NEUROIMAGE **3,** 1–9 (1996)
ARTICLE NO. 0001

Locating the Motor Cortex on the MRI with Transcranial Magnetic Stimulation and PET[1]

ERIC M. WASSERMANN,*,[2] BINSENG WANG,†,[3] THOMAS A. ZEFFIRO,* NORIHIRO SADATO,* ALVARO PASCUAL-LEONE,* CAMILO TORO,* AND MARK HALLETT*

**Human Motor Control Section, Medical Neurology Branch, National Institute of Neurological Disorders and Stroke, and †Biomedical Engineering and Instrumentation Program, National Center for Research Resources, National Institutes of Health, Bethesda, Maryland 20892-1428*

Received June 23, 1995

Transcranial magnetic stimulation with a focal coil was used to map the cortical representation of a hand muscle in four healthy subjects. In each subject, the three-dimensional locations of the magnetic stimulation positions and about 400 positions on the surface of the head were digitized. The amplitude-weighted center of gravity of each subject's map was found, and a line perpendicular to the local head surface was projected inward. The digitized heads were registered with the subjects' MRIs using the scalp contours. The coordinate transformations yielded by this process were used to map the stimulation positions and the perpendicular line into the MRIs. Brain areas imaged with positron emission tomography (PET) and ^{15}O-labeled water, activated by movement of the same muscle, were registered with the MRIs using the brain contours. In all cases, the magnetic stimulation lines encountered the surface of the brain at the anterior lip of the central sulcus and ran along the precentral gyrus a few millimeters anterior to the central sulcus, coming within 5–22 mm of all the PET activation maxima. This technique demonstrates the accuracy of transcranial magnetic stimulation for locating the primary motor area.

INTRODUCTION

Localization of motor representations in the human cerebral cortex began with the work of Penfield and colleagues (1937, 1954), who mapped the motor cortex by stimulating the cortical surface in conscious patients who were undergoing surgical procedures. These and subsequent experiments by Woolsey *et al.* (1952, 1979) showed significant interindividual differences, but suggested the presence of a motor homunculus in the area of the precentral gyrus, whose lower extremity fell on the mesial surface of the hemisphere and whose head lay at the lateral extreme of the gyrus, near the sylvian fissure. Modern work with intracortical microstimulation has shown the fine detail of the homunculus to be more of a discontinuous patchwork (Waters *et al.,* 1990), but with clustering of microregions representing movements of specific body parts that lie in roughly the classic somatotopic order.

Activation studies performed with positron emission tomography (PET) also have been used to identify motor representations in the brain. Many investigators (Ingvar and Philipson, 1977; Lauritzen *et al.,* 1981; Roland, 1984; Mazziotta *et al.,* 1985a,b) have reported that focal increases in cerebral blood flow and oxygen and glucose metabolism occur during various motor tasks. Further, Colebatch *et al.* (1991) described somatotopic differences in blood flow in motor areas during movement of upper limb joints. Using PET with ^{15}O-labeled water, with the images registered to MRIs, Grafton *et al.* (1991) found that areas in primary motor cortex where blood flow increased during movements of the tongue, finger, and toe were somatotopically located.

Transcranial magnetic stimulation (TMS) provides a noninvasive means of stimulating the cortex (Barker *et al.,* 1985). Refinement of the stimulating coil's shape (Cohen *et al.,* 1990b) has improved the focality of stimulation. Motor representations that activate muscles at different joints of the upper extremity can be distinguished on the scalp and are shown to fall in the predicted somatotopic pattern (Wassermann *et al.,* 1992), and the representations of adjacent fingers may be resolved (Wilson *et al.,* 1993).

Much effort has been directed at answering the ques-

[1] This work was presented in part at the annual meeting of the Society for Neuroscience, Anaheim, CA, November, 1992.

[2] To whom reprint requests should be addressed at Building 10, Room, 5N226, National Institutes of Health, 10 CENTER DR MSC 1428, Bethesda, MD 20892-1428.

[3] Dr. Wang was on leave from the State University of Campinas, Brazil.

1053-8119/96 $18.00

tions of how and where TMS excites descending motor pathways (Amassian and Cracco, 1987; Amassian *et al.,* 1987, 1989; Day *et al.,* 1988, 1989; Thompson *et al.,* 1989; Epstein *et al.,* 1990; Rothwell *et al.,* 1991), and investigators agree that the excitation of corticospinal neurons occurs within the cortex transsynaptically or, under some conditions, in the most superficial subcortical white matter. Much less, however, is known about where TMS impinges on the cortical surface to produce activity in a given muscle and the extent to which cortical motor maps derived by TMS agree with maps from other methods.

Head surface digitization and three-dimensional registration algorithms have been used successfully to map positions on the head into radiographic images (Wang *et al.,* 1994). In the present study, we used this technique to project points on the scalp, identified by TMS as corresponding to the motor representation of the hand, into the subject's MRI and activated PET scans.

SUBJECTS AND METHODS

Subjects were four healthy volunteers (one woman and three men), aged 22 to 35 years, including three of the investigators. All subjects were right handed by self report. The protocol was approved by the Institutional Review Board, and all subjects gave their written informed consent for the study.

