Functional Magnetic Resonance Imaging of Regional Brain Activity in Patients with Intracerebral Gliomas: Findings and Implications for Clinical Management

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Functional Magnetic Resonance Imaging (fMRI) was performed in seven patients harboring intracerebral gliomas proven by histological analysis using a noninvasive blood oxygen level-dependent technique based on the documented discrepancy between regional increases in blood flow and oxygen use in response to regional brain activation. We combined fMRI with conventional magnetic resonance imaging (MRI) during motor or language task activation experiments to investigate the potential usefulness of mapping regional brain activity as part of treatment planning in patients with intracerebral gliomas, in whom preservation of areas of functioning brain tissue is critical. Statistical fMRI maps were generated and directly mapped onto conventional MRI scans obtained at the same session. Of the five patients cooperative enough to remain motionless for the study and perform the task, the location of activation in the primary sensorimotor cortex on the side of the tumor was clearly displaced compared with that in the normal contralateral hemisphere in four patients. Four of the five tumors in these patients showed fMRI activation within the periphery of (or immediately adjacent to) areas of presumed tumor based on spin-echo MRI. In some patients with neurological deficit, the extent of activation was reduced on the side of the tumor as compared with the normal hemisphere. The supplemental motor area and the ipsilateral primary motor cortex were also reproducibly activated during motor tasks. We conclude that blood oxygen level-dependent fMRI can localize areas of cortical function in patients undergoing treatment planning for gliomas so that therapy can be directed away from regions of residual function. Our preliminary data suggest that functioning cortex within or adjacent to tumor margins can be demonstrated, which may correspond to partial preservation of clinical function. Our preliminary data also suggest that there may be a quantifiable difference on fMRI between activation in tumor-bearing cortex and activation in corresponding normal cortex in the contralateral hemisphere. We postulate that the magnitude of this difference may relate to the severity of patient deficit. (Neurosurgery 38:329–338, 1996)

Key words: Functional magnetic resonance imaging; Glioma; Magnetic resonance imaging, brain

Magnetic resonance imaging (MRI) has become recognized as the most sensitive and specific imaging modality for the diagnosis and follow-up of primary intracranial tumors. The use of intravenous contrast agents has also become common in the evaluation of these lesions, because contrast enhancement is thought to be beneficial in differentiating certain histopathological types of gliomas and in defining the extent and spread of tumors. The characteristics of infiltrative gliomas that are routinely demonstrated on MRI are entirely anatomically and morphologically based; that is, signal intensity patterns and the features of space-occupying lesions are a reflection of static gross and microscopic abnormalities. It has become standard practice to base treatment planning for gliomas on the
morphic abnormalities defined by these routine MRI techniques. Notwithstanding the (presumed) high sensitivity of MRI for gliomas, conventional imaging of these lesions leaves many important questions unanswered. For instance, it has been shown that tumor tissue frequently extends well beyond the margins of enhancement (13, 18, 22) and even beyond the borders of signal abnormality on T2-weighted MRI. Moreover, MRI signal intensity patterns and contrast enhancement characteristics are notoriously nonspecific (1). This nonspecificity, in conjunction with the knowledge that a vast majority of these lesions ultimately undergo surgical biopsy and/or debulking for definitive histological assessment, implies that it may not be essential or even realistic to determine histopathology with MRI. Rather, it may be even more important to identify residual function in nearby or involved cortex so that these areas can be avoided during surgery. It is also well known that the degree of neurological impairment in patients harboring gliomas in similar neuroanatomic locations on conventional MRI is variable. The infratentorial nature of certain gliomas (8) can be invoked to explain this phenomenon of partial preservation of function, in which tumor infiltrates but partially spares normal brain tissue and, therefore, spares brain function.

Blood oxygen level-dependent (BOLD) contrast imaging (26, 27) is a noninvasive functional MRI (fMRI) technique for localizing regional brain signal intensity changes in response to task performance (4, 28, 34). This technique uses no intravenous contrast agents and mainly depends on regional changes in endogenous intravascular paramagnetic deoxyhemoglobin (3). Signal intensity changes in BOLD fMRI are attributed to the documented mismatch between the increases in regional cerebral blood flow and cerebral blood volume and the much less profound increase in oxygen use in response to regional activation (14,15). As opposed to contrast bolus MRI techniques (5,6) and positron emission tomography (PET), the performance of BOLD fMRI measurements are not limited by contrast agent dose or radiation limits, so several activation experiments can be performed without these considerations.

