This manuscript reviews the current stance and the pertinent problems of transcranial magnetic stimulation (TMS) and functional magnetic resonance imaging (fMRI) as brain mapping methodologies. The missing structure-function relation limits the use of TMS, whereas the uncertainty about the functional significance of activated cortical regions might render interpretation of fMRI studies difficult. Advances in image processing, however, allowed for 3-dimensional real-time visual guidance of TMS and integration with fMRI data. We describe the method used to coregister TMS and fMRI and present examples where a multimodality neuroimaging approach might add to our understanding of normal and pathological brain function.

Keywords: functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), brain mapping

INTRODUCTION
In human brain mapping, 2 basic strategies are used to obtain information about cortical function representation: recording brain activity during task performance (the internal approach) and observing the effects of eliciting or extinguishing brain activity (the external approach).

Techniques using the internal approach include electromagnetically based (magnetoencephalographic and electroencephalographic) investigations and methods measuring hemodynamic and metabolic responses (positron emission tomography [PET] and functional magnetic resonance imaging [fMRI]) to neuronal activation. These techniques are based on electrophysiologic, hemodynamic, or metabolic changes that occur during task performance and therefore depend on the collaboration of the subject. The internal approach allows for imaging the correlate of ongoing behavior and thus cannot give information about the causal relationships between certain cortical regions and cognitive processes.

The external approach, on the other hand, does not depend on subject cooperation, as external stimuli are used to elicit or extinguish brain activity. This approach investigates whether a specific region of the brain is critical for implementing particular cognitive functions and therefore is able to answer questions about causal relationships between brain and function. Techniques employing the external approach include lesion analysis, transcranial electric stimulation, and transcranial magnetic stimulation.

These 2 approaches investigate the human brain from different perspectives and are therefore complementary. In the past several years, though, brain-mapping studies employing the internal approach have by far outnumbered those employing the external approach. This was due in part to problems in noninvasively correlating the site of stimulation with the stimulated cortical region, in part because of the lacking locality of the stimulators. In this article, we (a) describe a refined electromagnetic stimulation protocol that makes electromagnetic stimulation suitable for human brain mapping and (b) discuss how the integration of different brain-mapping modalities in a multimodal approach might add to our understanding of how the brain works.

PART 1: TRANSCRANIAL MAGNETIC STIMULATION

Methods and Physiology
In 1985, Barker et al introduced transcranial magnetic stimulation (TMS) as an electrophysiologic tool for investigating human motor cortex and its

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connectivities. TMS gave neurophysiologists a painless, safe, and easy-to-use method for noninvasive investigation of the motor system at hand (Barker et al, 1985). TMS is based on the principle of electromagnetic induction. The brief discharge of a capacitor induces a primary current within the stimulating coil. This primary current generates a magnetic field that passes nearly unattenuated through the scalp and the skull and induces a secondary current within the conductive brain tissue. TMS thereby activates the human brain’s cortical areas, which have pathways descending to the α-motoneurons of the spinal cord. Theoretical studies have computed the induced electric field under different stimulating coils and have found that focal stimulation is possible using specially designed coils called figure-eight coils (Brasil-Neto et al, 1992a). Investigations of the human motor system, especially mapping of the human motor homunculus, are based on the relationship between the averaged amplitude of the peripheral recorded compound muscle action potential (CMAP) and the density of cortical motoneurons in the area of stimulation. The presumed mechanism of focal TMS at low intensities is primarily via activation of excitatory corticocortical interneurons. These interneurons in turn excite the corticospinal motoneurons. The amount of excitatory cortical input determines the number of descending volleys to the spinal cord. Here, the excitatory input is temporally and spatially summated, and α-motoneurons are recruited according to Henneman’s size principle. The amplitude of the recorded CMAP is determined by the number of activated spinal motoneurons (Wassermann et al, 1992). At low-stimulus intensities and without background contraction, there is a nearly linear relationship between the amount of excitatory input at the spinal level and the CMAP amplitude of the respective target muscle. By moving the coil in small increments over the scalp and observing and interpolating the amplitude changes in the evoked CMAP, a mapping accuracy of up to 0.5 cm can be obtained (Krings et al, 1997b).