Cortical TMS

During TMS, subjects lay on a comfortable examination table with the head elevated approximately 60°. Surface EMG electrodes were applied over the first dorsal interosseous (FDI) muscle on the right hand. The hand was positioned in pronation at the subject's side. The EMG signals were recorded on a conventional electromyograph with filter settings of 100 Hz and 1 kHz. The EMG was used to monitor the results from individual trials of stimulation and to make on-line averages during the experiments. Signals were fed from the EMG machine to a desktop computer and stored at a sampling rate of 4 kHz.

A Cadwell high-speed magnetic stimulator (Cadwell Laboratories, Inc., Kennewick, WA), operating in single-pulse mode, and an 8-shaped coil composed of two loops of windings, each 4.5 cm in diameter, were used for cortical stimulation. The characteristics of this coil, which provides a focal magnetic stimulus at the intersection of the loops, are described in detail elsewhere (Cohen *et al.,* 1990b; Roth *et al.,* 1991). The coil was held tangential to the scalp with the handle pointing posteriorly.

The approximate optimal scalp position for activating the right FDI was found by stimulating a series of sites over the left hemisphere. Then, a 7 × 7-cm grid of points 1 cm apart, with the optimal position at its center, was measured and marked on the scalp. Additional points were added during the mapping if the excitable area extended beyond the grid. Each point was assigned coronal and sagittal coordinates, taking the optimal position as the origin.

Mapping was carried out by positioning the intersection (center) of the two loops of the coil over the points marked on the scalp and delivering 10 stimuli about 3 s apart to each point. The stimulus intensity was approximately 1.1 times the intensity needed to produce a motor evoked potential (MEP) in the FDI, which was visible at a display gain of 100 μV/cm on 10 of 10 trials. Starting near the center of the grid and working outward, we stimulated the grid positions until the MEP disappeared. The mapping sessions took less than an hour.

The 10 trials from each scalp position were rectified and averaged off-line. At each scalp position, the value of the 2-ms time bin in the average that contained the peak of the MEP was scaled as a percentage of the largest averaged response in that subject, and this value was assigned to the position. In a previous mapping study (Wassermann *et al.,* 1992), we found that the best measure for characterizing the center of an amplitude map was the amplitude-weighted mean position or center of gravity. This was computed by weighting the coronal and sagittal coordinates of each point according to its scaled amplitude and finding the average of all the weighted coordinates. The center of gravity was used for projection into the brain MR images.

PET and MRI Studies

For the PET study the subject lay supine with the arms at the sides. The subject was fitted with foam ear plugs to reduce ambient noise and eye patches to block patterned visual stimulation. A custom-molded thermoplastic face mask immobilized the subject's head to reduce head motion artifact. An intravenous catheter, which was used for the delivery of 33-mCi boluses of ^{15}O-labeled water, was placed in the left antecubital vein. The subject's right hand was comfortably supported, allowing free lateral movement of the right index finger.

Each subject was studied at rest and during active finger movement. (Subjects were also scanned under another condition: passive movement of the fingers by the examiner, the results of which are not included in this paper.) Under the rest condition, the subject lay quietly with the eyes closed. Under the active movement condition, the subject performed self-paced, repetitive abduction–adduction movements of the right index finger at a rate of 2 Hz. The movements were begun 30 s before injection of the tracer.

Changes in cerebral blood flow were measured by a modified autoradiographic technique (Herscovitch *et*

al., 1983; Raichle *et al.,* 1983). Images of cerebral blood flow were obtained by summing the activity occurring during the 60-s period following the first detection of an increase in cerebral radioactivity after the intravenous bolus injection of the ^{15}O-labeled water. No arterial blood sampling was performed and, thus, the images collected were those of tissue activity. Tissue activity recorded by this method is linearly related to regional cerebral blood flow (rCBF) (Fox and Raichle, 1984; Fox and Mintun, 1989).

The PET scans were made with a 15-slice PET scanner (Scanditronix Model PC2048-15B, Uppsala, Sweden) with 6.5-mm interslice spacing. Images of tissue radioactivity were reconstructed using filtered back projection (FWHM = 6.5 mm). To allow for complete tracer decay, scans were performed 12 min apart. Each subject had three scans at rest and three during active finger movement.

MR imaging was performed with a SIGNA 1.5-T (General Electric, Milwaukee, WI) MRI machine using an SPGR sequence that provided 124 contiguous sagittal 1.5-mm slices spanning the brain. Contours of the brain surface were drawn on each MR and PET image, resulting in two sets of contours, representing the brain surface as imaged in each modality. The coordinate transformation needed to transform PET into MRI coordinates was determined with the use of a surface-matching algorithm that determined the translation and rotation required to bring the two surfaces into optimal alignment (Pelizzari *et al.,* 1989). The CBF data were reformatted using bilinear interpolation and the coordinate transformation that was determined in the previous step. This resulted in two sets of 124 coplanar images that could then be superimposed. The rCBF was globally normalized to a mean of 100 ml/100 mg/min. Subtraction images were computed for movement minus rest and thresholded to show regions of activation that were more than 2 standard deviations above the mean for the whole brain. The subtraction images were then superimposed on the corresponding MR images. The central sulcus was identified on axial MR sections, according to the method of Berger *et al.* (1990), as the most posterior sulcus intersecting the midsagittal fissure.