In this study, we combined BOLD fMRI with conventional spin-echo imaging to investigate the potential usefulness of mapping regional brain activity as part of treatment planning in patients with intracerebral gliomas, in whom preservation of areas of functioning brain tissue is critical. We hypothesized that spared brain tissue within apparent tumor margins would be identifiable on fMRI in patients with infiltrative gliomas and partially preserved neurological function. We also hypothesized that a quantifiable difference in activation between abnormal and corresponding uninvolved cortex in the contralateral hemisphere can be demonstrated by fMRI, using tasks known to have significant bilateral cerebral representation (e.g., motor) (9, 23, 31, 32), and that the magnitude of this difference may correspond to the severity of neurological deficit.

PATIENTS AND METHODS

Patients

We performed fMRI studies on seven right-handed patients (ages 17–52 yr) with documented intracerebral gliomas in or near regions of primary motor or auditory cortex. Informed consent was obtained from all patients before they were entered into the study, which was approved by the Institutional Review Board and the Human Subjects Committee. Two of the seven patients were not able to cooperate for the study (all data were degraded by gross motion artifact) and, therefore, were excluded from further analysis. In the five cooperative patients, the specific histopathological diagnoses of glioblastoma (n = 2) or anaplastic astrocytoma (n = 3) were established by histopathological study in all patients, either before or after the MRI examination. Of these five patients, two showed motor deficits during clinical neurological examination, corresponding to the side of involvement by the tumor. Two other patients had word-finding difficulties but were otherwise intact, and one patient had cognitive changes but no focal deficit. No other neurological deficits were noted in these patients. None of the patients were taking medications that were thought to potentially affect cerebral blood flow.

MRI technique

All patients underwent both conventional MRI and fMRI. MRI was performed with a standard product quadrature whole-head transmit-receive coil on a 1.5-T GE Signa scanner (Signa, Milwauk ee, WI), using a prototype whole-body echoplanar imaging (EPI) gradient system capable of producing 2.3 G/cm with 150-microsecond switching times. Four cushions were used to comfortably immobilize the head. We used a multislice, single-shot, gradient echo, 64 × 64-matrix EPI for fMRI with a TR of 1000 to 2000 milliseconds, a TE of 50 to 70 milliseconds, and a flip angle of 90 degrees. In-plane resolution for the fMRI images equalled approximately 3 × 3 mm. Gradient strengths used in our patients ranged from 1.0 to 1.25 G/cm.

As a result of evolving improvements in hardware and software over the course of the study, images were acquired at 4 to 6 levels every 1 to 2 seconds in the four patients using single-activation experiments, and at 12 levels every 2 seconds in the three patients using multiactivation experiments, for total acquisition times of as long as 4 minutes (the two patients who could not adequately cooperate both underwent single-activation paradigms). Twenty seconds of dummy scans preceded all fMRI sequences. Corresponding axial spin-echo T1-weighted (TR, ≤600 ms; TE, ≤25 ms) or T2-weighted (TR, 3000 ms; effective TE, 80 ms) images were obtained at the same slice locations during the same imaging session for precise localization on subsequent superimposition maps. Each patient also had undergone complete pre- and postin­travenous contrast-enhanced conventional MRI studies within 10 days of the fMRI study at a separate imaging session.

fMRI activation paradigms

Activation paradigms were selected for each patient on the basis of lesion location, as demonstrated by sagittal and axial spin-echo MRI at the time of the fMRI study. In the first four patients studied, single-activation paradigms were used, in which a 40-second baseline of no activity was ensued by a
single 40-second period of task performance, after which 40 seconds of no activity ensued. Multiactivation (repeated task performance) paradigms in the three most recently studied patients involved six cycles of baseline/activation, each of which were 20 seconds in duration.

Motor activation tasks consisted of simple, self-paced, sequential (i.e., four, three, two, one, and repeat) unilateral or bilateral finger movements (digit movement was chosen to minimize head motion and because of the relatively large cortical representation of fingers and hands in humans [16, 17]). Patients were instructed on the task and then were allowed to briefly practice before any imaging. All patients performed the task as rapidly as possible, and their speeds varied according to neurological status. Of our motor paradigm patients, three were studied with a single-activation paradigm, whereas three were studied with a multiactivation paradigm. In one of these patients, in whom a left frontotemporal mass was present and difficulties in word finding were noted during clinical examination, a task designed to activate the inferior frontal lobe was also used (10, 19). In one patient with a temporal lobe mass, the activation protocol used auditory stimuli that were presented approximately one per second via the scanner intercom system, to which the patient responded by a slight flexion of the left hallux. The semantic judgment task, designed to activate superior temporal gyrus in this patient (11), required the patient to listen to a series of words and give a positive response for exemplars of the category “vegetables.” This task was compared with a resting baseline.

