Radiology

Brain Tumors: The Influence of Tumor Type and Routine MR Imaging Characteristics at BOLD Functional MR Imaging in the Primary Motor Gyrus[1]

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Purpose: To evaluate the effects of histologic features and anatomic magnetic resonance (MR) imaging characteristics of brain tumors on the functional MR imaging signal in the primary motor cortex (PMC), as false-negative blood oxygen level–dependent (BOLD) functional MR imaging activation can limit the accurate localization of eloquent cortices.

Materials and Methods: Institutional review board approval was obtained, and informed consent was waived for this HIPAA-compliant retrospective study. It comprised 63 patients referred between 2006 and 2014 for preoperative functional MR imaging localization of the Rolandic cortex. The patients had glioblastoma multiforme (GBM) (n = 20), metastasis (n = 21), or meningioma (n = 22). The volumes of functional MR imaging activation were measured during performance of a bilateral hand motor task. Ratios of functional MR imaging activation were normalized to PMC volume. Statistical analysis was performed for the following: *(a)* differences between hemispheres within each histologic tumor type (paired Wilcoxon test), *(b)* differences across tumor types (Kruskal-Wallis and Fisher tests), *(c)* pairwise tests between tumor types (Mann-Whitney U test), *(d)* relationships between fast fluid-attenuated inversion recovery (FLAIR) data and enhancement volume with activation (Spearman rank correlation coefficient), and *(e)* differences in activation volumes by tumor location (Mann-Whitney U test).

Results: A significant interhemispheric difference was found between the activation volumes in GBMs (mean, 511.43 voxels ± 307.73 [standard deviation] and 330.78 voxels ± 278.95; $P < .01$) but not in metastases (504.68 voxels ± 220.98 and 460.22 voxels ± 276.83; $P = .15$) or meningiomas (424.07 voxels ± 247.58 and 415.18 voxels ± 222.36; $P = .85$). GBMs showed significantly lower activation ratios (median, 0.49; range, 0.04–1.15) than metastases (median, 0.79; range, 0.28–1.66; $P = .043$) and meningiomas (median, 0.91; range, 0.52–2.05; $P < .01$). There was a moderate correlation with the volumes of FLAIR abnormality in metastases ($\rho = -0.50$) and meningiomas ($\rho = -0.55$). Enhancement volume ($\rho = -0.11$) and tumor distance from the PMC (median, 0.73 and range, 0.04–2.05 for near and median, 0.82 and range, 0.39–1.66 for far; $P = .14$) did not influence activation.

Conclusion: BOLD functional MR imaging activation in the ipsilateral PMC is influenced by tumor type and is significantly reduced in GBMs. FLAIR abnormality correlates moderately with the activation ratios in metastases and meningiomas.

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Blood oxygen level–dependent (BOLD) functional magnetic resonance (MR) imaging is a powerful noninvasive method used to map brain cortical function (1–3). Functional MR imaging has been shown to be useful in preoperative planning and risk assessment and as a guide to intraoperative cortical stimulation (4). Increasingly, functional MR imaging is being considered the standard of care in the preoperative work up of patients with brain tumors (5,6). Thus, there is much interest in identifying the factors that influence the accuracy of BOLD functional MR imaging in mapping functions such as motor and language.

The BOLD functional MR imaging contrast arises from changes in the ratio of deoxyhemoglobin and oxyhemoglobin in response to a behavioral paradigm (7,8). The BOLD functional MR imaging signal intensity is mainly obtained from the relationship between neural activity and changes in blood flow, blood volume, and the cerebral metabolic rate of oxygen (neurovascular coupling) (9–11). High-grade gliomas contain abundant abnormal neovasculature, which has been shown to have a dysfunctional autoregulation and a consequential compromise of the flow dynamics (neurovascular uncoupling). This abnormal neovasculature is thought to lead to a decreased functional MR imaging contrast between oxyhemoglobin and deoxyhemoglobin, leading to a muting of the BOLD effect (12–14). Previous smaller-scale studies have suggested that functional MR imaging activation volumes are truncated in the presence of tumors, particularly high-grade gliomas (15,16), thus making functional MR imaging potentially less reliable in peritumoral regions. It has been suggested that in addition to the histopathologic properties, other tumor properties (edema, volume, and location) and factors (prior brain surgery, age, motor deficits, and magnetic field strength) may influence BOLD functional MR imaging activation (17–19).