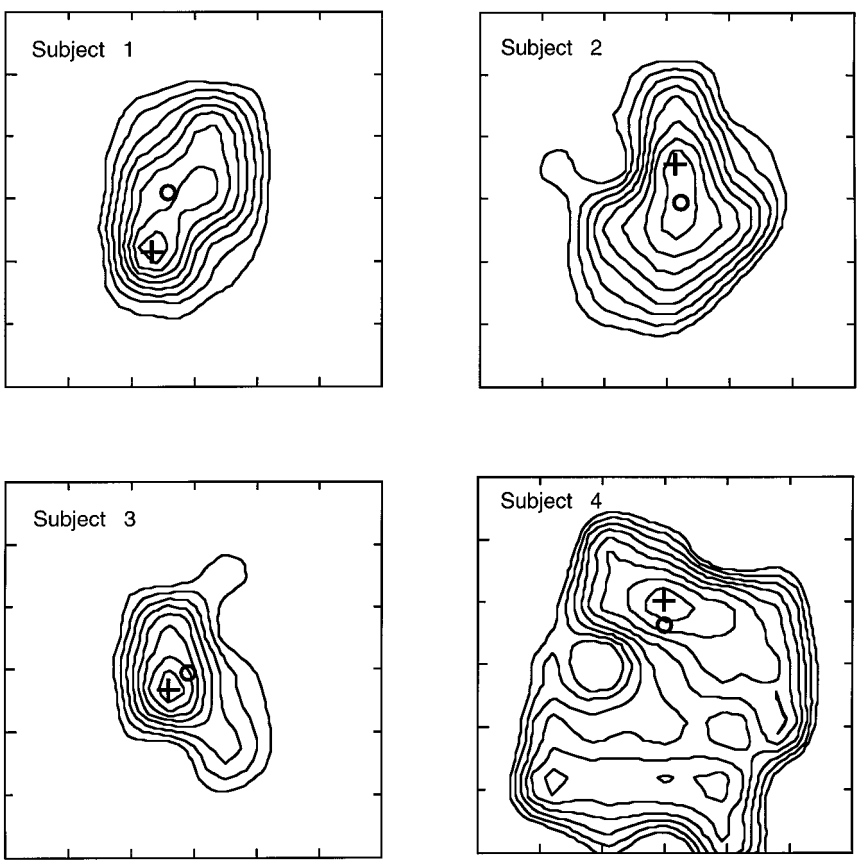
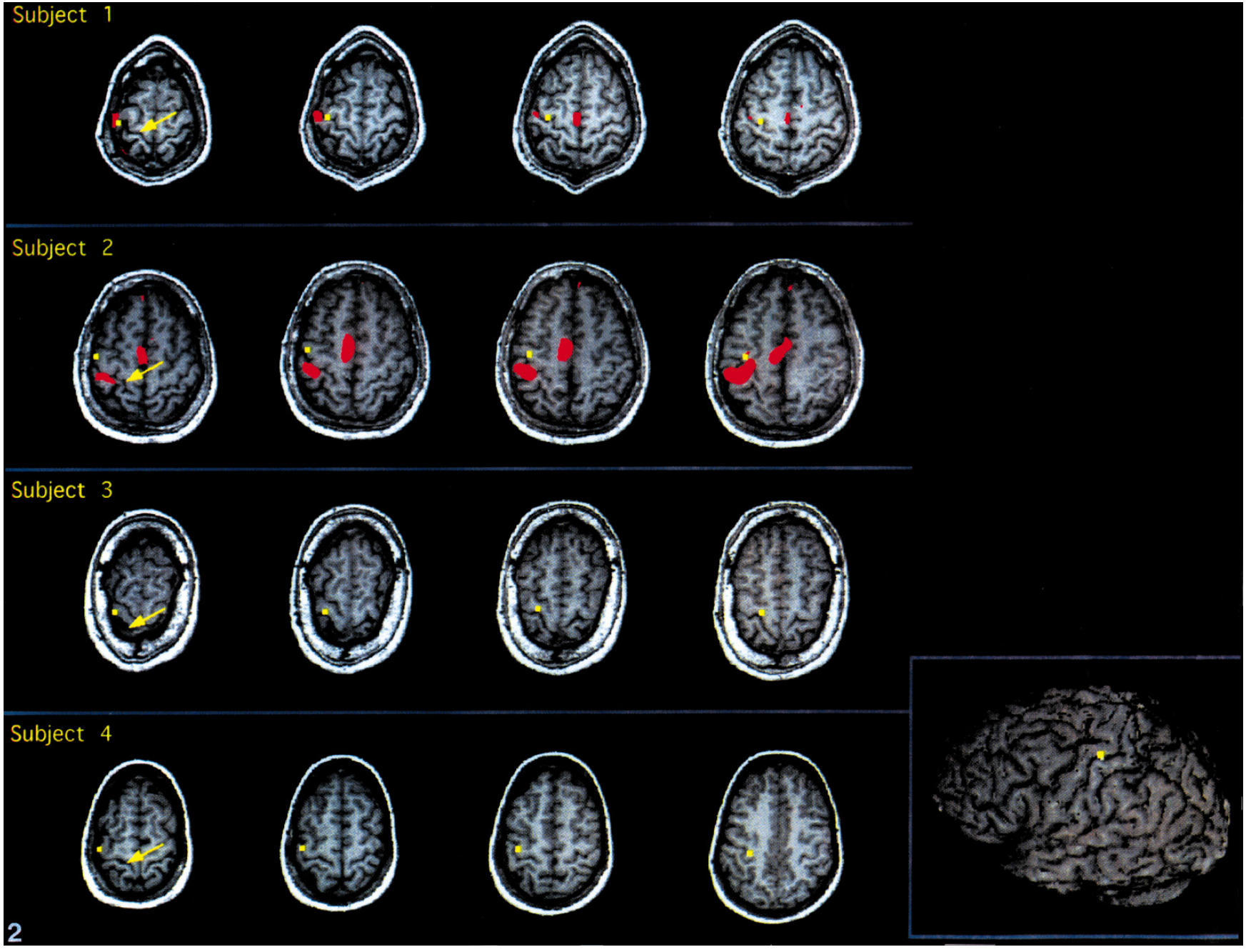