Data analysis
The raw image data were transferred via Ethernet to a SPARC workstation (Sun Microcomputers, Mountain View, CA) or to a Macintosh Quadra 700 (Apple Computers, Cupertino, CA) for reconstruction and analysis. A computer program was developed in IDL (Research Systems, Inc., Boulder, CO) for performing off-line image reconstruction and all data analysis. The program uses the widget routines of IDL to provide a graphical user interface to all program functions. The EPI image sets were smoothed in plane using a $3 \times 3$ kernel. An in-plane least squares motion correction was applied; that is, the image was shifted to minimize the squared difference between the image and the reference image (the image obtained just before the initiation of a given experiment).

Correlation maps (2) were generated using cross correlation between the input function (i.e., the task performance) and the image time-course intensity change on a pixel-by-pixel basis. Correlation maps were generated at each possible discrete time shift, in units of TR, using a convenient property of the Fourier transform. The time shift at which the correlation was maximum in each pixel was selected for further processing. Cutoffs for both correlation coefficient and percent activation were used in viewing the resulting maps. To further reduce the contribution of random pixel noise, isolated pixels were removed by opening the thresholded maps with a two-pixel structuring element using the morphological erosion and dilation operators.

The IDL program permits viewing of the correlation maps at a specific time shift or as a maximum correlation map. In addition to the correlation cutoff, an activation threshold of 0.5% was used in displaying the maps. When viewing the maximum correlation map, a time-shift cutoff of 12 seconds was set to segment positive and negative correlations. That is, correlation maximums occurring within 12 seconds (or 12/TR time shifts) were given positive values, and those occurring after 12/TR time shifts were given negative values. Correlation thresholds that resulted in $P$ values of $<0.01$ were used for viewing the functional maps. $P$ values for the maximum cross correlation maps were determined as follows. $P$ values for the correlation maps were determined from the complementary error function ($\text{erf}$). For $N$ images and a correlation threshold of $\text{cor}$, the $P$ value for a preselected pixel at a single time shift can be determined from Equation 1, as follows: $P = 1 - \text{erf}(\text{cor} \cdot \sqrt{|N|}) / (\sqrt{2})$ where $P = 1 - \text{erf}$. For the maximum correlation map that samples across all time shifts, $P_{\text{max}} = 1 - (1 - P_{\text{cor}})^{12} \approx 8$ (Equation 2). The nearest neighbor-corrected $P$ value ($P_{\text{nn}}$) is determined by the following equation: $P_{\text{nn}} = P_{\text{max}} \cdot (1 - [1 - P_{\text{max}}] \div 8$ (Equation 3). A Bonferroni correction ($P_{\text{bon}}$) is also applied for an alpha level of 1500 pixels (which is a generous estimate), so $P_{\text{bon}} = 1 - (1 - P_{\text{cor}})^{1500}$ (Equation 4).

This analysis assumes a gaussian distribution from the error function. Also, $P_{\text{bon}}$ is the $P$ value for any pixel achieving threshold value and does not presuppose a positive or negative activation. The $P$ value for positive activations is actually different from that for negative activations, depending on the value of the time-shift cutoff. For positive activations, the value of $N$ in Equation 2 would be time-shift cutoff/TR. Thus, with a time-shift cutoff of 12, positive activations are more significant than negative activations. Similarly, they are more significant than $P_{\text{bon}}$ as it is determined here.

All quantitative analysis was performed on original $64 \times 64$ data; superimposed activation maps onto spin-echo images were interpolated to $256 \times 256$ for display. The thresholded activation maps were overlaid onto T1- or T2-weighted axial images at the same slice location. Images demonstrating gross motion were disqualified from further analysis. The location of significant activity, as defined by our methods, was noted and compared with the location of spin-echo-defined regions of presumed tumor by direct mapping of activation correlation maps onto spin-echo images. Regions of interest analysis was performed on activated regions in or near expected anatomic locations. The mean percent activation, the mean correlation coefficient, and the number of voxels meeting activation criteria in the regions of interest as well as the time-shift distribution of the activated voxels were automatically determined.

For the two most recent patients with tumors involving the motor cortex, in whom we used our multislice multiactivation protocol, an activation index (AI) (number of activating pixels on the side of the abnormality + number of activating pixels on the normal side) was calculated as a relative value for each patient and compared with clinical findings to determine its possible relationship to severity of clinical deficit. Our ratio-
nale for calculating such an index only in these patients was based on the presumption that quantitative analysis was appropriate only in patients in whom the complete extent of potential brain activity was studied. This index was considered in light of previously documented bilateral representation of unilateral motor function (23), which was recently shown to be more prominent for left motor cortex activation, particularly in right-handed patients.