False-negative BOLD functional MR imaging activation can limit the accurate localization of eloquent cortices. The purpose of our current study was to study the effects of histologic features and anatomic MR imaging characteristics of brain tumors on the functional MR imaging signal in the primary motor cortex (PMC).

We hypothesized that *(a)* BOLD functional MR imaging activation ipsilateral to the tumor would be significantly lower in patients with high-grade gliomas than in patients with metastases or meningiomas and *(b)* the volume of fluid-attenuated inversion recovery (FLAIR) abnormality, the volume of enhancement, and tumor location would affect the ipsilateral BOLD functional MR imaging activation.

Advances in Knowledge

- The volume of blood oxygen level–dependent (BOLD) functional MR imaging activation is significantly reduced in glioblastomas multiforme (GBMs) ipsilateral to the tumor ($P < .01$) but not in metastases ($P = .15$) or meningiomas ($P = .85$).
- The volume of the fluid-attenuated inversion recovery abnormality correlates moderately with the ipsilateral BOLD functional MR imaging activation in metastases ($\rho = -0.50$) and meningiomas ($\rho = -0.55$).
- There was no correlation between the volume of BOLD functional MR imaging activation and volume of enhancement ($\rho = -0.11$) or tumor location ($P = .14$).

Implications for Patient Care

- BOLD functional MR imaging maps should be interpreted with caution in patients with GBMs undergoing preoperative functional MR imaging for the localization of eloquent cortices adjacent to brain tumors.
- Conversely, BOLD functional MR imaging activation appears less affected in metastases and meningiomas.

Materials and Methods

Subjects

Institutional review board approval was obtained for this Health Insurance Portability and Accountability Act–compliant retrospective study, and the need to obtain informed consent was waived. Among patients consecutively referred for preoperative localization of the Rolandic cortex between June 2006 and October 2014, only subjects who met the following criteria were included: *(a)* the patient could perform the bilateral finger-tapping task; *(b)* the patient had a newly histopathologically confirmed glioblastoma multiforme (GBM), metastasis, or meningioma; *(c)* the tumor was unilateral; and *(d)* the patient had not previously undergone brain surgery.

Eighty-one patients were screened, and 74 met the initial criteria. After we reviewed the data, 11 patients were excluded (four patients with GBMs, five patients with metastases, and two patients with meningiomas) because of functional MR imaging studies that were contaminated with movement artifacts or displayed a low signal-to-noise ratio that resulted in nonspecific activation. As a result, 63 patients (31 men and 32 women; age range, 24–93 years; mean age, 62 years) were enrolled in the study: 48 patients (73%

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Abbreviations:
BOLD = blood oxygen level dependent
FLAIR = fluid-attenuated inversion recovery
GBM = glioblastoma multiforme
PMC = primary motor cortex

Author contributions:
Guarantor of integrity of entire study, V.H.F.d.A.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, V.H.F.d.A., K.K.P., A.I.H.; clinical studies, V.H.F.d.A., K.K.P., N.M.P., A.I.H.; experimental studies, K.K.P.; statistical analysis, V.H.F.d.A., K.K.P., K.M.W., A.I.H.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

of the cohort) were between 50 and 70 years, six patients (10% of the cohort) were younger than 50 years, and nine patients (17% of the cohort) were older than 70 years of age. Patients were assigned to different groups on the basis of tumor pathologic type, and the pathologic breakdown was 20 GBMs, 21 metastases, and 22 meningiomas. Details are provided in Table E1 (online).

