Decrease in BOLD fMRI Activation Volume due to Abnormal Neovasculature and Metabolite Levels in Brain Tumor Patients

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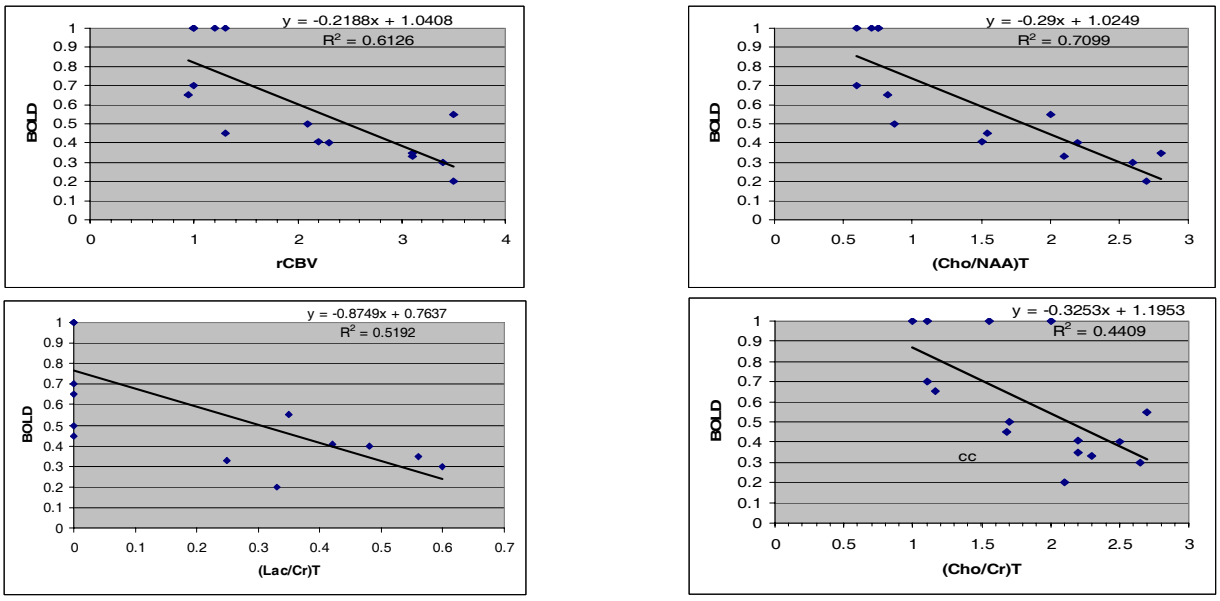
Introduction: Accurately determining the location and activation volume of eloquent cortices adjacent to brain tumors by BOLD fMRI is important for presurgical planning and for understanding the mechanism of the BOLD phenomena. Increased cerebral blood volume (CBV) and decreased BOLD fMRI activation volume in the primary motor cortex (PMC) have been seen in patients with glioblastoma multiforme (GBM) (1-3). These prior studies concluded that in patients with GBM's the presence of abnormal tumor neovasculature leads to decoupling of neuronal activity and blood flow, which results (at least in part) in the observed decrease in BOLD signal. The goal of the present study was to test the hypothesis that tumor factors reflected by abnormal metabolite levels could account for a decrease in BOLD fMRI signal separate from that accounted for by the presence of abnormal neovasculature.

Method and Materials: 15 patients with 9 GBMs, 3 metastases, 1 meningioma, 1 anaplastic astrocytoma, and 1 oligodendroglioma were scanned by using a 1.5T General Electric (GE) TwinSpeed MRI scanner. All tumors were located near to the PMCs, and 7 GBMs were located directly on the PMCs. The protocol included high resolution axial T2 or T1-weighted spin echo images (256x256 matrix, 21 axial slices, 4.5 mm slice thickness with 0 gap), BOLD fMRI with bilateral finger tapping (gradient echo EPI, TR/TE =4000/40 msec), Dynamic susceptibility contrast (DSC) perfusion MRI (gradient echo EPI, TR/TE =1000/40 msec, 0.1 mmol/kg Gd at 3cc/sec) and multi-voxel ^{1}H 3D MRSI (PRESS sequence, TR/TE=1000/144 msec, 8x8x8 matrix). The slices for the fMRI, perfusion, and MRSI scans were selected to match the locations of T2 or T1-weighted images. The fMRI data were analyzed using AFNI. Image processing was performed using correlation coefficients to threshold the activation volumes of the PMC. The significant threshold was set at $P<0.05$, typically for a correlation coefficient of 0.4-0.5. The rCBV values of both PMCs were calculated by integrating the areas under the curve of the gadolinium bolus. The ratios of fMRI activation and rCBV for the tumor sides (T) to the non-tumor sides (NT) in the PMCs were calculated by fMRI(T/NT) and rCBV(T/NT). The Cho/NAA, Cho/Cr and Lac/Cr ratios for both PMCs were calculated using GE's FuncTool software, and for the Lac/Cr ratios less than 0.1 (i.e., "under-detected") were labeled as zero. A linear regression method was applied for establishing the relationships between BOLD fMRI activation volume with rCBV and the metabolite levels. For evaluating statistical significant correlation between two parameters in the relationships, we used a "p" less than 0.05 as the standard.