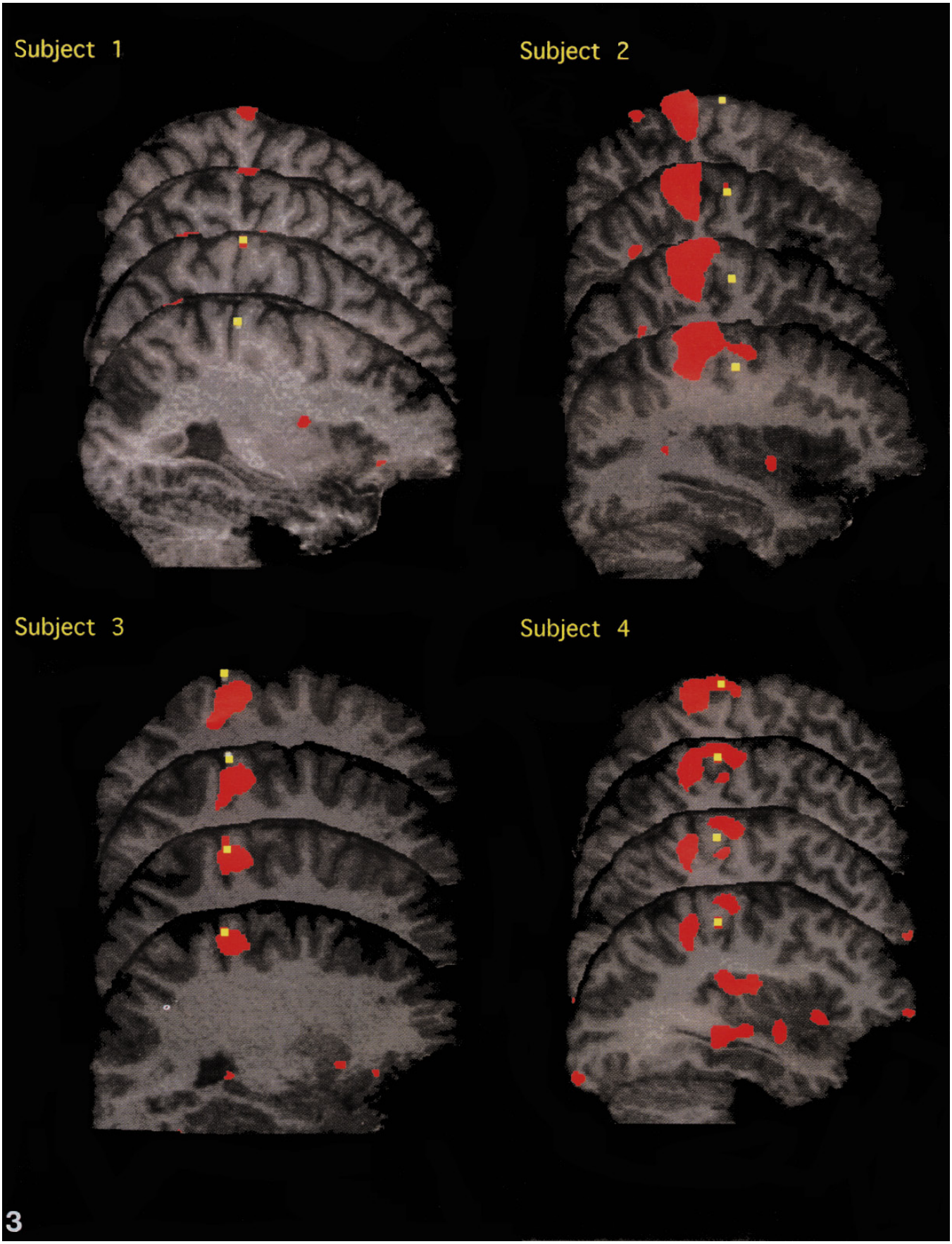