RESULTS

Two of the seven patients (one single-activation, one multiactivation paradigm) were unable to be diagnosed (one patient was degraded by gross motion, and one could not cooperate for task performance because of cognitive deficits). Activation was demonstrated in expected primary sensorimotor areas in the remaining five patients in some or all series.

Of five patients cooperative enough to remain motionless for the study and perform the task, the location of activation in primary sensorimotor cortex on the side of the tumor was clearly displaced compared with that in the normal contralateral hemisphere in four patients. Four of the five tumors showed fMRI activation within the periphery of (or immediately adjacent to) areas of presumed tumor on the basis of spin-echo MRI abnormality.

In the five cooperative patients using our motor paradigm, neither of the 2 single-activation experiments yielded significant activation in contralateral primary motor cortex (Area 4 or M1) and 11 of 11 multiactivation experiments yielded significant activation in primary motor cortex contralateral to the side of the hand performing the task, with intensity changes ranging from 0.6 to 1.6% (using 0.5% as the minimum magnitude to meet our threshold value). No activation in the lateral premotor cortex (lateral aspect of 6aa) was observed in any of our motor paradigm tasks at our significance thresholds. Small regions of activation were also detected in the ipsilateral primary motor cortex in three of our unilateral motor task experiments (two right hand motion and one left hand motion) using our statistical significance criteria.

All four primary auditory cortex activation experiments in the one patient examined with this paradigm demonstrated significant activation in the superior temporal lobes (three of four bilaterally and one of four only in the left temporal lobe), with magnitudes of activation ranging from 2.0 to 5.3% (mean, 3.0%). The neuroanatomic localization of activation was consistent with that of prior studies (7). No consistent difference in magnitude was noted between the left and right temporal lobes. The extent of activation in the superior temporal lobes was greater on the left than the right side in all four experiments (left mean, 41.5 pixels; right mean, 15.0 pixels). In a multislice paradigm designed to activate the inferior frontal lobe, two of three experiments yielded significant activation, with magnitudes of activation ranging from 2.2 to 2.6%. In this paradigm, bilateral inferior frontal and bilateral temporal lobe activation was noted.

In two tumor patients with motor deficits in whom our multiactivation paradigm was used, an AI for primary motor cortex was calculated (the results in the third patient in whom the multiactivation paradigm was used were severely degraded by motion). In one patient (L.W.), separate repeated unilateral and bilateral motor experiments were conducted, whereas in the other patient, only separate unilateral task experiments were conducted. On all experiments in L.W., a quantitatively reduced extent of activation (i.e., less total number of pixels with activation) was noted on the side with the tumor (average AI, ~0.31 pixels on unilateral task comparisons and ~0.14 pixels on bilateral task). In the other patient (J.S.), small and variably sized regions of activation were detected, with an average AI of ~0.91 pixels.

The supplemental motor area (SMA) in the mesial aspect of the superior frontal gyri (either the medial aspect of 6aa or M2) (31) showed significant activation in all 11 multiactivation motor task paradigms performed in two patients, including unilateral and bilateral task performance, with intensity changes ranging from 0.6 to 0.9%. The SMA activation was seen in tasks using either the impaired or the normal hand.

The extent of activation (number of pixels) for the SMA was always smaller than that for the contralateral primary sensorimotor cortex in any given experiment in one patient (J.S.) in the other patient (L.W.), with a neurological deficit involving the right hand, the extent of SMA activation (mean, 56 pixels with the right hand task and 38 pixels with the left hand task) was larger when the impaired hand performed the task. Bilateral tasks resulted in extents of activation in the SMA that were similar to those of the unilateral hand tasks (bilateral task mean, 40; unilateral task mean, 47). This SMA association cortex activation was notably reproducible both in location and in number of pixels (extent), relative to that of primary sensorimotor cortex on repeat experiments in the same patient (Figs. 1–3). The magnitude of activation in the SMA was always slightly lower than the magnitude of activation within the primary motor cortex in the same experiment. This quantifiable difference in magnitude of activation was noted when unilateral tasks were performed (normal hand as well as impaired hand), bilateral task performance was used, and SMA activity was compared with contralateral primary sensorimotor cortex.

Other small positive and occasionally small negative regions of activation were also seen in other areas of the brain (e.g., the frontal lobes, the parietal association cortex, the subcortical structures) in 3 of 11 multiactivation motor task experiments and in 6 of 7 superior temporal or inferior frontal task experiments. These regions were not quantitated for extent of activation (or suppression) in this analysis. Generally, multiactivation paradigms yielded less activation than did single-activation paradigms in locations other than the primary motor cortex or the SMA.