MR Imaging Parameters

The MR data were acquired with either a 1.5-T (19 patients, with five GBMs, five metastases, and nine meningiomas) or 3.0-T (44 patients, with 15 GBMs, 16 metastases, and 13 meningiomas) TwinSpeed imager (GE Medical Systems, Milwaukee, Wis) with a standard eight-channel head coil. Functional images were acquired with a single-shot T2*-weighted gradient-echo echo-planar imaging sequence with the following parameters: repetition time msec/echo time msec, 4000/40 for 1.5 T and 4000/35 for 3.0 T; 90° flip angle; 128 × 128 matrix; 4.5-mm section thickness with no intersection gap; 24-cm field of view; and 34–36 oblique sections. T1-weighted spin-echo images (400/14, 256 × 256 matrix, 4.5-mm thickness), T2-weighted spin-echo images (4000/102, 256 × 256 matrix; 4.5-mm thickness), FLAIR images (10 000/106; inversion time, 220 msec; 90° flip angle; 256 × 256 matrix; 4.5-mm thickness), and T1-weighted three-dimensional spoiled gradient-recalled acquisition in the steady state, or GRASS, images (6.9/3, 15° flip angle, 256 × 256 matrix, 1.5-mm thickness, 240-mm field of view) were acquired so that we could superimpose functional images on structural images.

Functional MR Imaging Task

A block-designed paradigm of alternating rest (40 seconds) and active (20 seconds) periods was performed with each patient. The task consisted of 90 volumes for a total of six cycles each of stimulation and rest periods. All patients performed self-paced finger tapping involving digits one through five on both hands. Task instructions were delivered aurally. Cortical activation associated with task performance was monitored with real-time software (Brainwave RT; Medical Numerics, Germantown, Md).

Functional MR Imaging Data Processing

Raw functional MR imaging data were transferred to a Linux workstation and were analyzed with AFNI (Analysis of Functional NeuroImages, *http://afni.nimh.nih.gov*) (20). Each data set was inspected for artifacts and head motion. The functional data were then realigned, corrected for head motion against a reference image, and smoothed with a Gaussian 4-mm full-width-at-half-maximum filter to increase the signal-to-noise ratio. Linear trend was removed if necessary. Statistical maps of activation were generated by using cross-correlation analysis (21). A modeled waveform corresponding to the task block was cross correlated with all pixel time courses to identify stimulus-locked responses. Functional activation maps were generated at a threshold of $P < .001$ and were used to determine the volume of BOLD functional MR imaging activation within the PMC.

Functional MR imaging activation volumes.—A region of interest was manually drawn around the PMC, defined as the entire precentral gyrus, on a section-by-section basis in both hemispheres. All measurements were supervised by a fellowship-trained neuroradiologist with 20 years of experience in functional MR imaging.

Because functional MR imaging activation volumes can be threshold dependent (22), three thresholds were used to compare functional MR imaging activation volumes (from a maximal correlation score of 0.62 determined by multiple comparison correction, a minimal correlation score of 0.4, and an in-between score of 0.5). Statistical significance was set at $P < .001$. We normalized the number of activated voxels measured in the PMC of the hemisphere ipsilateral to the tumor to the contralateral side to account for differences seen as a result of gyral volume. A normalization method (13) was applied to determine relative and adjusted functional MR imaging activation ratios, as follows:

$$\text{relative volume} = \text{Vmc}(t)/\text{Vmc}(n),$$

where Vmc*(t)* is the gyral volume of the PMC in the ipsilateral hemisphere and Vmc*(n)* is the gyral volume of the PMC in the contralateral hemisphere. Relative activation was calculated with the following equation

$$\text{relative activation} = \begin{bmatrix} \text{VA}(t)/\text{VA}(n)_{\text{OR1}} \\ +\,\text{VA}(t)/\text{VA}(n)_{\text{OR2}} \\ +\,\text{VA}(t)/\text{VA}(n)_{\text{OR3}} \end{bmatrix} \Big/ 3,$$

where VA*(t)* is the functional MR imaging activation volume in the ipsilateral PMC, VA*(n)* is the functional MR imaging activation volume in the contralateral PMC, and OR is the *r* value ($OR_1 = 0.62$, $OR_2 = 0.5$, $OR_3 = 0.4$). To calculate the adjusted activation, we divided the relative activation by the relative volume.

To determine the volumes of the FLAIR abnormality and contrast enhancement, a region of interest was manually drawn on each section for each patient where this abnormality was present. To obtain the volume, the areas of the regions of interest were summed and multiplied by the section thickness. These measurements were performed by using BrainLab (23). To determine the distance of the tumor to the PMC, we overlaid the functional images onto the T1-gadolinium-enhanced images. If the distance from the closest border of enhancement was within one gyrus from the PMC, the tumor was classified as "near." All other tumors were considered "far."