FIG. 1. Contour maps derived from averaged responses to 10 trials of TMS at scalp sites 1 cm apart in four subjects. Open circles indicate amplitude-weighted centers of gravity (see text). Crosses indicate sites with the highest amplitude averaged response. Contours represent 12.5 percentiles of the maximal averaged response. Scale around frames is in centimeters. Upward on the map is anterior on the head, and left is left.


Subject 1
Subject 2
Subject 3
Subject 4
2


Subject 1
Subject 2
Subject 3
Subject 4
3

Head Digitization and Image Registration

A three-dimensional magnetic digitizer (Polhemus, Colchester, VT) was used to measure the coordinates of the grid points. In addition, approximately 400 points were sampled from each subject's head surface (Wang *et al.,* 1994). The digitized head surface was aligned with the head contours obtained from the same subject's MRI using a surface registration algorithm (Pelizzari *et al.,* 1989). The rotation and translation values provided by the registration of the head surfaces were used to make the coordinate transformations needed to map scalp positions into the MRIs (Wang *et al.,* 1994). The precision of this mapping process was estimated as 6 mm, provided that all digitized data were obtained in the same session. The grid of TMS positions was sometimes digitized in different sessions or on different days from the head surface sampling. In these cases, a least-mean-square error algorithm was used to register the grid with the head surface. The intersession registration could add 5.7 mm to the measurement uncertainty (Wang *et al.,* 1994).

The digitized points were fitted by a sphere using the modified least-mean-square error function proposed by Lükenhöner *et al.* (1990). The center of this best-fitting sphere was also mapped from the digitized head into the corresponding MRI. The line connecting the center of the sphere with the center of gravity was assumed to be the perpendicular projection of the center of gravity into the brain. The intersection of this line with each sagittal MRI section was computed and marked on the MRI slice by masking a region of 3 × 3 pixels with its center at the intersection. Transaxial MRI sections were obtained from the sagittal images using a reslice program available as part of the MIRAGE software developed by the Department of Nuclear Medicine at the Warren Grant Magnussen Clinical Center, National Institutes of Health (Bethesda, MD).

RESULTS

Magnetic Stimulation

In all subjects, stimulation of a circumscribed area of the central scalp 5–6 cm to the left of the vertex produced MEPs in the right FDI. In all subjects except one, TMS maps of these areas had single-amplitude peaks located near their centers. In the other subject, the map was more complex and irregular (Fig. 1, subject 4). The centers of gravity fell within 1 cm of the position where stimulation produced the largest averaged response in all cases. The maps tended to be elongated in the sagittal plane.

Projection of TMS Points into the MRI and Registration with PET

In all four subjects the line projecting the center of gravity of the magnetic stimulation map into the brain intersected the surface of the brain just anterior to the central sulcus (Figs. 2 and 3) and maintained this position on several successive slices as it passed ventromedially into the brain.

In each subject, finger movement resulted in increased cerebral blood flow in the sensorimotor cortex about midway along the length of the central sulcus. In subjects 1, 3, and 4, the TMS line passed very near or coincided with the 2 standard deviation PET activation area in a superficial region of the motor cortex near the anterior lip of the central sulcus (Figs. 2 and 3). In subject 2, the TMS line met the surface of the brain at the anterior lip of the central sulcus but did not encounter the 2 standard deviation PET activation area, which, in this case, was mostly posterior to the central sulcus (Figs. 2 and 3). Analysis of the three-dimensional images showed that the TMS line passed an average of 13 mm from the maximally activated pixel in the motor cortex on the PET scan. The individual distances were 6 mm for subject 1, 19 mm for subject 2, 22 mm for subject 3, and 5 mm for subject 4.

DISCUSSION

Transcranial magnetic stimulation with the 8-shaped coil is able to distinguish the representations of different upper extremity parts on the scalp in one dimension (Cohen *et al.,* 1990a), and, when combined with appropriate statistical methods, in two dimensions (Wassermann *et al.,* 1992). However, the relationship of the scalp map to the underlying cortical topography has not been explored. To determine the site of activation on brain imaging, Epstein *et al.* (1990) attempted to locate the site of stimulation for a finger movement on the individual subject's MRI and concluded that it was at the depth of a gyral crest, or about 1.5 cm from the surface of the scalp. However, this result may be of limited applicability because, in their calculations, the authors treated the area of activation as a point rather than a three-dimensional zone.

FIG. 2. Axial MRI slices 4 mm apart shown in dorsal to ventral order (left to right) from four subjects show the intersection of the TMS line with each slice (yellow squares). Areas of >2 standard deviations of PET activation (red areas) are shown for subjects 1 and 2, in whom the relation of the TMS line and the PET activation area were seen better in the axial plane. Slices are viewed from above, such that upward on the figure is anterior and left is left. Arrows indicate the central sulcus. (Inset) Volume rendered image of the brain of subject 4 shows projection of the TMS line onto the brain surface (yellow square).

