Reorganization of the cortical control of movement due to brain tumor growth: evidence from the hemodynamic response function of the supplementary motor area

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Introduction

Reorganization of the cortical control of movement due to adjacent lesions has received recent attention. However, proving that reorganization has occurred by fMRI remains difficult since the neovasculature of malignant brain tumors has been shown to cause an artefactual decrease in fMRI activation (pseudoreorganization)[1,2]. In order to avoid the confounding effects of tumor itself, we focused on patients in whom the tumor invaded the primary motor cortex (PMC) but not the supplementary motor area (SMA). The SMA is considered important for motor programming and execution and is crucial in temporal organization of movements during sequential performance of movements. BOLD fMRI studies have demonstrated SMA activation occurring prior to the PMC[3,4] in healthy controls. The aim of this study was to assess 1) the volume of fMRI activation, 2) the time to peak (TTP) of the hemodynamic response function (HRF) in the SMA and the PMC, during both a block and an event-related motor paradigm in healthy controls and patients with brain tumors. We hypothesize that as the brain tumor invades the PMC, reorganization will occur with the SMA taking over some of the function of the PMC. This reorganization will be characterized by 1) an increase in the volume of fMRI activation in the SMA on the side with the brain tumor and 2) a change in the HRF of the SMA so that it more closely resembles that of the PMC.

Subjects and Functional Tasks

Four patients with glioblastoma multiforme (GBM) were included in this study. The lesion affected the PMC in all subjects. Seven healthy volunteers with no history of neurological illness were recruited for a comparison. A block motor paradigm (TR= 4000 msec; active for 20 sec and rest for 40 sec, 90 images) consisting of sequential finger to thumb tapping in both hands in response to an auditory cue was used to measure the volume of activation in the SMA and PMC. In addition, two event-related motor paradigms consisting of right or left hand finger tapping (TR=1000 msec; active for 4 sec and rest for 20 sec, 144 images) were also used to measure an impulse response function in the SMA and PMC. Prior to fMRI scanning, these motor paradigms were practiced outside of the scanner environment until it was clear that subjects understood the task and were able to comply. Patient's task performance was monitored.

Method and data Analysis

T1-weighted images for 21 contiguous axial slices were acquired for the anatomical reference images. Functional images were acquired with a gradient echo EPI sequence (TR=4000/1000 ms; TE=40 ms; 128×128 matrix; 240 mm FOV; 4.5 mm in thickness). 3D T1-weighted anatomical images were also acquired with a spoiled gradient-recalled acquisition in the steady state (GRASS) sequence. After the functional scans, the anatomic scans were repeated after GD-DTPA. Subject's head motion was minimized using straps and foam padding. Image processing and statistical analysis were performed with AFNI[5] software. The reconstructed fMRI data were aligned using a 3D rigid-body registration method. The cross-correlation method was used to analyze data obtained from block paradigm. To minimize large vessel effects, voxels where the standard deviation of the signal change exceeded 5 percent of the mean signal intensity was set to a value of zero. To analyze data obtained from event-related paradigm, deconvolution analysis was used to estimate, to 16 seconds (16 images), the hemodynamic impulse response function of the fMRI signal on a voxelwise basis with the use of stimulus based vectors. Volume of activation (in mm^3) was measured in the PMC and SMA based on the activation map obtained from the block-paradigm. Impulse response function obtained from the event-related paradigm was used to measure the TTP. Maximally activated cluster of 4 pixels in the PMC and SMA of contralateral and ipsilateral tumor side were chosen for TTP analysis. The TTP was measured by fitting the impulse response function with a gamma variate function[3]. TTP of the PMC was compared to the TTP of the SMA in both contralateral and ipsilateral tumor side. For control subjects, TTPs in the SMA and PMC in both left and right hemispheres (LH, RH) were compared.

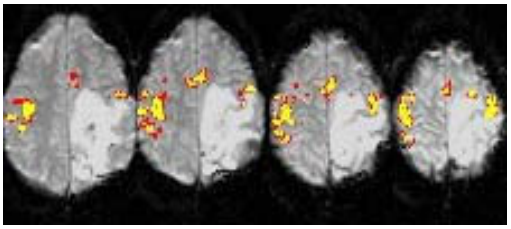
Results

Volume of activation: For 4 out 4 patients, volume of activation in the PMC was decreased on the side ipsilateral to the tumor compared to the contralateral side. 2 out 4 patients showed an increase in the volume of activation in the SMA ipsilateral to the tumor (Figure 1). All control subjects showed that the volume of activation in the PMC of the left hemisphere was greater than that of the right hemisphere, however it was not significantly different (a paired t-test; $p < 0.92$). Volume of activation in the SMA was equally distributed in both hemispheres. *Time to Peak*: For control subjects, the averaged TTP difference between PMC and SMA was 1.0 sec with no difference between two hemispheres. For 4 GBM patients, the TTP difference between PMC and SMA was 1.5 sec, 1.9 sec, 0.7 sec, and 1.3 sec on the side contralateral to the tumor and 0.5 sec, 0.1 sec, 0.1 sec, and 0.4 sec on the side ipsilateral to the tumor (Figure 2 as an example). The TTP difference between two sides to the tumor was statistically significant ($p<0.003$).

Discussion

The data support the hypothesis that as a malignant brain tumor invades the PMC, the SMA appears to take over some of the function. First, there is a greater volume of fMRI activation on the side ipsilateral to the tumor. This cannot be explained by an artefactual effect of the tumor on the fMRI signal since in all cases, the tumor did not involve the SMA. Secondly, the HRF of the SMA begins to take on the appearance of the PMC (Fig. 2). This result supports the concept that the SMA may be taking over the primary motor execution function rather than motor planning (the traditional role of the SMA) when the functional process of the PMC becomes hindered by tumor growth. Reorganization of the cortical motor cortex is an important phenomenon which might describe the diversity of motor deficits in patients with tumors close to or invaded to the primary motor cortex. Our results show that the role of the SMA becomes more important when a tumor invaded the PMC and time to peak of the hemodynamic response can be used to interpret the reorganization of the motor system based on the temporal pattern.

Figure 1. Activation map of a 24 year old woman with GBM in the left parietal cortex.



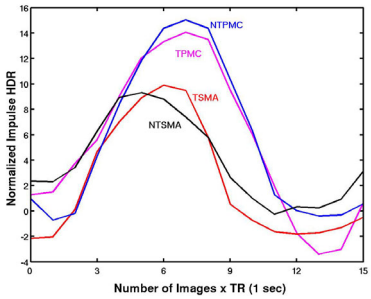


Figure2. Impulse response function in the SMA and the PMC (TPMC: PMC ipsilateral to the tumor; NTPMC: PMC contralateral to the tumor)

References

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