Statistical Analysis

Differences between hemispheres within each pathologic group were tested with the paired Wilcoxon signed-rank test. Differences across tumor types were tested with the Kruskal-Wallis test for continuous variables and the Fisher exact test for categoric variables. Pairwise tests between tumor types were conducted by using the Mann-Whitney *U* Test. The relationships between both FLAIR abnormality and tumor volume with BOLD activation were analyzed by

Figure 1

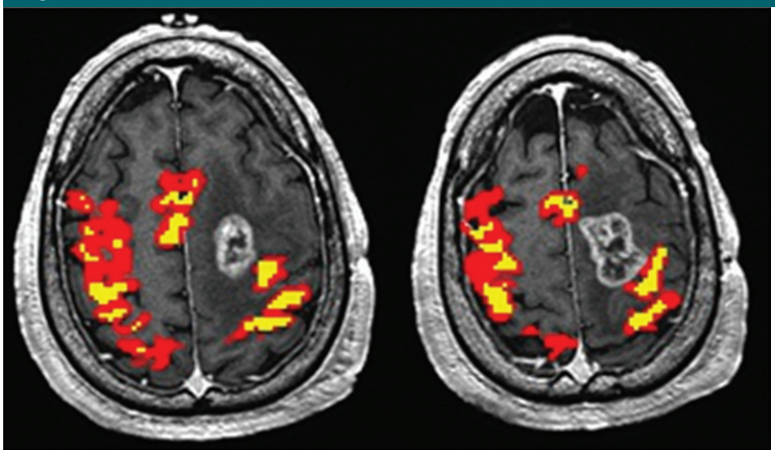

Figure 1: Maps of BOLD functional MR imaging motor activation in a 59-year-old man with a GBM adjacent to the left PMC. Axial functional MR T2*-weighted gradient-echo echo-planar sequence images are superimposed on T1-weighted spin-echo anatomic reference images. Color = BOLD functional MR imaging activation following a range of *r* values (yellow, ≥0.1; 0.5 < red < 0.7). BOLD signal intensity reduction peaks in high-grade gliomas, as evidenced by the asymmetric BOLD functional MR imaging pattern in the hemisphere ipsilateral to the tumor.

Figure 2

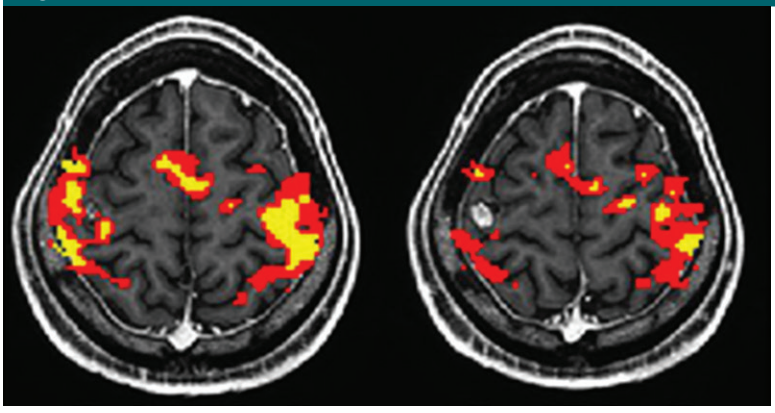

Figure 2: Maps of BOLD functional MR imaging motor activation in a 24-year-old man with a metastasis in the right PMC. Axial functional MR T2*-weighted gradient-echo echo-planar sequence images are superimposed on T1-weighted spin-echo anatomic reference images. Color = BOLD functional MR imaging activation following a range of *r* values (yellow, ≥0.1; 0.5 < red < 0.7). BOLD functional MR imaging activation is moderately reduced in noninfiltrative intra-axial tumors.

using the Spearman rank correlation coefficient, and the Bonferroni correction was used to adjust *P* values for the four tests performed. Finally, the differences in BOLD functional MR imaging activation volumes by tumor location were determined by using the Mann-Whitney *U* Test. All statistical tests were two sided, and the level of significance was set at $P < .05$. Statistical analyses were performed by using R (version 3.0.1; R Development Core Team).