In some cases, time-shift maps constructed at different time delays from the onset of task performance showed slight differences in the regional pattern of activation regarding the time at which specific regions attained activation that met correlation coefficient and magnitude thresholds. For instance, in one patient, SMA activity meeting these statistical requirements preceded most primary right sensorimotor cortex activity. In this patient, the apparent time course of the
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FIGURE 1. Unimpaired left hand motor task activation map in a patient with a left posterior frontal glioma. Note significant activation in the expected location of the right hemispheric primary sensorimotor cortex during a motor task involving a normally functioning left hand. Significant activation is also seen near the midline in the mesial portion of the superior frontal gyrus, corresponding to the SMA. (Yellow and red indicate the highest and the high magnitudes of positive activation, respectively; blue indicates negative activation).

SMA and the right (normal side) and left (abnormal side) primary sensorimotor cortex activations all differed somewhat (Fig. 4).

DISCUSSION

BOLD fMRI is a recently described noninvasive technique for localizing brain function (24, 26, 35), which allows multiple task activation experiments to be performed and repeated without the limitations of radiation dose and contrast agent dose that are found in other cerebral blood flow measurement techniques. Although many questions remain regarding such fundamental concepts as the relative contributions of magnetic susceptibility versus inflow to the task-related signal changes using BOLD fMRI and the precise anatomic sites from which these signal changes are generated (capillaries, postcapillary venules, and/or larger veins, etc.), several recent reports illustrate the potential value of BOLD fMRI as a tool to investigate regional cerebral physiology in response to a variety of stimuli.

In this study, we attempted to bring this technique into the clinical setting by examining patients harboring primary intracranial tumors. EPI implementations of fMRI as used in our protocol allow multislice acquisitions, which we think are essential for brain activation maps in the clinical setting, because a priori knowledge of sites of activation is obviously not possible but is unnecessary if the entire brain is imaged. Successful demonstration of BOLD contrast heavily depends on patient cooperation in both performing the activation task and remaining motionless. Therefore, very rapid imaging is critical in fMRI in the clinical setting, not only for studying the temporal profile of activation (if desired) (Fig. 4) but also, more importantly, because patients with intracranial lesions are often limited in their ability to hold still. Even with the EPI mode of acquisition in our study, two of our seven patients were not able to sit still. Unfortunately, sedation does not seem to be a useful option for facilitating a motion-free examination, because psychoactive agents would reduce cooperativeness with task performance and might confound data from experiments that propose to study brain function. Clearly, clinical uses of BOLD fMRI will be limited to selected patients.

In our patients with tumors reported herein, fMRI activation was often identified in the periphery of, or immediately
FIGURE 3. Bilateral hand motor task activation map in patient with a left posterior frontal glioma. Note significant activation in the expected locations of the right hemispheric primary sensorimotor cortex and a smaller region of left hemispheric activation during a motor task involving both hands in a patient with right hand weakness. Significant activation is also seen near the midline in the mesial portion of the superior frontal gyrus, corresponding to the SMA. The relative extent of activation between the left and the right sensorimotor cortices is similar to that noted by comparing the unilateral experiments illustrated in Figures 1 and 2. (Yellow and red indicate the highest and the high magnitudes of positive activation, respectively; blue indicates negative activation).

adjacent to, spin-echo-defined tumor tissue. Activation in or near the periphery of tumors defined by spin-echo MRI was noted in both cognitive and motor task experiments. Histopathological studies have documented that, despite their seemingly well-circumscribed appearance on conventional MRI, infiltrative gliomas are usually ill defined and typically show irregular infiltration of normal brain at their margins (8). Partial sparing of clinical function in our patients coupled with the demonstration of fMRI activity in the periphery of or adjacent to apparent tumor tissue suggests that these infiltrative lesions partially spare normal brain tissue in these patients. This finding of activity on fMRI within (or immediately adjacent to) the periphery of gliomas has important clinical implications, because preservation of residual function in these patients who will undergo debulking or biopsy is highly desirable, yet this tissue may appear to be involved with tumor at surgery. Determining whether functioning tissue is present within apparent tumor margins would also assist in deciding whether to proceed with stereotactic biopsy or debulking with radical resection. Moreover, the anatomic localization of residual brain function is an important consideration for radiosurgery or brachytherapy so that radiation can be directed away from such areas. The presence of function within apparent tumor tissue could also imply that tumor progression will eliminate residual function.