Mapping of a subject typically takes place with the subject at rest and with the coil placed tangentially on the scalp with the handle pointing backward and perpendicular to the central sulcus. After determination of the resting motor threshold of the small hand muscles, sites approximately 1 cm apart over an array centered on the central sulcus are stimulated. This array is determined by the size of the cortical output map and typically consists of 4 × 6 sites. Multiple stimuli are applied to each site to prevent CMAP amplitude variability due to cortical fluctuations in excitability (Kiers et al, 1995). CMAPs are recorded from the muscles of interest using Ag–AgCl surface electrodes applied with a muscle-belly-tendon montage, filtered and recorded by electromyography.

Motor System
TMS has been established as a noninvasive tool for investigating the central nervous motor system both in patients and normal subjects (Chiappa, 1994). Clinical applications of TMS include monitoring the integrity of the spinal cord during back surgery (Herdmann et al, 1993), assessing rehabilitation prognosis after stroke (Berardelli et al, 1990) or during coma (Zentner and Epner, 1988), investigating the development of the spinal tract (Muller et al, 1991), and measuring the central nervous conduction time under various pathologic circumstances including multiple sclerosis (Hess et al, 1987) and spinocerebellar degeneration (Claus et al, 1990), to name a few.

TMS mapping of the human motor cortex has been used to assess the cortical representation of muscles of the upper and lower extremities and of the face in normal subjects and in patients with mirror movements, amputations, and brain tumors (Cruccu et al, 1990; Cohen et al, 1991; Levy et al, 1991; Wassermann et al, 1992; Verhagen Metman et al, 1993). Maps showed a large degree of short- and long-term consistency within an individual and demonstrated the expected somatotopy of different muscle groups along the mediolateral axis. TMS mapping even allowed the representation of individual hand muscles in the primary motor cortex to be reliably and reproducibly mapped (Wilson et al, 1993). Motor system reorganization was demonstrated in normal subjects following experimental deafferentation (Brasil-Neto et al, 1992b), in motor task learning in normal subjects (Pascual-Leone et al, 1995), and in patients with peripheral and central lesions (Topka et al, 1991). The common element observed with TMS in all these studies is a marked functional plasticity in the cortex with an ability to remodel its excitatory bias according to changes in peripheral nervous system activities, the demands of motor performance enforced from higher levels of consciousness, or the enhanced activity consequent to the increased demands. However, cortical representation maps were typically related to bony landmarks defined by the International 10–20 system of electrode placement. Therefore, no study was able to relate maps to individual cortical anatomy.

Language and Other Cortical Functions
When investigating the motor system, TMS is used to excite cortical neurons and thereby produce an efferent response. In the evaluation of higher cortical functions including language testing, however, TMS is typically used to interfere with specific cortical functions, which leads to the interruption of cognitive processes. To disrupt cortical activity, the induced electrical charge following single-pulse TMS is often insufficient. Instead, rapid-rate TMS (rTMS) with fast repetition rates (up to
100 Hz) is necessary to map these functions. rTMS provides an interesting new window into brain function by creating transient deficits in normal subjects (Pascual-Leone et al, 1991). Therefore, cognitive neuroscience researchers might find a use for this new method in mapping and timing cortical activity (Flitman et al, 1998). So far, rTMS has been successfully used to determine the lateralization of the motor speech area by stimulating over frontotemporal regions while subjects counted or named pictures. In these studies, a high concordance with the intracarotid amytal (Wada) test as the gold standard for speech lateralization was found (Jennum et al, 1994). It was suggested that rTMS might be helpful in the noninvasive investigation of hemispheric dominance for presurgical planning of temporal lobe surgery. Other higher cortical functions tested included memory and visual processing. Memory processes (verbal recall) were specifically disrupted with rTMS when stimulating over left midtemporal and bilateral frontal areas, and selective visual extinction was produced by stimulating over the contralateral parietal lobe (Pascual-Leone et al, 1994). However, safety concerns have so far limited the use of rTMS in larger patient and normal subject populations.

Limitations of TMS
The anatomical representation of cortical function using conventional TMS mapping techniques is related to bony landmarks, typically defined by electrode positions of the International 10-20 system. Maps of the human motor cortex are not related to the individual 3-dimensional (3D) gyral anatomy but are instead restricted to a 2-dimensional (2D) grid based on bony landmarks of the skull (Steinmetz et al, 1989). This form of representation has 2 major drawbacks—the distortion that occurs when a 2D map is represented on a 2D coordinate system and the missing relation between the stimulated cortical area and the scalp position over which the coil was positioned. The variability of the individual cortical anatomy in relation to bony landmarks renders interindividual comparison very difficult and prevents establishing a structure–function correlation. This correlation, however, is essential for any brain-mapping methodology. Although cortical motor output maps demonstrated the somatotopic order of the motor region, they could not be used for presurgical planning of surgery near the central region. Moreover, the mapping of higher cortical functions was made impossible, and TMS was restricted in its possible applications.

