

Plasticity of the Motor Cortex in Patients with Brain Tumors and Arteriovenous Malformations: A Functional MR Study

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Objective: Test the hypothesis about the potential role of functional MRI (fMRI) to evaluate the plasticity of the cortical motor areas in patients with brain tumors and brain arteriovenous malformations (AVMs) and measurement of the lesion-to-fMRI activation distance for predicting risk of new motor deficit after surgery.

Material and Method: This was a retrospective study. The present study population enrolled eight patients with motor cortex lesions. Cortical motor representations were mapped in these patients harboring tumor or AVMs occupying the region of primary motor cortex (M1). Five patients had known diagnosis of primary brain tumor including glioblastoma multiforme, ($n = 1$), diffuse astrocytoma ($n = 2$), dysembryoplastic neuroepithelial tumor (DNET) ($n = 1$) and unknown pathology ($n = 1$). Three patients had known diagnosis of brain AVMs. Three patients showed hemiparesis at the time of presentation. Focal/generalized seizure or headache was present in the remaining patients. Simple movements of both hands were performed. Localization of the activation in the affected hemisphere was compared with that in the unaffected hemisphere and evaluated with respect to the normal M1 somatotopic organization. Distance between the location of the fMRI activation (M1) and margin of the lesion was recorded.

Results: Cortical activation was found in two patterns: 1) functional displacement within affected M1 independent of the structural distortion induced by the tumor or AVMs ($n = 7$) and 2) presence of activation within the non-primary motor cortex without activation in the affected or unaffected M1 ($n = 1$).

Conclusion: Brain tumor or AVMs led to reorganization within the somatotopic affected M1 and can expand into non-primary motor cortex area. Distortion of the anatomy alone by the space-taking lesion did not influence the location of the reorganized cortex. No particular type of reorganization pattern could be predicted. fMRI could be localized reorganized cortex and was found to be a useful tool to assess the lesion-to-activation distance for predicting risk of new motor deficit after surgery. The present study thus emphasizes the importance of considering additional fMRI with structural MRI to evaluate individual differences in cortical plasticity for treatment planning, particularly in the neurosurgical procedure.

Keywords: Plasticity, Motor cortex, Brain tumors, Arteriovenous malformations, Functional MR

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Conventional MR imaging, which provides precise topographic localization of brain tumors or brain arteriovenous malformations (AVMs), is an essential tool for therapeutic planning. Surgeons or interventionists not only want to know the anatomic location alone but also consider functional organization, especially the motor cortex⁽¹⁾. Localization of the functional cortex by visual inspection of

anatomical landmarks such as sulcal pattern is often difficult to predict due to variation of the cortical anatomy, distortion by a space-taking lesion and perilesional edema⁽¹⁰⁾.

Functional MRI (fMRI) can be used to map changes in brain hemodynamic that correspond to mental operations extending traditional anatomical imaging to include maps of human brain function⁽²⁾. Of the currently available approaches, only fMRI based on blood oxygenation level dependent (BOLD) contrast has the potential for widespread application because it is noninvasive, has superior spatial and temporal resolution, does not involve radiation exposure and can be performed with widely available

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MR instruments. These advantages have enabled the unique capability to perform repeated study within subject mapping, which is necessary to study individual variability associated with learning and neural plasticity⁽³⁾.

BOLD is based on signal changes from local reduction in deoxyhemoglobin during neuronal activity in the brain. Since deoxyhemoglobin is paramagnetic, it alters the T2*-weighted MRI signal⁽⁴⁾. Thus, deoxyhemoglobin is sometimes referred to as an endogenous contrast enhancing agent serving as the source of the signal for fMRI. Using an appropriate image sequence, human cortical functions can be observed without the use of exogenous contrast enhancing agents on a clinical strength scanner (1.5-Testa)^(5,6).

Functional activity of the brain determined from the MR signal has confirmed known anatomically distinct processing areas in the visual cortex⁽⁴⁾, the motor cortex^(7,8), and Broca's area of speech and language-related activities⁽⁹⁾. Anatomical location of the motor system is pointed at the primary motor cortex, supplementary motor area, dorsal premotor area, parietal area, and cingulate motor area.

Several studies have addressed the beneficial use of fMRI, pre-surgically to identify the central sulcus and eloquent cortex in patients with tumors or AVMs^(11,12). The previous report showed that brain AVMs lead to reorganization within somatotopic representation in motor cortex and non-primary motor areas⁽¹⁾. In addition, another study found that fMRI helps to identify the relationship between the brain tumors near central sulcus and the location of motor cortex^(13,14). A general conclusion was that non-invasive preoperative mapping of the motor cortex allows for a better prepared surgical approach and better patient information⁽¹⁵⁾.