Results

BOLD Functional MR Imaging Activation Volumes in Ipsilateral PMC versus Contralateral PMC

Only the GBM group demonstrated a significant difference in the BOLD functional MR imaging activation volumes in the tumor-containing hemisphere compared with the contralateral hemisphere ($P < .01$). In contrast, there were no significant interhemispheric BOLD functional MR imaging volume differences in the PMCs of patients with metastases ($P = .15$) or meningiomas ($P = .85$). Representative functional MR imaging maps of motor activation in different tumor types are shown in Figures 1–3. The BOLD functional MR imaging activation volumes are shown in Table 1.

Effect of Tumor Type on BOLD Functional MR Imaging Activation

In patients with GBMs, we observed the greatest decrease of the BOLD functional MR imaging activation ratios in the tumor-containing hemisphere, before (mean difference, −39%) and after (mean difference, −44%) normalization to the gyral volume of the PMC ($P < .01$). Compared with those in GBMs, the ipsilateral normalized BOLD functional MR imaging activation ratios were reduced to a lesser degree in patients with metastases (mean difference, −19%; $P = .043$) and were affected least in the meningioma group (mean difference, 0%; $P < .01$). There was no significant difference between metastases and meningiomas ($P = .065$). Differences in normalized BOLD functional MR imaging activation across tumor types are shown in Figure 4.

Effect of Other Tumor Properties on BOLD Functional MR Imaging Activation

There was a moderate inverse correlation between the ipsilateral adjusted BOLD functional MR imaging activation ratios of all tumors and the corresponding volumes of FLAIR abnormality ($\rho = -0.56$, $P < .001$). This relationship is presented in Figure 5.

Figure 3

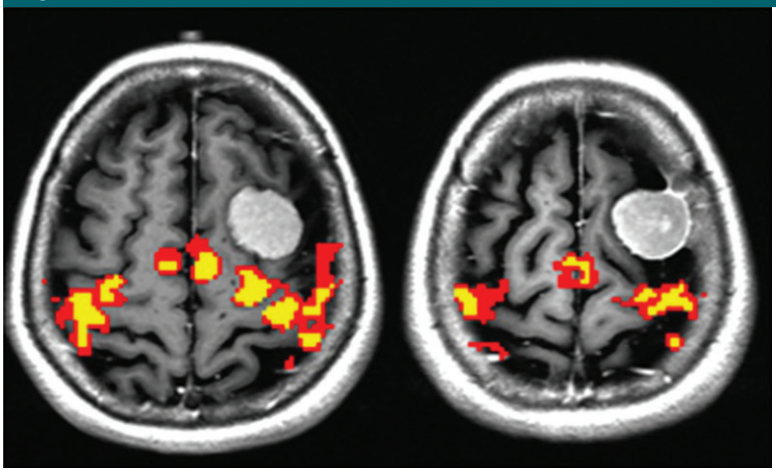

Figure 3: Maps of BOLD functional MR imaging motor activation in a 59-year-old woman with a meningioma located far to the left of the PMC. Axial functional MR T2*-weighted gradient-echo echo-planar sequence images are superimposed on T1-weighted spin-echo anatomic reference images. Color = BOLD functional MR imaging activation following a range of *r* values (yellow, ≥0.1; 0.5 < red < 0.7). BOLD functional MR imaging signal is minimally changed in patients with extra-axial tumors, as indicated by the symmetric interhemispheric BOLD functional MR imaging activation.

Table 1

BOLD Functional MR Imaging Activation Volumes in the Contralateral and Ipsilateral PMC

	GBM		Metastasis		Meningioma	
Activation Volume	Contralateral PMC	Ipsilateral PMC	Contralateral PMC	Ipsilateral PMC	Contralateral PMC	Ipsilateral PMC
Mean ± standard deviation	511.43 ± 307.73	330.78 ± 278.95	504.68 ± 220.98	460.22 ± 276.83	424.07 ± 247.58	415.18 ± 222.36
Range	151.67–1296.33	16.00–1038.00	175.00–1052.00	97.67–1265.00	128.33–936.33	78.00–981.00
P value*	<.01		.15		.85	

* *P* values were calculated with the two-tailed Mann-Whitney *U* Test. $P < .05$ indicated significance.