Stereotactic Transcranial Magnetic Stimulation
Recent advances in image processing have allowed refinement of current TMS mapping strategies by combining nuclear magnetic resonance (NMR) imaging modalities with TMS using a 3D digitizer to measure the position of the stimulating coil and map this position onto a MRI data set. A frameless stereotactic system (FSS), which is rigidly fixated to the stimulating coil, is used to correlate scalp stimulation sites with the underlying brain anatomy in real time—thereby combining the anatomical accuracy as provided by MRI with the functional motor specificity as provided by TMS and introducing stereotactic TMS (STMS) as a new brain-mapping modality. The accuracy of this new technique was validated by correlating STMS maps with cortical output maps obtained with direct electrical cortical stimulation (DECS; Krings et al, 1997b) and to IMRI motor output maps (Krings et al, 1997a). In addition to the structure–function correlation of STMS, this technique further allowed for integrating different brain-mapping methodologies by providing a common coordinate system for DECS and IMRI maps.

Coregistration of anatomical NMR data to TMS sites during the TMS session is obtained with the aid of an FSS, which consists of a jointed mechanical arm functioning as a stereotactic 3D digitizer plus a computer workstation (Fig. 1). Optical encoders in each of the 5 joints of the arm continually measure the angular position of the joint and transmit this information to the computer graphics workstation, which computes the spatial position of the tip of the arm in real time and plots it on the MRI data set of the individual’s head (Krings et al, 1998a, 1998b).

The subject’s head is spatially coregistered to the MRI by means of fiducial markers identified both on the MRI data set after imaging is completed and on the head during the TMS session. From those 2 sets of coordinates is calculated a matrix transformation that allows the computer to display the coordinates of the arm tip on the 3D MRI in real time. As the arm tip is moved around the subject’s head, its position is graphically displayed on the 3D MRI data set in the sagittal, coronal, and axial plane in real time. The arm tip must be modified in 2 ways for use with magnetic stimulation. First, an adapter is built to attach the arm tip rigidly to the stimulating coil so that the peak electrical field, which is induced under the intersection of both loops of the coil, is collinear with the distal arm tip. Second, the perceived length of the distal arm tip is modified in the stereotactic arm software so that, when the coil is applied to the scalp, the computer displays the location on the cortical surface where the peak electric field and therefore the stimulation are most likely to occur. The localization error of this system primarily results from inaccuracies in the identification and matching of the fiducial markers on the MRI and on the subject’s head. Typically, this error is quantified by the software of the FSS as
the discrepancy between the actual spatial localization of the landmarks on the subject as compared to that predicted by MRI in all 3 dimensions. Coregistration has to be reestablished if an error greater than 3 mm is detected during or between stimulation series. In this way, inaccuracies due to undetected motion of the subject's head are avoided.

**Clinical Applications of STMS**

Combining the stimulating coil with an FSS has several advantages. Reproducibility of TMS maps is increased, as the system can be easily recalibrated after patient movement and during each stimulation train, and the angle and the position of the coil on the scalp can be held constant and verified by real-time visual guidance using the FSS. Understanding the relationship between underlying cortical anatomy and the scalp stimulation site is especially important when evaluating higher cognitive functions with TMS and can be accurately assessed using this method. STMS also extends prior mapping studies by demonstrating in 3 dimensions the functional localization of different muscles over the cortical convexity, rather than superimposed on a distorted 2D view. Furthermore, the functional information related to the individual’s anatomy is indispensable for presurgical planning.

The utility of STMS for presurgical planning depends mainly on the spatial resolution and the application error of the method by which TMS is used. The approximate smallest area of stimulation at rest with a commercially available figure-eight coil (lobe diameter, 7 cm) is an area of 1 to 2 cm². At first glance, this area seems too large to yield useful mapping information. However, increased resolution can be obtained by moving the coil in small increments and observing the amplitude changes in the evoked peripheral CMAP and interpolating a peak location. Moreover, stimulating just over threshold and without facilitation can enhance accuracy. The inherent localization error of the stereotactic system depends mainly on calibration accuracy and typically ranges from 2 to 8 mm (Spetzger et al, 1995).