FIG. 3. Sagittal slices 2–4 mm apart from four subjects in lateral to medial order (top to bottom) show areas of >2 standard deviations of PET activation (red areas) and the intersection of the TMS line with each slice (yellow squares). Slices are viewed from the right, such that upward on the figure is dorsal and left is posterior.

The PET results in this study showed activation related to finger movement near the central sulcus in all subjects. Subject 2 had a large active zone that appeared to be located posterior to the central sulcus with only a small amount of activation near the anterior bank. This could reflect a preponderance of activation in somatosensory areas by reafference from the moving finger. On the other hand, the degree of accuracy of the registration of PET and MRI scans has never been established, and errors in this process may have caused mismatches with the MRI. TMS appeared to locate the central sulcus with considerable precision in all subjects.

TMS and PET would be expected to identify essentially the same region of cortex since near-threshold, nonfocal TMS and liminal degrees of voluntary muscle activation produce activity in the same spinal motoneurons (Hess *et al.,* 1987). On the other hand, the active regions on PET may not correspond precisely to the site of activation by TMS. Indeed, based on current estimates of the decay of the induced electrical current with distance from the magnetic source (Roth *et al.,* 1991), it is unlikely that significant stimulation can occur deep in the central sulcus, where the bulk of PET activation occurred in some subjects and where classic mapping studies (Penfield and Boldrey, 1937; Penfield and Jasper, 1954; Woolsey *et al.,* 1979) have found the representation of the fingers. Angular error in the TMS trajectories caused by failure to hold the coil tangential to the scalp or by poor fitting of the local head surface to a sphere may also have contributed to discrepancies between TMS and PET localization of the hand motor area in individual subjects.

Several lines of evidence suggest that, under most conditions, the predominant mechanism responsible for activation of corticospinal neurons by TMS is transsynaptic (Amassian *et al.,* 1987, 1989; Day *et al.,* 1989; Thompson *et al.,* 1989; Rothwell *et al.,* 1991), which further suggests that the site where TMS acts on the brain to activate hand muscles is not identical to the motor representation of the hand found by direct electrical stimulation. The topology of cortical folding may be a factor in determining which cortical elements are excited by TMS. Day *et al.* (1989) speculated that TMS delivered at a moderate intensity with a large circular coil centered at the vertex would selectively activate intracortical elements oriented parallel to the surface of the brain (horizontally oriented fibers would lie on the gyral crest) rather than radially oriented descending cells or fibers running vertically in the wall of the central sulcus. In our study, an 8-shaped coil was applied directly over the central area, but the same principle is likely to apply. This idea is also supported by differences between the latencies of MEPs to TMS and transcranial electrical stimulation as well (Rothwell *et al.,* 1991). The rapid decay of the magnetic stimulus with distance and the evidence for transsynaptic activation of motor pathways suggest to us that the site of action of TMS probably lies anatomically superficial to, and physiologically upstream from, the classic representation of the hand as defined by cortical surface stimulation.

In a primate study, Huntley and Jones (1991) found prominent clustering of labeled cells a few millimeters anterior (on the unfolded cortex) to sites where intracortical microstimulation produced digit movements after injections of a retrograde tracer at those sites. These clusters tended to coincide with low threshold sites for producing movements at more proximal forelimb joints. Such connections from sites in the primary motor cortex, slightly anterior (superficial) to the classic hand representation, may be the first neural link in the chain mediating activation of hand muscles by TMS. The increased synaptic activity and blood flow that result in the ^{15}O signal with hand movement may occur downstream in the dendritic field of the corticospinal cells targeting the hand muscles.

One other technical factor could have caused some apparent anterior displacement of the magnetic stimulation trajectory. That factor is "brain sag," the tendency for the brain to flatten posteriorly when the subject is supine, as ours were, for MRI scanning. Since TMS was done with the subjects at approximately 30° of recumbency, there might have been some mismatch of this type between the TMS and MRI data.

Our results in a limited sample suggest that the combination of TMS and projection into the MRI is an accurate means of locating the motor cortex noninvasively. The limit of spatial resolution of TMS maps generated with multiple averaged trials, using the 8-shaped coil, has been estimated at about 5 mm (Brasil-Neto *et al.,* 1992). This is essentially the same as the estimate given by Grafton *et al.* (1991) for their PET maps. We have not estimated the accuracy of our registered PET scans, but the evidence presented here suggests that TMS is a far more accurate means of localizing the center of a motor representation; PET may be better at defining its boundaries.

The use of the center of gravity, which is derived from the results of TMS at multiple scalp positions, decreases the vulnerability of the technique to erroneous readings at single locations. However, in most cases, the location of maximum response could apparently be safely substituted for the center of gravity if a sufficient number of trials are given at each location.

Various noninvasive techniques have been used to locate brain lesions or anatomical features. For example, three-dimensional reconstructions of PET and MRI scans have been used to identify the locations of seizure foci with respect to brain and head features (Fishman *et al.,* 1991). Others (Orrison and Lewine, 1993; Buchner *et al.,* 1994) have used dipole analysis of somatosensory evoked potentials and magnetoencephalography to identify the somatosensory cortex on the

MRI. The present technique for locating the primary motor area is considerably simpler and less expensive than many others and is probably just as accurate. If the accuracy of TMS mapping is borne out in a larger number of subjects, it could be of utility in planning brain surgery. An important use for this information may be to enable investigators using transcranial stimulation to use the motor representation of the hand as a reliable landmark on the scalp in order to locate other areas of the cortex.