Often the only viable portion of a glioblastoma is found in a peripheral zone of the lesion, which adds complexity to this issue (33). It is also well documented in necropsy and in vivo (13) studies that conventional MRI often underestimates the extent of gliomatous infiltration, such that tumor tissue can extend several centimeters beyond signal intensity abnormality. Corroborative evidence of nonvisible extent of glioma in patients has been provided by high-dose contrast agent studies (37), in which abnormal enhancement was identified in a majority of patients well beyond areas of abnormality on T2-weighted MRI. Our preliminary work suggests that fMRI may become a useful tool in the routine preoperative assessment of these patients.

The underlying tissue composition in regions of fMRI activation in or near the borders of these tumors remains unclear, particularly in the patients with glioblastomas. Glioblastomas, in particular, are known to incite exuberant endothelial proliferation of the microvasculature in non-neoplastic brain parenchyma immediately adjacent to, but notably outside, infla-
trating tumor margins (33, 36). The presence of such a pathological alteration would create a milieu that might facilitate a vascular-based response to regional brain function, such as that which is elicited by task performance fMRI. It is not clear at this early stage in the investigation of fMRI whether the fMRI response itself is altered in the presence of abnormal vessels with abnormal vasoreactivity and abnormal permeability, such as those that are often found in gliomas. Our finding of fMRI activation just beyond the periphery of spin-echo MRI abnormality and possibly even beyond actual tumor tissue might be based on the same mechanism that produces the reported contrast enhancement well beyond hyperintensity on T2-weighted MRI described in high-dose gadolinium studies (37). However, the presence of normal brain parenchyma itself would be adequate for fMRI activation to be detected. Unfortunately, it is particularly difficult to obtain pathological confirmation of these areas because normal uninvolved brain parenchyma at or near margins of infiltrative tumors are purposefully avoided during neurosurgical debulking.

The localization of primary sensorimotor cortex using similar fMRI studies has been validated with invasive cortical mapping in prior studies (21). However, some variation in the magnitude of fMRI signal changes in primary sensorimotor cortex in response to activation experiments is reported in the literature by different groups. This apparent inconsistency in the literature is probably a result of many factors, including differing acquisition techniques, volume averaging, nonstandardized task performance, variation in statistical testing of data, and even seemingly correlated but artificial changes caused by motion (20). Our range of signal intensity changes for the primary sensorimotor cortex is consistent with the predicted value at 1.5 T (3) and most of the previously published data. It should be also be realized that no large series of such experiments with normal patients has been published to date, so conclusions about patients harboring abnormalities must be interpreted with caution. We also recognize that the most appropriate or optimal statistical methodology in the analysis of fMRI data has not yet been formulated and that considerable investigation on defining such techniques continues. Moreover, the value and meaning of statistical tests in isolation are debatable in task activation fMRI studies of the brain because statistical measures fail to consider important nonstatistical components of the data, such as the neuroanatomic location of the activation. In our study, strict statistical tests and other methods were included in the data analysis based on correlation analysis of the temporal course of activation changes and the input function of the paradigm. Although our thresholds may be somewhat arbitrary, we used strict significance criteria (2) to achieve a high confidence level for areas of activation. Our more recent multiactivation motor experiments generated activation maps with fewer areas of correlated signal intensity change outside of primary sensorimotor areas (Figs. 1–3), even when reconstructed at lower correlation thresholds. It is possible that our significance thresholds were too strict in this study compared with those of some other investigators, so our regions of fMRI activation may indeed be inappropriately smaller than necessary. Despite our strict threshold criteria and nearest neighbor requirement, we still identified the ipsilateral primary sensorimotor cortex in some patients and SMA cortex activation in motor task experiments, regions reported to have activation, albeit reduced, in some prior fMRI reports (30). The fact that our motor task involved a relatively simple motion may have contributed to the lack of activation in premotor cortex (31). Multiactivation input paradigms should generate more accurate activation maps of complex functions by similar reductions in contributions of random noise, thereby requiring lower thresholds to obtain statistically significant data.