From data comparing DECS and STMS, we were able to estimate the accuracy of this method. Motor evoked potentials (MEPs) larger than 75% of the maximum MEP for a given muscle mapped to within 5 mm of the cortical motor area as determined by DECS with a probability of 75% and within 10 mm with a probability of 100%. MEP responses smaller than 50% of maximum never mapped closer than 5 mm to their respective cortical area. TMS mapping of the genioglossal muscle demonstrated even better correlation with DECS presumably because its cortical representation is more confined than that of the arm and finger muscles (Krings et al, 1997b). Using fine stimulation grids and interpolation, a spatial resolution of 0.5 cm is therefore readily obtainable.
**Methods and Physiology**

The physiologic basis of fMRI is thought to be a local hemodynamic change during neural activity (Kwong et al, 1992). Neuronal activity in the cortex produces increases in tissue metabolism and regional cerebral blood flow (rCBF). A localized increase of neuronal activity is accompanied by aerobic metabolism, which leads to an increase in deoxyhemoglobin. This is followed immediately by compensatory blood flow and volume redistribution from within the capillary bed, which occur so rapidly that any decrease in oxyhemoglobin levels is difficult to register even with imaging spectroscopy (Malonek and Grinvald, 1996).

There is then a delayed increase in the oxyhemoglobin concentration, as the increase in oxygen delivery is higher than the consumption of oxygen in the activated tissue. rCBF is regulated by the amount of neuronal activity—by alterations in the concentration of the K+ ion, which is released by neural activity, or by other metabolic factors such as lactate, or by neurogenic vascular coactivation possibly mediated by nitric oxide. It has been further hypothesized that the magnitude of the change in rCBF is directly influenced by the size of the responsive area and by the number of active neurons. Taking these assumptions into consideration, it is likely that cortical areas with more and a higher density of cortical motoneurons produce a larger increase in rCBF and venous oxygenation than cortical areas with fewer motoneurons (Krings et al, 1997a).

T2* changes are used to detect changes in CBF, cerebral blood volume (CBV) and oxygenation. Deoxyhemoglobin is more paramagnetic than surrounding tissue, resulting in a higher magnetic inhomogeneity and a lower T2* signal intensity; a decrease in the concentration of deoxyhemoglobin thus leads to a more homogeneous environment and a higher signal intensity (Kwong et al, 1992). These properties have been used extensively to evaluate hemodynamic changes during physiologic activation.

**Limitations of fMRI**

Some problems with fMRI must be considered and accounted for using elaborate data analysis.

1. **Motion Correction.** One challenge during fMRI is the problem of head motion during image acquisition. As scanners equipped with echo planar imaging (EPI) can obtain images of the whole head during a fraction of a second, motion occurring within a single scan is of less importance than motion occurring between different scans. Patient cooperation and rigid head fixation play a major role in avoiding these movement artifacts. However, minimal head movements cannot be excluded from any study. Random movements of the subject will decrease the overall signal-to-noise ratio. In this case, motion correction algorithms should reduce the overall noise level and thereby increase the relative signal level. However, artifacts due to stimulus-synchronous movements of the head, which typically occur during forced motor activation, mimic brain activation, as the signal change will be correlated with the task paradigm. This artifact typically occurs at the edges of the brain, as the brightness differences at adjacent voxels is most pronounced. Motion correction algorithms account for both random and stimulus-correlated motion and thereby increase both the statistical strength (by increasing the signal-to-noise ratio) and the validity (by reducing motion-correlated artifacts) of the functional activation (Hajnal et al, 1994; Weisskoff, 1995).

2. **Statistical Tests.** Another problem of fMRI is its low contrast-to-noise or contrast-to-artifact ratio. MRI signal changes on brain activation vary according to the used task, the sequence parameters, and the scanner hardware but are typically on the order of 2% to 5% from the baseline condition. These changes in MRI signal intensity are only slightly more pronounced than changes in the MRI intensity occurring by chance or due to physiologic noises such as respiration, cardiac rhythm, or brain pulsation. Therefore, elaborate statistical tests must be employed to discern noise from activation (Kwong, 1995).

3. **“Brain or Vein?”** One major limitation of fMRI is the still unknown relationship between the localization of the depicted task-related hemodynamic changes and the cortical area of neuronal activity. This so-called brain-or-vein problem describes the lack of knowledge as to whether large draining veins, which have no close relationship to the areas of cerebral activation or small parenchymal venules in close proximity to the sites of neuronal activity, are depicted during BOLD fMRI. The size and nature of the involved blood vessels and their spatial relationship to the activated cortex are not precisely known. Functional imaging studies related to hemodynamics are subject to concerns that the techniques might be depicting larger blood vessels downstream from the actual activation site, especially given that Kwong et al (1992) observed an activation response time of...
Therefore, the fMRI scan must be volume-rendered. A photograph can be merged with the fMRI scan. (gyri, sulci, veins) at the intraoperative sites. This numbered tags and of the relevant cortical anatomy image-processing strategies may be used.