REFERENCES

Amassian, V. E., and Cracco, R. Q. 1987. Human cerebral cortical responses to contralateral transcranial stimulation. *Neurosurgery* **20:** 148–155.

Amassian, V. E., Quirk, G. J., and Stewart, M. 1987. Magnetic coil versus electrical stimulation of monkey motor cortex. *J. Physiol. (London)* **394:** 119P. [Abstract]

Amassian, V. E., Maccabee, P. J., Cracco, R. Q., and Cracco, J. B. 1989. Basic mechanisms of magnetic coil excitation of the nervous system in humans and monkeys: Application of focal stimulation of different cortical areas in humans. In *Magnetic Stimulation in Clinical Neurophysiology* (S. Chokroverty, Ed.), pp. 73–111. Butterworth, Stoneham, MA.

Barker, A. T., Jalinous, R., and Freeston, I. L. 1985. Noninvasive magnetic stimulation of human motor cortex. *Lancet* **1:** 1106–1107.

Berger, M. S., Cohen, W. A., and Ojemann, G. A. 1990. Correlation of motor cortex brain mapping data with magnetic resonance imaging. *J. Neurosurg.* **72:** 383–387.

Brasil-Neto, J. P., McShane, L. M., Fuhr, P., Hallett, M., and Cohen, L. G. 1992. Topographic mapping of the human motor cortex with magnetic stimulation: Factors affecting accuracy and reproducibility. *Electroencephalogr. Clin. Neurophysiol.* **85:** 9–15.

Buchner, H., Adams, L., Knepper, A., Rüger, R., Laborde, G., Gilsbach, J. M., Ludwig, I., Reul, J., and Scherg, M. 1994. Preoperative localization of the central sulcus by dipole analysis of early somatosensory evoked potentials and three-dimensional magnetic resonance scanning. *J. Neurosurg.* **80:** 849–856.

Cohen, L. G., Hallett, M., and Lelli, S. 1990a. Noninvasive mapping of human motor cortex with transcranial magnetic stimulation. In *Magnetic Stimulation in Clinical Neurophysiology* (S. Chokroverty, Ed.), pp. 113–119. Butterworth, Stoneham, MA.

Cohen, L. G., Roth, B. J., Nilsson, J., Dang, N., Panizza, M., Bandinelli, S., Friauf, W., and Hallett, M. 1990b. Effects of coil design on delivery of focal magnetic stimulation. Technical considerations. *Electroencephalogr. Clin. Neurophysiol.* **73:** 350–357.

Colebatch, J. G., Deiber, M.-P., Passingham, R. E., Friston, K. J., and Frackowiak, R. S. J. 1991. Regional cerebral blood flow during voluntary arm and hand movement in human subjects. *J. Neurophysiol.* **65:** 1392–1401.

Day, B. L., Dressler, D., Maertens de Noordhout, A., and Marsden, C. D. 1988. Magnetic stimulation of the human brain can activate different neuronal elements when the magnetic field direction is reversed. *J. Physiol. (London)* **401:** 46P. [Abstract]

Day, B. L., Dressler, D., Maertens De Noordhout, A., Marsden, C. D., Nakashima, K., Rothwell, J. C., and Thompson, P. D. 1989. Electrical and magnetic stimulation of human motor cortex: Surface EMG and single motor-unit responses. *J. Physiol. (London)* **412:** 449–473.

Epstein, C. M., Schwartzenberg, D. G., Davey, K. R., and Sudderth, D. B. 1990. Localizing the site of magnetic brain stimulation in humans. *Neurology* **40:** 666–670.

Fishman, E. K., Magid, D., Ney, D. R., Chaney, E. L., Pizer, S. M., Rosenman, J. G., Levin, D. N., Vannier, M. W., Kuhlman, J. E., and Robertson, D. D. 1991. Three-dimensional imaging. *Radiology* **81:** 321–337.

Fox, P. T., and Mintun, M. A. 1989. Noninvasive functional brain mapping by change-distribution analysis of averaged PET images of H2150 tissue activity. *J. Nucl. Med.* **30:** 141–149.

Fox, P. T., and Raichle, M. E. 1984. Stimulus rate dependence of regional cerebral blood flow in human striate cortex demonstrated by positron emission tomography. *J. Neurophysiol.* **51:** 1109–1120.

Grafton, S. T., Woods, R. P., Mazziotta, J. C., and Phelps, M. E. 1991. Somatotopic mapping of the primary motor cortex in humans: Activation studies with cerebral blood flow and positron emission tomography. *J. Neurophysiol.* **66:** 735–743.

Herscovitch, P., Markham, J., and Raichle, M. E. 1983. Brain blood flow measured with intravenous H2150. I. Theory and error analysis. *J. Nucl. Med.* **24:** 782–789.