We found a weak correlation between BOLD functional MR imaging activation and FLAIR volumes in GBMs ($\rho = -0.33$, $P = .62$). The correlations were moderate in magnitude in metastases ($\rho = -0.50$, $P = .082$) and meningiomas ($\rho = -0.55$, $P = .033$).

There was a significant difference in tumor volume between the three pathologic types ($P < .001$). The tumors were, on average, larger in the meningioma group (median volume, 24 cm^3) compared with the intra-axial lesions: GBMs (median volume, 17 cm^3) and metastases (median volume, 5 cm^3).

For all tumors taken together, the ipsilateral adjusted BOLD functional MR imaging activation ratios did not correlate with tumor volume ($\rho = -0.11$). For subgroup analysis, there was no evidence of correlation in GBMs ($\rho = -0.20$), metastases ($\rho = -0.05$), and meningiomas ($\rho = -0.15$). The results are presented in Table 2.

Figure 4

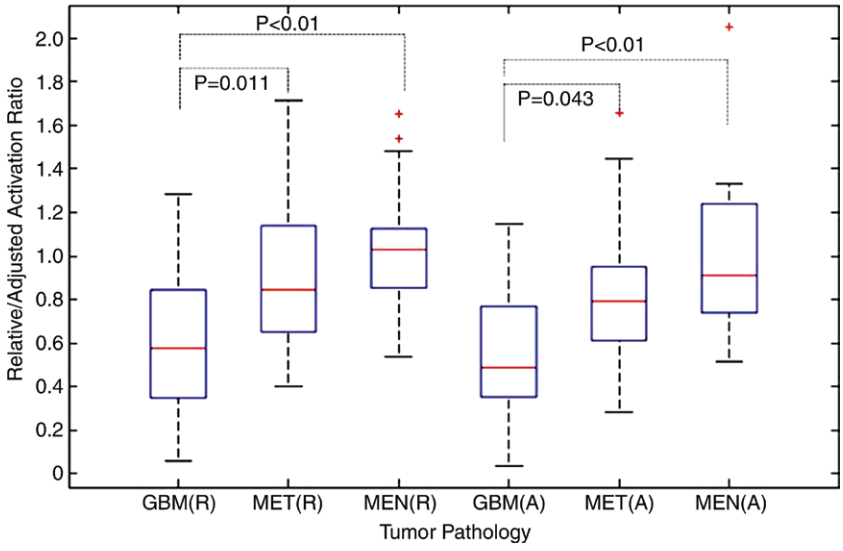

Figure 4: Box plot shows relative *(R)* and adjusted *(A)* BOLD functional MR imaging activation ratios according to tumor type. Line in each box = the median, and the horizontal boundaries of the boxes = the first and third quartiles. The vertical error bars extend to 1.5 times the first and third quartiles. Outliers (+) are plotted as individual points. *P* values were calculated with the two-tailed Mann-Whitney *U* Test. $P < .05$ indicated significance.