Results: For the 15 patients with brain tumors, BOLD fMRI activation volume ratios ranged from 0.2 to 1.0 (mean = 0.59), while rCBV ratios in the PMCs ranged from 3.5 to 1.0 (mean = 2.03). (Cho/NAA)T, (Cho/Cr)T, and (Lac/Cr)T ratios ranged from 2.8 to 0.6 (mean = 1.52), 2.65 to 1.0 (mean = 1.86), and 0.6 to 0 (mean = 0.20), respectively, while (Cho/NAA)NT and (Cho/Cr)NT ratios ranged from 0.8 to 0.46 (mean = 0.58), and 1.30 to 0.95 (mean = 1.11), respectively. All (Lac/Cr)NT ratios were under-detected level. The (Lac/Cr)T ratios were not zero for only these 7 GBMs located directly on the PMCs. The mean (Lac/Cr)T and the standard deviation (SD) of the 7 GBMs were 0.43 (0.13). Their mean BOLD and rCBV ratios were 0.36 (0.11) and 3.01(0.55), respectively, and were significantly different from those of the remaining eight cases with the mean BOLD ratio of 0.79 (0.24) and the mean rCBV ratio of 1.23 (0.38) (p=0.0011 and 0.00022, respectively). The correlations between BOLD and rCBV, (Cho/NAA)T, (Lac/Cr)T, and (Cho/Cr)T for all 15 patients were fitted and shown in figure 1 (a-d).

Figures 1 (a-d): Correlations between rCBV ratio, (Cho/NAA)T, (Lac/Cr)T, and (Cho/Cr)T and BOLD ratio (i.e., BOLD fMRI activation volume ratio) for all 15 patients.



Discussions: The BOLD signal for a brain tumor patient is determined by multiple factors, including but no limited to cerebral blood flow (CBF), cerebral metabolic rate of oxygen (CMR02) and CBV. Our results for the seven GBMs in the PMC suggest that the presence of abnormal neovasculature (indicated by high rCBV ratios) may result in decoupling of neuronal activity and blood flow, corresponding to a muted BOLD response. An inverse relationship between rCBV and the BOLD fMRI ratios was found (figure 1a, r=0.78 and p=0.0006) for all 15 brain tumor patients additionally supporting the decoupling effect. Attenuated BOLD signal activation volume was further linked to increased metabolic levels on the tumor side: Cho/NAA (r=0.84, $p=8.89*10^{-5}$), Lac/Cr (r=0.72, p=0.0025), Cho/Cr (r=0.66, p=0.0074) (figures 1b, 1c, and 1d). No significant relationships were found for the BOLD ratio and the spectroscopy metabolites on the non-tumor side. Since the spectroscopy values: Cho/NAA)T correlated better with the BOLD ratios than rCBV, it would appear that there are factors other than the presence of neovasculature that cause a decrease in BOLD fMRI signal. An increase in (Cho/NAA)T reflects neuronal dysfunction and/or loss whereas an increase in (Cho/Cr)T indicates tumor cell proliferation (4). As the consequence, BOLD signal may be decreased due to the presence of fewer functional neurons. An increase in Lac/Cr indicates the presence of hypoxia to the point where the increase in CMRO2 cannot be compensated by the already maximally dilated blood vessels. Blood vessels that are already maximally dilated cannot further dilate which will essentially eliminate basis of the BOLD response. Our multi-modal approach, utilizing conventional MRI, BOLD fMRI, proton MRSI, and DSC perfusion MRI, demonstrates the potential for improving our ability to interpret BOLD fMRI signal in brain tumor regions.

References: 1. Holodny, AI, et al., AJNR Am J Neuroradiol, 1999, 20: 609-612. 2. Hou BL, et al., NeuroImage, 2006, 32: 489-497. 3. Hou BL, et al., ISMRM2006, #606. 4. Cady, EB, Childs Nerv. Syst., 2001, 17:145-149.