The purpose of the present study was to support the potential usefulness of fMRI as a part of treatment planning to map cortical reorganization in patients with brain tumors and AVMs directly involving primary motor cortex and measuring lesion-to-fMRI activation distance for predicting risk of new motor deficit after surgery.

Material and Method

Patients

This was a retrospective study from the database of patients with brain tumors or AVMs who underwent fMRI between January 2000 and September 2006 for the localization of the motor cortex area. The

present study population included eight patients (3 male and 5 female) whose age ranged from 10 to 40 years (mean age, 28 years). All patients must have the lesions involving primarily the rolandic area and including the central sulcus, the precentral gyrus, the postcentral gyrus or the paracentral lobule, and occupied the somatotopically expected M1 representation. Five patients had known diagnosis of primary brain tumor such as glioblastoma multiforme (GBM), WHO grade IV (n = 1), diffuse astrocytoma WHO grade II (n = 2), dysembryoplastic neuroepithelial tumor (DNET) WHO grade I (n = 1) and unknown pathology report (n = 1). Three patients had known diagnosis of brain AVMs. All patients performed both finger tapping and/or palm scratching methods. Demographic data, locations of the lesions, clinical presentations, histopathology, and treatment of each patient were summarized in Table 1.

Image techniques

Anatomical images

Morphologic imaging was performed during the same imaging session with a 1.5-T scanner (Signa HDxt; General Electric HealthCare, Milwaukee, WI, USA) with echo-planar capabilities and a standard whole-head transmit-receive coil including acquisition of the sagittal and axial T1-weighted sequence (TR/TE = 460/14, section thickness = 5 mm, gap 1.5 mm), axial T2-weighted and fluid-attenuated inversion recovery FLAIR sequence (TR/TE = 4000/89.4, 9000/133) and coronal gradient sequence (TR/TE = 700/20). In case of brain AVMs, additional axial PD sequence (TR/TE = 3000/11.8, section thickness = 3 mm, no gap) and 3D time-of-flight MRA were performed.

fMRI images

BOLD-fMRI studies (single-shot echo-planar imaging: 2000/40, flip angle = 60; voxel size = 2.5 x 2.5 x 5 mm) covered the primary and non-primary motor areas with eight to eleven sections. Forty images per section were acquired during ten alternating periods of rest-task performance. The motor task paradigm involved repetitive finger-to-thumb opposition. All fingers were used simultaneously. The palm scratching task paradigm was also used in some patients who presented with hemiparesis. The active hand was positioned beside the body on the imager table to minimize involvement of other muscle groups. Before the subjects were positioned in the MR systems, they were instructed as to how to keep their head still and how to perform the finger-to-thumb opposition

Table 1. Summary of patient information

Patient No.	Sex/age	Location	Clinical presentation	Pathology	Treatment
1	F/36	Bilateral precentral and postcentral gyri	Right hemiparesis	GBM	Loss follow-up
2	F/23	Left central sulcus and paracentral lobule	Right hemiparesis	AVM	Surgery
3	M/40	Right postcentral gyrus	Generalized seizure	Astrocytoma	Surgery
4	F/10	Left postcentral gyrus	Focal seizure	DNET	Surgery
5	F/18	Right precentral gyrus	Generalized seizure	AVM	Stereotactic radiotherapy
6	M/39	Right precentral gyrus	Generalized seizure	Astrocytoma	Surgery
7	F/31	Right postcentral gyrus	Headache	AVM	Endovascular intervention
8	M/33	Right precentral and postcentral gyri	Left hemiparesis	Tumor	Missing

GBM = glioblastoma multiforme; AVM = arteriovenous malformation; DNET = dysembryoplastic neuroepithelial tumor

movements at a rate of approximately one per second. Functional images were acquired in blocks of five control (rest) images followed by five activation images. Each cycle of five rest and five activation images was repeated at ten seconds.

fMRI Imaging data analysis

Neuronal activation maps were color-coded according to the statistical significance of difference between the rest and activation states and overlaid over the anatomical T1-weighted images for anatomical reference. For the statistical analysis and additional post-processing, the authors used special software (Iviewbold). The results of fMRI were made as presence or absence of activation in the primary or non-primary motor cortex areas and distance from the margin of the lesions to the activation at M1 areas were measured.