Figure 5

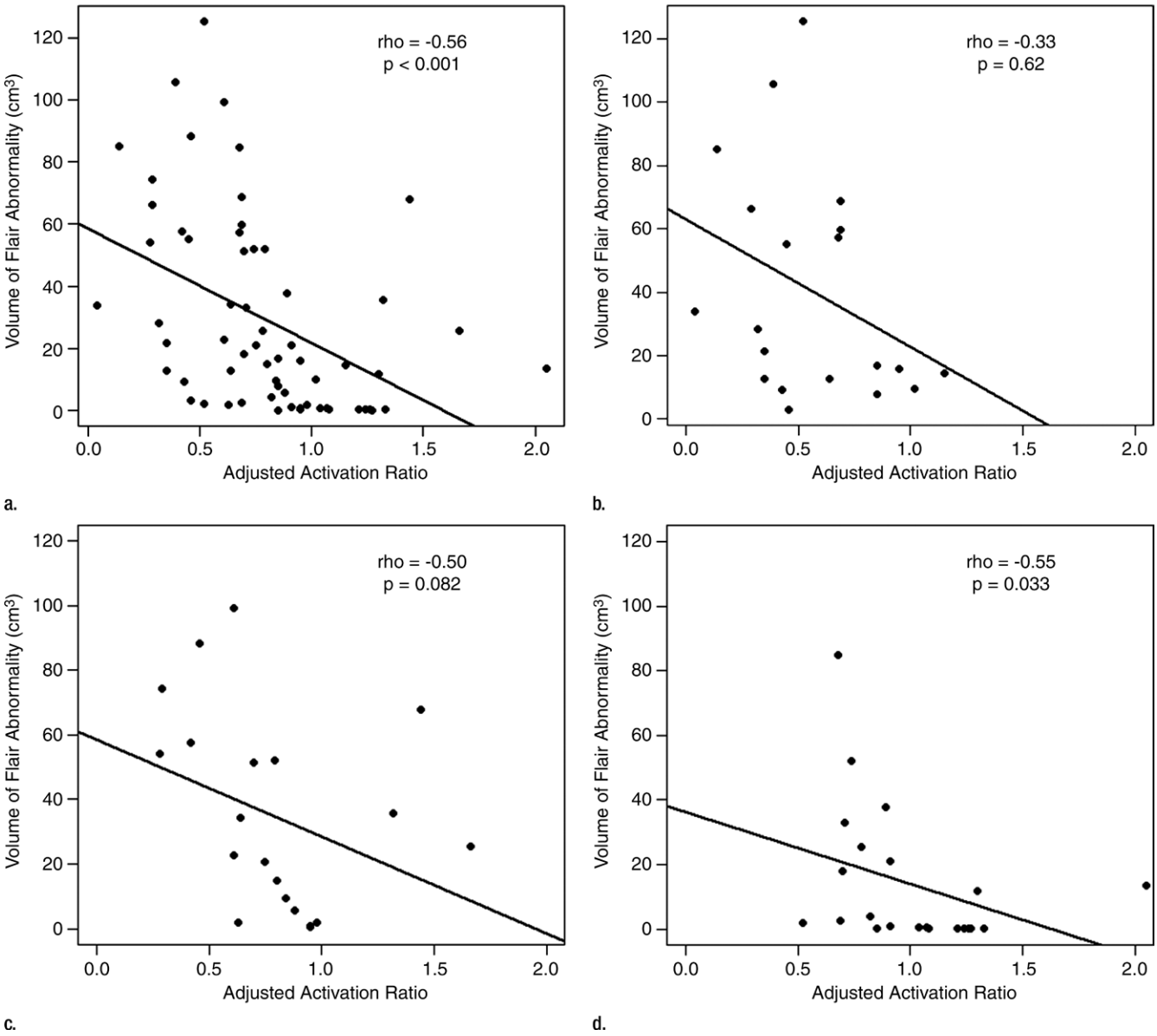

Figure 5: Correlation between BOLD functional MR imaging activation and FLAIR abnormality volume. Scatterplots show BOLD functional MR imaging adjusted activation versus FLAIR abnormality volume for **(a)** all tumors and for each subgroup of tumor type: **(b)** GBMs, **(c)** metastases, and **(d)** meningiomas.

For all tumors taken together, there were no significant differences in the ipsilateral adjusted BOLD functional MR imaging activation ratios between patients with far (n = 13) and those with near (n = 50) lesions to the PMC (P = .14). The statistical analysis was not performed for each subgroup of tumor type because of an insufficient sample size (Table 2).

Discussion

We found that BOLD functional MR imaging activation is significantly reduced within the primary motor gyrus of the tumor-containing hemisphere in patients with GBMs, but not in metastases and meningiomas. The effect of tumor type must be taken into account in clinical settings, as a potentially muted BOLD functional MR imaging response in the eloquent cortex may compromise correct presurgical planning, with increased risk of postoperative deficits. Therefore, BOLD functional MR imaging maps should be interpreted with caution, particularly in the assessment of patients with glioma. Conversely, BOLD functional MR imaging may be more reliable in other types of tumors.

Table 2

Effect of FLAIR Volume, Tumor Distance, and Volume of Enhancement on BOLD Functional MR Imaging Activation

Parameter	GBM ($n = 20$)	Metastasis ($n = 21$)	Meningioma ($n = 22$)	*P* Value
FLAIR volume (cm^3)	24.87 (3.11–125.40)	2.23 (0.04–84.76)	25.44 (0.39–99.36)	.002*
Tumor distance†				.34‡
Far	3 (15)	3 (14)	7 (32)	
Near	17 (85)	18 (86)	15 (68)	
Volume of enhancement (cm^3)	17.02 (3.34–84.29)	5.14 (0.68–32.49)	24.34 (1.95–142.40)	<.001*

Note.—Unless otherwise specified, data in parentheses are medians, with the range in parentheses.