Physiologic data with the fMRI results, two different approaches to visualize cortical functions are important.

4. Low Specificity. Multiple areas of the brain are active during the voluntary performance of a motor task, but not all of them have pathways descending to the spinal-cord α-motoneurons. Planning of the task, coordination of the temporal sequence of the performance, and coactivation or even inhibitory effects within the cortex may be represented as fMRI-activated brain areas. Therefore, fMRI of the motor system does not answer the question about the functional significance of activated cortical regions.

Because of these problems and potential pitfalls, cross-validation with brain-mapping modalities using different approaches to visualize cortical functions are important.

Multimodality Imaging
Multimodality imaging offers various approaches to reach the goal of integrating and thereby cross-validating fMRI data with electrophysiologic data.

The gold standard against which every brain-mapping modality must be tested is DECS during open brain surgery (Penfield and Boldrey, 1937). DECS is typically performed with a handheld bipolar probe (eg, 2-mm ball tips, 5-mm spacing) and a constant current stimulator (eg, 50-Hz, biphasic, pulse width 1.0 ms) broadly over the exposed cortical surface. Sensorimotor responses can be mapped either by asking the conscious patient to describe what is felt after a stimulus is presented and by observing motions of the upper extremity or by recording motor evoked potentials of muscles with the patient under anesthesia. Each cortical site must be tested at least twice to ensure reproducibility. Stimulation sites are typically marked intraoperatively with sterile numbered tags. To combine these intraoperative electrophysiologic data with the fMRI results, two different image-processing strategies may be used.

One approach is to take a photograph of the sterile numbered tags and of the relevant cortical anatomy (gyri, sulci, veins) at the intraoperative sites. This photograph can be merged with the fMRI scan. Therefore, the fMRI scan must be volume-rendered and fused with a 3D anatomic MRI scan, which can be performed using conventional image-processing tools (eg, ANALYZETM, Mayo Clinic, Rochester, MN; MPI Tool, Cologne, Germany). These image-processing tools also allow for free rotation of the fused images and therefore for demonstrating functional data in the same angle in which the intraoperative site was photographed. The intraoperative photograph can now be fused with the 3D MRI set by means of anatomical landmarks (sulci, gyri, veins)and the location of the sterile numbered tags can thereby be directly compared to the preoperative functional data (Fig. 2).

An alternative approach to fuse intraoperative DECS data with fMRI data is to use an FSS (Krings et al, 1998a). As described earlier, this navigational system can demonstrate the 3D location of the arm tip on an MRI scan in real time. When pointing at the stimulation site from which motor evoked potentials are recorded, the FSS calculates the 3D coordinates of the stimulation points and records them in the MRI data set. During image postprocessing, both fMRI and DECS data are therefore displayed in the same coordinate system, enabling an even better coregistration of both techniques (Fig. 3).

In addition, an FSS can be used to coregister STMS data (obtained by the technique already described) with fMRI data. Using this method, noninvasive electrophysiologic information can be fused with fMRI data. This broadens the spectrum of normal subjects and patients who can be investigated with an integrated brain-mapping protocol employing both electrophysiologically and hemodynamically based methods (Figs. 4 and 5).

Applications
One major limitation of fMRI is the still unknown relationship between the localization of the depicted task-related hemodynamic changes and the cortical area of neuronal activity. As fMRI depicts hemodynamic changes in the human brain, it is subject to the concern that larger vessels downstream from the actual site of neuronal activation are depicted instead of neuronal tissue (Krings et al., 1999). This problem becomes especially important if fMRI results are used for presurgical mapping of functional cortical areas in relationship to underlying brain lesions (Krings et al, 1998c). Cross-validation with other mapping methodologies is therefore important in determining the spatial resolution of fMRI and the validity of the results. It is only because of new imaging technologies that the integration and therefore cross-validation of fMRI have been made possible. Using this integrated approach, we were able to validate fMRI findings. Other implications of the integrated brain-mapping approach are as follows.

