head position is not disturbed).

9. Slide the MR scanner bed back into scan position in the scanner and perform the interleaved TMS/fMRI study.

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