* *P* value was computed by using the Fisher exact test. $P < .05$ indicated significance.

† Data are numbers of patients, with percentages in parentheses.

‡ *P* value was calculated with the Kruskal-Wallis test.

Previous small-scale studies have suggested that BOLD functional MR imaging activation is significantly reduced in high-grade gliomas, which affect the neovasculature (and presumably uncouple the neurovascular response), compared with that in tumors that do not (13,24–26). However, much evidence in the field results from the analysis of small-sized cohorts of gliomas compared against a heterogeneous group of other tumor types, or with a focus on the incidence of postoperative deficits. Contrary to histopathologic features, the analysis of the anatomic MR imaging characteristics of the tumors and their possible effects on BOLD functional MR imaging signal remain poorly understood.

In this current study, we recruited a larger population to evaluate the influences of three different types of brain tumor on BOLD functional MR imaging in the primary motor gyrus. Our findings seem to concur with the hypothesis that abnormal tumor neovasculature, a pathologic hallmark of GBMs, contributes to neurovascular uncoupling, which might lead to a decrease in BOLD functional MR imaging activation at the ipsilateral hemisphere (14,18,19,27). Yet, we draw attention to the fact that the significant interhemispheric difference in BOLD functional MR imaging activation observed in GBMs, but not within metastases and meningiomas, does not prove per se that there is a difference in this respect between the three tumor types.

Furthermore, we observed that BOLD functional MR imaging activation correlated weakly with the volume of FLAIR abnormality surrounding the area of tumor enhancement in GBMs in comparison with the other tumors. With respect to gliomas, a number of recent articles have shown that the abnormal vascular reactivity extends past the radiologic boundaries of the tumors seen at routine MR imaging (4,13,28). Our results concur with those of Lüdemann et al (29), who did not find any relationship between BOLD functional MR imaging activation and tumor edema (defined as T2-weighted hyperintensity) in a retrospective case-control study of 22 patients (of whom 18 had gliomas) and 11 control subjects, notwithstanding a larger population in the present study. Perhaps the apparent effect is essentially due to abnormal neovasculature in the area of FLAIR abnormality and possibly even beyond. Finally, the other MR imaging features examined, volume of enhancement and tumor location, did not seem to play a role. The explanation may be that BOLD response is inherently a vascular phenomenon, which is marginally affected by tumor size (18,27). However, this should be interpreted with caution, as the exact determination of tumor volumes at routine MR imaging is difficult in gliomas, in which borders are often ill defined (30). The lack of an effect of tumor distance to the PMC may also be supported by the aforementioned studies that demonstrated neurovascular uncoupling past the radiologic borders of the tumors (4,28,31).

Our study had limitations. We included patients imaged at different magnetic field strengths, which is known to significantly affect the BOLD functional MR imaging signal intensity and variability (17). Although we performed intrasubject interhemispheric ratio comparisons to account for the field strength bias, the ratio only partially compensates it, assuming the bias levels to be equally distributed in each hemisphere. Furthermore, the ratio does not eliminate the variability of the functional MR imaging signal. A robust approach should include the field strength as a covariable. Also, it is known that the amplitude of BOLD functional MR imaging signal is directly related to task performance (32). In this study, a modeled waveform corresponding to the task block was cross correlated with all pixel time courses to identify stimulus-locked responses and the corresponding brain activity. Instead, a more reliable approach should quantify the actual behavior output (eg, with an apparatus measuring real-time motor behavior) so that task performance can be cross correlated with the observed BOLD functional MR imaging signal. Finally, we did not account for the effects of the possible use of steroids, and the negative findings may just reflect insufficient power.

In conclusion, BOLD functional MR imaging activation is significantly reduced in the ipsilateral primary motor gyrus in patients with GBMs, but not in the other tumor types. The volume of the FLAIR abnormality correlates

moderately with the ipsilateral BOLD functional MR imaging activation in metastases and meningiomas, whereas the other anatomic MR imaging characteristics of the tumors did not play a role.

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