As our mapping protocol is noninvasive and free of any known risks, electrophysiologic data can
readily be obtained noninvasively from normal subjects and patients. Thus, one possible future role for the STMS mapping technique is the assessment of motor reorganization. New pathways that may contribute to the MEP after motor recovery (e.g., cortical unmasking of “sleeping” motor areas secondary to disinhibition; switching to pathways other than the corticospinal tract) can be detected and related to cortical anatomy. If brain activation during the performance of a motor task is not restricted to the primary sensorimotor cortex, the question about the functional motor significance of these findings can be answered in part by using this TMS technique to differentiate the subset of cortical areas with descending pathways from the larger area that shows activity on fMRI or PET. Preliminary results in patients recovering from stroke suggest that some new areas of fMRI activation with a motor task do not have direct peripheral motor system connections. Moreover, as rTMS is now available for the evaluation of language function, language mapping or lateralization may become an important application for our integrated mapping technique. Different approaches to investigating the human brain reveal additional information about each technique and the underlying brain physiology. Combining the anatomical accuracy and focality of fMRI with the functional motor system specificity of TMS therefore constitutes a useful brain-mapping methodology. We conclude that the combination and integration of different brain-mapping methodologies cross-validate these new techniques and reveal additional information that cannot be obtained by each method alone. Advances in image processing, data analysis, and computation have given both the clinician and the researcher powerful tools with which to investigate the human brain.
Figure 3. Stereotactic transcranial magnetic stimulation (STMS) and direct electrical cortical stimulation (DECS) map in a patient undergoing presurgical evaluation. Preoperative and intraoperative data were fused using the frameless stereotactic system already used for STMS. Thereby, direct comparison of STMS and DECS is possible. The perceived length of the distal arm tip was modified in the stereotactic arm software so that, when the coil was applied to the scalp, the computer displayed the cortical location where the peak electric field and therefore the stimulation most likely occur (intersection of the oblique white area and the horizontal line). In the right panel, the peak compound muscle action potential is obtained at the intersection of the vertical and horizontal lines. Because of intraoperative brain shift, this area seems to lie within the tumor but was in fact located anteriorly in the gray matter. The distance between STMS and DECS was 4 mm.

Figure 4. Coregistration of functional magnetic resonance imaging (fMRI) and stereotactic transcranial magnetic stimulation (STMS) in a patient with a left frontal meningioma. fMRI (right frame) following finger opposition reveals a widespread activation in the primary sensorimotor area, presumably due to sensory feedback with concomitant activation within S1. fMRI was obtained with a T2*-weighted multislice gradient echo Echo planar imaging (EPI) sequence (TR/TE/FA, 4000/40/40) and was overlaid on a 3-dimensional (3D) fast field echo (FFE) sequence also used for displaying the STMS responses (TR/TE/FA, 30/4.5/30). Activation is also observed at the tumor margin—presumably representing a large draining vein. The white oblique line demonstrates the direction of the coil in 3D; the point of intersection demonstrates the presumed area of stimulation. The compound muscle action potential (CMAP) of the abductor pollicis brevis was recorded during electromyography. Of all activated regions during fMRI, the primary motor cortex was exclusively activated by STMS. A multimodal approach to mapping the motor cortex therefore helps in differentiating the various cortical areas involved in motor processing visualized during fMRI and might be, as demonstrated in this case, helpful for the patient in preoperative assessment of cortical function.
Figure 5. Coregistration of functional magnetic resonance imaging (fMRI) and stereotactic transcranial magnetic stimulation (STMS) in a healthy right-handed subject. During fMRI, the subject was asked to move his left hand (repetitive finger-to-thumb-pad opposition), which resulted in a large activation within the right precentral gyrus (arrowhead) and a smaller activation within the ipsilateral (left) primary motor cortex (arrow) on 2 subsequent axial slices. When stimulating over the latter area, no compound muscle action potentials (CMAPs) could be elicited. In this case, the multimodal approach helps in evaluating the functional significance of the ipsilateral activation observed during fMRI. As we were not able to demonstrate CMAPs from this cortical area to the ipsilateral hand muscles, we can conclude that the fMRI activation is presumably not related to a direct innervation of the left hand by both motor cortices. With fMRI alone, this information would not be available. The ipsilateral activation seen in this patient might relate to activation following crossed inhibition, as was demonstrated by Chiappa et al (1995). As the firing of inhibitory neurons (and excitatory neurons) might lead to an increase in cerebral blood flow in their respective cortical areas, fMRI activation may be perceived in the ipsilateral inhibited cortex.

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