An AI was used in an attempt to establish a relative yet quantifiable internal standard by which activation in the pathological side could be compared with that in the normal side while minimizing the effects of choice of activation thresholds on the total number of activated pixels. The relative nature of this quantity may also compensate for some of the effects of volume averaging that certainly affect fMRI data by virtue of spatial resolution limitations. The AI may also allow patient-to-patient comparisons and semiquantitative correlations to clinical deficits. A similar attempt to quantify fMRI data in normal volunteers has been reported (9). Although we have too few patients to show a definite correlation between the AI and the clinical deficit, the reproducibility and asymmetry of the AI in a given patient with neurological deficit suggest that a quantifiable assessment of fMRI data, such as the AI, may be useful as an objective correlate of subjective clinical dysfunction. The side-to-side comparison is problematic, however, because of the documented asymmetry even in normal volunteers in motor tasks (23) and is further confounded by inconsistent ipsilateral motor cortex activation. For instance, Kim et al. (23) reported a 4-T fMRI study of 10 right-handed and 5 left-handed normal patients using similar hand motor tasks. In that study, the left motor cortex was substantially activated during both ipsilateral and contralateral movements in left-handed patients (contralateral/ipsilateral AI, 5.4 pixels) and even more activated in right-handed patients (contralateral/ipsilateral AI, 1.3 pixels). In that study, on the contrary, the right motor cortex was predominantly activated during contralateral (left) hand movements (contralateral/ipsilateral AI, 29.9–36.8 pixels); that is, the right motor cortex was only minimally activated during right hand motion. It is clear that a larger series of normal volunteers must be studied to define statistically significant abnormalities in motor activation asymmetry to determine whether quantitative data, such as the AI, can be evaluated in a given patient.

A highly consistent region of activation within the superior frontal gyri, correlating to the SMA cortex (16, 17) for voluntary movement, was demonstrated in motor task experiments (Figs. 1–4). In the one patient (L.W.) with a mutually activation motor task paradigm who was able to tolerate repeated unilateral and bilateral task experiments, the location and total extent of this superior frontal gyrus activation, as well as the magnitude of the intensity change, was notably consistent from experiment to experiment (Figs. 1–3). The magnitude of this putative SMA activation was consistently lower than that of primary sensorimotor cortex activation. The activation of
the SMA has been noted by previous investigators using PET (29, 31, 32) and fMRI (30) in unilateral task activation experiments. As is the implication of our data, the magnitude of the regional cerebral blood flow in this region has also frequently been reported to be lower than that of the primary sensorimotor cortex (29, 31, 32). In our study, bilateral task performance and unilateral task performance by the normal hand evoked total numbers of pixels of activation similar to that in the superior frontal gyrus. In one patient, SMA activity was larger in extent (although similar in magnitude) when the impaired hand performed the task (Figs. 1 and 2). Although the precise hierarchical role of the supplementary motor cortex during voluntary movement is controversial, we postulate that this discrepancy is further evidence for such a role, in that impaired ability to perform a task might change input from cerebral centers thought to relate to initiation of “voluntary” motion (i.e., involuntary control of voluntary functions). Our technique of time-shift mapping (Fig. 4) also implies that fMRI techniques may be able to define temporal modulation of regional brain activation. We have recently applied this time-domain analysis to a small series of normal patients, who also showed differences in peak activation between the SMA and the primary sensorimotor cortex (unpublished data), although further study is clearly needed to determine its validity as well as its importance, if any, in patients harboring lesions.

A few pixels of negatively correlating activation, located mainly but not exclusively in frontal lobe locations, were identified in several patients. This had also been noted, without explanation, in a prior study using a similar motor paradigm in two of six normal patients (30). By our technique, correlation maximums occurring within 12 seconds (or 12/TR time shifts) are given positive values and those occurring after 12/TR time shifts are assigned negative values. Therefore, “negative activation” can include activation that is delayed but positive in absolute value as well as activation that is negative in absolute value. Although we cannot now definitively explain many of these findings, it is likely that using the unique capability of fMRI to obtain data on individual patients rather than relying on the interpatient averaging used in PET will reveal unexpected activation, especially in more complex tasks. Moreover, negative correlation or, more precisely, suppression is a phenomenon recognized in the neuroscience literature, as seen in the inhibitory interactions involved in sound localization experiments (25) and in PET experiments involving anticipation of sensory stimuli (12). Greater patient numbers and optimization of data analysis are needed to further define with certainty these types of more complex findings.

In summary, BOLD fMRI is a feasible way to localize areas of cortical function in patients undergoing treatment planning for intracerebral abnormalities, such as gliomas. These preliminary data suggest that functioning cortex within or adjacent to spin-echo MRI-defined tumor margins of infiltrative gliomas can be demonstrated. This technique may provide pretreatment maps for both surgical and radiation therapy so that therapy can be directed away from regions of residual function. Decisions about diagnostic surgical procedures can also be influenced by these findings. Therefore, notwithstanding the many uncertainties regarding the anatomic and physiological basis for signal changes on BOLD fMRI, as well as the unsettled methodology of statistical analysis for such data, we think that patients harboring such lesions may be candidates for fMRI before surgery. Our preliminary data also suggest that there may be a quantifiable difference on fMRI between activation in tumor-bearing cortex and activation in corresponding normal cortex in the contralateral hemisphere. We postulate that the magnitude of this difference may relate to the severity of patient deficit.

