

# The Characteristics of BOLD Hemodynamic Response Function of the Primary Motor Cortex in Patients with High Grade Brain Tumors

K. Peck<sup>1,2</sup>, B. Hou<sup>1,2</sup>, N. Petrovich<sup>2</sup>, P. Gutin<sup>3</sup>, A. Holodny<sup>2</sup>

<sup>1</sup>Medical Physics, Memorial Sloan-Kettering Cancer Center, New York, New York, United States, <sup>2</sup>Radiology, Memorial Sloan-Kettering Cancer Center, New York, New York, United States, <sup>3</sup>Surgery, Memorial Sloan-Kettering Cancer Center, New York, New York, United States

## Introduction

Blood oxygenation-level dependent (BOLD) functional MRI is a clinically useful technique for preoperative mapping of eloquent cortices in patients with brain tumors. Previous studies have shown that apparent decreases in the magnitude of the activation volumes within and in the vicinity of the primary motor cortex (PMC) may arise from lesion-induced neurovascular uncoupling and/or prior surgery effect (1,2,3). However, understanding brain function of tumor patients requires information not only on the spatial localization of activation, but also on its temporal evolution. The hemodynamic response is a result of increased neuronal synaptic activity. However, patients with a high grade glioma may develop compensatory changes in local cerebral vasculature with a resultant loss of vascular reactivity. As the result, different patterns of BOLD hemodynamic properties compared to the controls may be expected from the areas in/around malignant tumors. In previous studies, time-resolved fMRI studies have been performed to investigate temporal differences in different cortical areas in normal human volunteers (4) and stroke patients (5). The aim of this study was to use time-resolved BOLD fMRI to investigate time dependent HDR within PMC in the presence of an adjacent brain tumor, relative to healthy control subjects. For this purpose, we measured the percent signal change, time to peak (TTP), and full width at half maximum (FWHM) of the BOLD hemodynamic response within the bi-hemispheric PMC of both groups.

## Subjects and Functional Tasks

Seven right-handed brain tumor patients (ranging in age from 24 to 71 years) in whom a glioblastoma multiforme (GBM) invades or is directly adjacent to the PMC were included. Seven right-handed healthy volunteers (ranging in age from 23 to 46 years), with no previous history of neurological illness, were included to serve as controls. Two event-related motor paradigms, consisting of right- or left-handed finger tapping (TR=1000 msec; repetitions=6; active period (4 images) = 4 sec; rest period (20 images) = 20 sec) were used to produce impulse response functions (IRF) as well as activation areas in the PMC. This task yielded a total of 144 images. Prior to fMRI scanning, these motor paradigms were practiced outside of the scanner environment until subjects acknowledged an understanding of the task, and could execute the task successfully.

## Method and data Analysis

T1-weighted images for 10 contiguous axial slices were acquired for the anatomical reference images. Functional images were acquired with a gradient echo EPI sequence (TR=1000 ms; TE=40 ms; 128x128 matrix; 240 mm FOV; 4.5 mm in thickness) with 1.5T GE scanner. 3D T1-weighted anatomical images were also acquired with a spoiled gradient-recalled acquisition in the steady state (GRASS) sequence. Subject's head motion was minimized using straps and foam padding. Image processing and statistical analysis were performed with AFNI software (6). The reconstructed fMRI data were aligned using a 3D rigid-body registration method. To reduce false positive activity, we set to zero voxels where the standard deviation of the acquired time series exceeded 8 percent of the mean signal intensity. A deconvolution analysis (6) was applied to the entire signal time series in order to derive the hemodynamic impulse response function on a voxel-wise basis. From this data, four IRFs corresponding to maximally-activated clusters (4 pixels) in both the contralateral (CL) and ipsilateral (IL) PMC to the tumor, were chosen for following analysis. Selection of these pixels was based on a single representative slice demonstrating the maximum tumor volume. The averaged IRF was fitted using a gamma-variate function and then using the fitted IRF, 1) percent signal change relative to the baseline, 2) TTP defined as the time interval between the stimulus onset and the time corresponding to the maximum signal intensity, and 3) full width at half maximum (in second), were measured. For control subjects, the same analysis was applied for both left and right hemispheres.

## Results

Statistical parametric maps showing PMC activation in both tumor patients and controls were generated at a significant threshold ( $p<0.0001$ , uncorrected). The histogram below shows the mean and standard deviations on the measurements by group and the following results were obtained (Figure): **Percent signal change:** A paired t-test comparing both CL and IL PMCs in patients indicates that there was no significant difference in percent signal change ( $p=0.71$ ). There also was no significant difference in PMCs between the hemispheres of controls ( $p=0.30$ ) or when we compared the controls to the hemispheres with tumor ( $p=0.26$ ). **FWHM:** A paired t-test yielded a p-value of 0.05, indicating that there was a trend showing a significant difference in FWHM of the HDR between CL and IL PMCs in tumor patients. Additionally we found no differences in hemispheres of the controls, ( $p=0.19$ ). The Wilcoxon two sided test yielded a p-value of 0.20, again indicating no significant difference between the tumor patients and the controls. **Time to peak:** The p-value of 0.31 indicated that there was no significant difference in time to peaks between the CL and IL PMCs in patients. Additionally, there was no difference in time to peak between the hemispheres of healthy controls. Using an exact Wilcoxon two sided test we found that there may be a trend showing a difference in time to peak between the tumor patients and the controls ( $p=0.056$ ).

## Discussion

We quantitatively investigated the BOLD fMRI impulse response function of the PMC in patients with high grade glioma. Hemodynamic parameters obtained through the IRF in the IL PMC were contrasted with those of the CL PMC. Interestingly, using a brief event-related motor movement, percent signal change showed no differences in both IL and CL PMC in tumor patients. The same result was obtained from a comparison between tumor and controls. The range of the TTP after initiation of movement was 6.8 to 7.6 sec and 6.2 to 7.8 sec for IL and CL to the tumor respectively, and 6.8 to 7.2 sec and 6.6 to 7.5 sec for left only and right only hand performance in controls respectively. It appears that tumor patient's PMC have longer TTPs compared to that of controls. The loss of arteriole-capillary-venous bed support to the tissue in the vicinity of the tumor may cause a compensatory change, which could lead a delay in blood flow coming into the PMC. FWHM measurement showed a trend that FWHM of IL PMC was about 0.7 sec wider than that of CL PMC in tumor patients, reflecting a prolonged response in the vicinity of the tumor. The hemodynamic response is the result of increased neuronal synaptic activity and includes contributions from increases in blood flow, blood volume, and the proportion of oxygenated relative to deoxygenated hemoglobin. However, in the vicinity of the tumor, normal BOLD mechanism may not be expected.

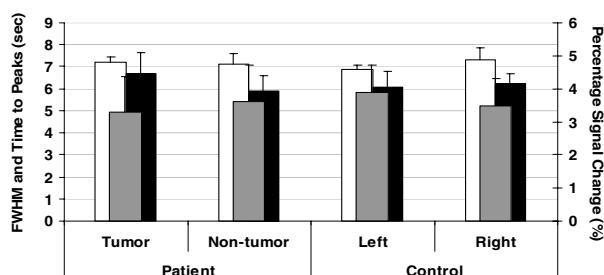


Figure: Histogram showing averaged time to peak (white), FWHM (black) and percent signal change (grey) in the primary motor cortex. The data were compared between ipsilateral (Tumor) and contralateral (Non-Tumor) to the tumor, and between tumor patients and controls.

## References

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