Results

fMRI images showed signal intensity changes in the range of 1% to 3% between rest and activation conditions for all patients. This gave an assurance that the fMRI signal had a significant parenchymal contribution.

Activation sites varied among subjects. Activation was found in the primary motor area (M1) within the central sulcus, including the posterior bank of the precentral and the anterior bank of the postcentral gyrus, as well as in the paracentral lobule. Activations also were seen in the supplementary motor area (SMA) within the superior frontal gyrus, bordered posteriorly by the paracentral sulcus; in dorsal premotor area

(PMd) along the precentral sulcus and its junction with the superior frontal sulcus; in the parietal areas (PA) along the intraparietal sulcus involving the adjacent superior and inferior parietal lobules.

Detailed analysis of the activated primary and non-primary motor areas during contralesional hand movement of each subject, and the lesion-to-activation distance were demonstrated in Table 2. In seven patients (patients 1-4, 6-8) with brain tumors and AVMs showed functional displacement within the affected M1 areas (Fig. 1, 2). The displacement did not follow the structural distortion induced by the lesions. Patients 6 and 8 also showed activation within the contralateral unaffected M1. In addition, there were activations with non-primary motor areas bilaterally, predominantly at the SMAs. One patient (patient 5) with AVM showed activation within contralateral non-primary motor cortex (PA) without activation in the affected or unaffected M1 (Fig. 3). The distance from the margin of lesions to activation (M1) less than 5-mm and more than 10-mm ranges were found in the patients 3, 4, and patients 7, and 8 respectively. In all patients, the authors were able to determine parenchymal activation in the unaffected primary motor cortex during ipsilesional hand movement.

Discussion

The introduction of fMRI in the early 1990s, with deoxyhemoglobin acting as an endogenous paramagnetic contrast agent and its local changes in concentration leading to an alteration in the T2*-weighted image signal⁽¹⁶⁾, has brought new

Table 2. Activated primary and nonprimary motor areas during contralesional hand movement and lesion-activation distance

Patient No.	M1i	M1c	SMAi	SMAc	PAi	PAC	PMdi	PMdc	Lesion-activation distance (mm)
1	+	-	-	-	+	-	-	-	10
2	+	-	+	+	+	+	-	-	10
3	+	-	+	+	-	-	-	-	0
4	+	-	+	+	-	+	-	+	4
5	-	-	-	-	-	+	-	-	-
6	+	+	+	-	+	+	-	-	7
7	+	-	+	+	-	+	-	+	12
8	+	+	+	+	+	+	+	+	20

+ = indicates presence, - = indicates absence of activation

M1 = primary motor cortex; SMA = supplementary motor areas; PMd = dorsal premotor areas; PA = parietal areas
c = indicates contralateral, i = indicates ipsilateral to lesion

perspectives to the preoperative evaluation of functional areas of the cortex.

BOLD contrast as a physiological basis of fMRI is recognized to arise from a decreased level of paramagnetic deoxyhemoglobin in a region of interest during a steady-state condition compared with an activation period. An increased energy requirement associated with neuronal activity is met mostly by oxidative glucose consumption⁽¹⁷⁾. After the onset of brain activity, a signal is sent to the feeding arteriole to dilate. This results in an increased cerebral blood flow in the downstream capillaries, which is larger than the increase in oxygen consumption. Hence, oxygen increases at the venular side of the capillaries and in

the venous vessels. Furthermore, it has been shown that the increased blood flow at the capillary level is caused by an increase in blood flow velocity⁽¹⁸⁾, which consequently decreases deoxyhemoglobin, resulting in increased signal in fMRI image.

It has been shown that fMRI with BOLD contrast is capable of evaluating cortical activity noninvasively and in a task-specific manner^(19,20). Rene K et al⁽²¹⁾ suggested that fMRI is a valuable tool for assessing motor function in patients with brain tumors. Hatem A et al⁽¹⁾ revealed that for brain AVMs involving the M1 motor cortex the activation patterns extend to primary and non-primary motor areas. The results of the present study supported the hypothesis