Hess, C. W., Mills, K. R., and Murray, N. M. F. 1987. Responses in small hand muscles from magnetic stimulation of the human brain. *J. Physiol. (London)* **388:** 397–419.

Huntley, G. W., and Jones, E. G. 1991. Relationship of intrinsic connections to forelimb movement representations in monkey motor cortex: A correlative anatomic and physiological study. *J. Neurophysiol.* **66:** 390–413.

Ingvar, D. H., and Philipson, L. 1977. Distribution of blood flow in the dominant hemisphere during motor ideation and motor performance. *Ann. Neurol.* **2:** 230–237.

Lauritzen, M., Henriksen, L., and Lass, N. A. 1981. Regional CBF during rest and skilled hand movements by Xe-133 inhalation and emission CT. *J. Cereb. Blood Flow Metab.* **1:** 385–391.

Lükenhöner, B., Pantev, C., and Hoke, M. 1990. Comparison between different methods to approximate an area of the human head by a sphere. In *Auditory Evoked Magnetic Fields and Electric Potentials* (M. Grandori, M. Hoke, and G. L. Romani, Eds.), Vol. 6, pp. 103–118. Karger, Basel.

Mazziotta, J. C., Huang, S. C., Phelps, M. E., Carson, R. E., MacDonald, N. S., and Mahoney, D. K. 1985a. A noninvasive positron computed tomography technique using oxygen-15-labelled water for the evaluation of neurobehavioral task batteries. *J. Cereb. Blood Flow Metab.* **5:** 70–78.

Mazziotta, J. C., Phelps, M. E., and Wapenski, J. 1985b. Human cerebral motor system metabolic responses in health and disease. *J. Cereb. Blood Flow Metab.* **5** (Suppl.)**:** S213–S214.

Orrison, W. W. Jr., and Lewine, J. D. 1993. Magnetic source imaging in neurosurgical practice. *Perspect. Neurol. Surg.* **4:** 141–147.

Pelizzari, C. A., Chen, G. T. Y., Spelbring, D. R., Weichselbaum, R. R., and Chen, C. T. 1989. Accurate three-dimensional registration of CT, PET, and/or MR images of the brain. *J. Comput. Assist. Tomogr.* **13:** 20–26.

Penfield, W., and Boldrey, E. 1937. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* **60:** 389–443.

Penfield, W., and Jasper, H. 1954. *Epilepsy and the Functional Anatomy of the Human Brain.* Little, Brown, Boston.

Raichle, M. E., Martin, W. R. W., Herscovitch, P., Mintun, M. A., and Markham, J. 1983. Brain blood flow measured with intravenous H2150. II. Implementation and validation. *J. Nucl. Med.* **24:** 790–798.

Roland, P. E. 1984. Organization of motor control by the normal human brain. *Hum. Neurobiol.* **2:** 205–216.

Roth, B. J., Saypol, J. M., Hallett, M., and Cohen, L. G. 1991. A theoretical calculation of the electric field induced in the cortex during magnetic stimulation. *Electroencephalogr. Clin. Neurophysiol.* **81:** 47–56.

Rothwell, J. C., Thompson, P. D., Day, B. L., Boyd, S., and Marsden, C. D. 1991. Stimulation of the human motor cortex through the scalp. *Exp. Physiol.* **76:** 159–200.

Thompson, P. D., Rothwell, J. C., Day, B. L., *et al.* 1989. Mechanisms of electrical and magnetic stimulation of human motor cortex. In *Magnetic Stimulation in Clinical Neurophysiology* (S. Chokroverty, Ed.), pp. 121–143. Butterworth, Stoneham, MA.

Wang, B., Toro, C., Zeffiro, T. A., and Hallett, M. 1994. Head surface digitization and registration: A method for mapping positions on the head onto magnetic resonance images. *Brain Topogr.* **6:** 185–192.

Wassermann, E. M., McShane, L. M., Hallett, M., and Cohen, L. G. 1992. Noninvasive mapping of muscle representations in human motor cortex. *Electroencephalogr. Clin. Neurophysiol.* **85:** 1–8.

Waters, R. S., Samulack, D. D., Dykes, R. W., and McKinley, P. A. 1990. Topographic organization of baboon primary motor cortex: Face, hand, forelimb, and shoulder representation. *Somatosens. Motor Res.* **7:** 485–514.

Wilson, S. A., Thickbroom, G. W., and Mastaglia, F. L. 1993. Transcranial magnetic stimulation mapping of the motor cortex in normal subjects. The representation of two intrinsic hand muscles. *J. Neurol. Sci.* **118:** 134–144.

Woolsey, C. N., Settlage, P. H., Meyer, D. R., Sencer, W., Hamuy, T. P., and Travis, A. M. 1952. Patterns of localization in precentral and supplementary motor areas and their relation to the concept of a premotor area. *Res. Publ. Assoc. Res. Nerv. Ment. Dis.* **30:** 238–264.

Woolsey, C. N., Erickson, T. C., and Gilson, W. E. 1979. Localization in somatic sensory and motor areas of human cerebral cortex as determined by direct recording of evoked potentials and electrical stimulation. *J. Neurosurg.* **51:** 476–506.