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**REFERENCES**


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COMMENTS

Atlas and colleagues have successfully used functional magnetic resonance imaging (fMRI) techniques to obtain preoperative localizations in four of seven patients with hemispheric gliomas. This new noninvasive procedure offers the possibility of a preoperative functional assessment conducted at the same time as the routine MRI examination. As the authors point out, success depends on patient cooperation with the mapping task and ability to remain motionless during the study. Magnetic resonance equipment manufacturers are making this functional capability available on most new systems, and upgrades are available for many older systems.

The signal changes allowing detection of functional activation on MRI probably relate to a combination of changes in blood oxygenation and inflow enhancement within the vessels. It is important to recognize that a majority of these signal changes may be observed within large cortical veins, not necessarily at the neuronal source. The method is best suited for studying functional activity amenable to on/off task activation paradigms that can be played out over 1 to 2 minutes. Very brief, transient brain activity and steady-state processes are more difficult to address with this technique. Nonetheless, the authors and other groups using similar techniques have shown promising preliminary data for the mapping of sensory, motor, visual, auditory, memory, and language functions.

Several other methods are under investigation for preoperative functional brain assessment, including transcranial magnetic stimulation, electroencephalogram-based methods, magnetoencephalography, and positron emission tomography (PET) (2). In particular, the combination of magnetoencephalography coregistered to magnetic resonance images (magnetic source imaging) seems to provide a reliable way to locate...
the central sulcus (1, 3). It remains to be determined which of these methods or combination of methods will prove to be most reliable and cost-effective in routine clinical practice.

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One of the most exciting aspects of contemporary neurosurgery is the increasing ability to image the brain. Atlas et al. demonstrate functional imaging. This is the fastest growing area in neuroscience, and it promises to add considerably to our understanding of the complex interactions of brain regions in producing motor outputs. It is likely that functional MRI rather than PET or single photon emission computed tomography will carry us into the 21st century in brain imaging.

Exciting ability to map eloquent areas preoperatively rather than by the Wada test or stimulation with subdural electrodes is demonstrated here.

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Modern functional imaging techniques can be used to map human cortical and subcortical function in health and disease. This has been clearly demonstrated by PET measurements of cerebral metabolism and blood flow and, more recently, by the ability to use MRI with conventional or specially modified equipment to detect different states of neuronal activity based on varying concentrations of oxy/deoxyhemoglobin in the venous blood. This, combined with conventional electrophysiological mapping techniques, as well as structural images from high-resolution MRI and intraoperative recordings with optical intrinsic signal imaging, provides a broad armamentarium for both preoperatively and intraoperatively evaluating brain function. Atlas and colleagues describe the use of functional MRI to map regional cerebral brain activity in patients with gliomas. The importance of such data is obvious. Functional MRI provides a means by which to not only identify critical functional cortical areas but also evaluate changes in their positions induced by displacement from mass lesions of their functional reorganization as a result of chronic, long-standing disease processes.

When performing such studies, or assessing reports about them, it is important to remember the considerable variability in both structural and functional anatomy of normal healthy individuals. With the addition of disease-induced changes, caution must be used to avoid a rigid stereotyped picture of the functional organization of the human cortex. Although this is clearly true for neocortical areas, the same holds true for primary sensory and motor regions. In the report by Atlas et al. patients are used as their own controls and responses are compared with the contralateral and presumed "normal" hemispheres. It is still not clear what the functional effects of unilateral disease might be on the presumed "normal" contralateral hemisphere, and such information will only be obtained by comparing large numbers of patients with brain lesions with even larger populations of normal control patients. Fortunately, these noninvasive in vivo functional imaging techniques allow for such data to be collected.

Cerebral blood flow measurements with PET and functional MRI activation studies examine hemodynamic events that are some physiological "distance" from the neuronal activity that induces flow changes. As such, one should not always expect a spatially coincident pattern to emerge when comparing sites of changes in blood flow with sites of changes in neuronal activity. This is particularly true with functional MRI, in which the presumed signal change originates from venous drainage of activated parenchymal sites. Studies that seek to determine the degree of spatial coincidence among electrophysiological changes, PET cerebral blood flow measurements, and functional MRI activity changes will help to determine how colocalizing these processes are. Despite these notes of caution, it is clear that functional brain mapping techniques will provide new and important tools to the neurosurgeon in planning safer and more informed surgical procedures.

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ANNOUNCEMENT

World Federation of Neurosurgical Societies Meeting

The World Federation of Neurosurgical Societies has announced that Sydney, Australia will be the site of their XIIth International Congress, to be held in 2001.