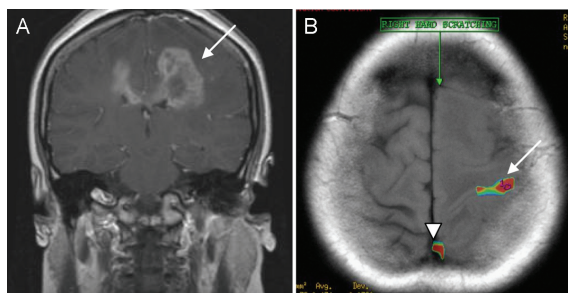


Fig. 1 Patient 1 with glioblastoma multiforme
A) Coronal T1-weighted MR image with gadolinium shows heterogeneous enhancing butterfly like mass at deep white matter of bilateral fronto-parietal lobes and splenium of the corpus callosum (arrow)
B) fMRI during right hand movement, there are activation at the affected left M1 motor area (arrow) which displaced supero-lateral to the lesion about 10 mm and at the left PA (arrowhead)

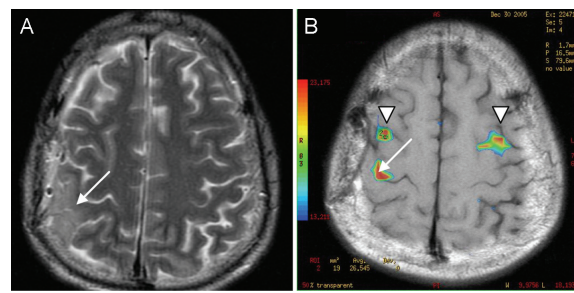


Fig. 2 Patient 3 with diffuse astrocytoma
A) Axial T2-weighted image shows an ill-defined inhomogeneous hypersignal T2 mass involving the right postcentral gyrus (arrow)
B) fMRI during movement of the left hand shows activation of the right primary motor area (arrow). Note displaced closely to medial aspect of the lesion. Also note activation of the non-primary motor areas at SMA bilaterally (arrowhead)

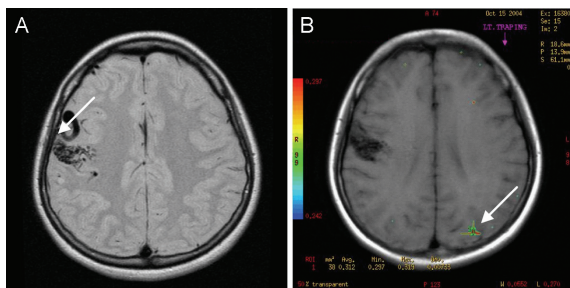


Fig. 3 Patient 5 with arteriovenous malformation
 A) Axial PD image shows AVMs at the right precentral gyrus (arrow)
 B) fMRI during left hand movement, there is no activation at the affected right M1 motor cortex, however, minimal signal activation in the non-primary motor area (contralateral PA) is seen (arrow)

that reorganization of motor function can occur after CNS damage induced by brain tumors, including low and high grades and brain AVMs, the so-called plasticity. Cortical reorganization in the present study showed two patterns: 1) functional displacement within the affected M1 motor area (patients 1-4 and 6-8), and 2) functional change taken over from non-primary motor area (patient 5). Considerable evidence suggests that recovery of function after CNS damage depends on the maturity of the brain at the moment the damage has incurred. Recovery of the function is generally greater when brain damage occurs early in life rather than adulthood. Remaining areas of the brain are able to take over behavioral functions that normally occur in the damaged areas, and that the brain possesses a greater ability to compensate in its immature than in its mature state⁽¹⁾.

The modified vascular bed of the surrounding tissue of brain tumors, especially in high-grade gliomas, can alter the BOLD effect⁽¹⁸⁾. Maldjian JA et al⁽²⁰⁾ reported a reduction of the vascular response in tumor-bearing cortex and postulate that the magnitude of this decrease relates to the severity of motor deficit, which has not yet been proven. However, it seems that the fMRI signal persists even in gross infiltrative cortical regions⁽²²⁾. In addition, Shinoura N et al⁽¹³⁾ demonstrated that the plasticity might occur secondary to changes in hemodynamics rather than regeneration of neurons. The perilesional cortex, the ipsilateral primary motor area, and secondary motor areas have activation in proportion to the size of lesion or degree of paresis. Ipsilateral pathways may also act as a functional

reserve after damage to contralateral routes. The amount of crossing corticospinal fibers varies considerably, ranging between total crossing and no crossing at all.

Hatem A et al⁽¹⁾ assumed that BOLD signal occurs in regions affected by AVMs. However, the hemodynamic perturbations in AVMs may impede the BOLD signal, leaving nervous activation hypothetically undetected. Roberta MS et al⁽²³⁾ suggested that vascular malformations had a high incidence of artifacts, caused by internal static local field gradient, which is blood product in AVM that distorts the image or attenuates the signal intensity. This was found in the patient 5 with AVM, who had no weakness but no activation seen in the affected M1 motor area. Until now, the interfering hemodynamic effects of AVMs with the fMRI signal resulting from BOLD contrast have not been determined⁽¹²⁾.

fMRI data have proved to be an extremely valid preoperative tool that closely agrees with the results from intraoperative cortical stimulation. This invasive technique requires additional craniotomy that increases expenses, morbidity and mortality. Combination of structural MRI and fMRI provide valuable information to the neurosurgeon during pre-operative planning even in the presence of distorting brain lesion⁽¹⁰⁾. Although the patients may undergo endovascular treatment, the functional status of the brain can be tested by local injection of the anesthetics. fMRI provides noninvasively physiologic questions related to cortical reorganization by providing information concerning extensive brain territory⁽¹⁾. fMRI is an additional and useful tool to assess the risk of a new motor deficit after surgery. Rene K et al⁽²¹⁾ suggested that a lesion-to-activation (M1) distance of less than 5 mm is associated with a higher risk of neurological deterioration. Within a 10-mm range, intraoperative cortical stimulation should be performed. For a lesion-to-activation distance of more than 10 mm, a complete resection can be achieved safely. However, the visualization of fiber tracks is desirable to complete the representation of the motor system.

The choice of the task paradigm of activation is of paramount importance in fMRI studies. The signal can vary with the paradigm chosen⁽¹⁹⁾ and the amplitude, speed, and force with which the paradigm is performed⁽²⁴⁾. The authors used two standardized paradigms for all patients and found training sessions before scanning to be very helpful in improving the task execution and patient motivation. The authors

agree with other authors that a simple task remains the paradigm of choice for fMRI scanning⁽²⁵⁾.

Conclusion

In both tumor and AVMs involving the M1 motor cortex, fMRI is a simple and available MRI technique to map cortical reorganization so-called plasticity that extends not only to primary but also to non-primary motor areas. Distortion of the anatomy caused by the tumor or AVMs does not influence the location of the reorganized cortex. fMRI is also a useful tool to assess the lesion-to-activation distance for predicting risk of new motor deficit after surgery. The present study emphasizes the importance of considering additional fMRI with structural MRI to evaluate individual differences in cortical plasticity.

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Potential conflicts of interest

None.

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การตรวจหาการจัดเรียงตัวใหม่ของเปลือกสมองที่ควบคุมการเคลื่อนไหวในผู้ป่วยที่มีเนื้องอกในสมองและกลุ่มความผิดปกติของหลอดเลือดในสมองโดยใช้เอกซเรย์คลื่นแม่เหล็กไฟฟ้า (Functional MRI)

โจชนา ตันติยาทร, ลลิตา วุฒิพิลากร, กมลมาศ เลหาวิริยะกมล

เมื่อมีเนื้องอกในสมองและความผิดปกติของหลอดเลือดในสมองเกิดขึ้นที่บริเวณเปลือกสมองที่ควบคุมการเคลื่อนไหว เปลือกสมองส่วนนี้สามารถมีการจัดเรียงตัวใหม่ (reorganization) ภายในเปลือกสมองตำแหน่งนั้นเองหรือสามารถขยายไปเปลือกสมองตำแหน่งอื่นได้ ผลจากการกดเบียดต่อเนื้อสมองที่เกิดขึ้นทางกายวิภาคโดยตรงไม่ได้มีอิทธิพลต่อตำแหน่งของเปลือกสมองที่เรียงตัวใหม่นั้นและไม่สามารถคาดการณ์ตำแหน่งที่แน่นอนได้ fMRI เป็นการตรวจโดยใช้คลื่นแม่เหล็กไฟฟ้าสามารถใช้หาตำแหน่งของเปลือกสมองที่เรียงตัวใหม่ได้โดยแสดงเป็นสัญญาณ (activation) เกิดขึ้นนอกจากนี้ยังสามารถวัดระยะห่างระหว่างสัญญาณกับขอบของพยาธิสภาพเพื่อคาดการณ์ความเสี่ยงในการเกิดอาการอัมพฤกษ์ขึ้นใหม่จากการผ่าตัด การศึกษาขึ้นเพื่อสนับสนุนการใช้ fMRI ร่วมกับการตรวจคลื่นแม่เหล็กไฟฟ้าพื้นฐาน (conventional MRI) ในการวิเคราะห์ในผู้ป่วยแต่ละบุคคลซึ่งมีความแตกต่างกัน เพื่อช่วยในการวางแผนการผ่าตัด
