BOLD Response in Pediatric Brian Tumor Patients during Treatment

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Introduction

Functional MRI (fMRI) is a promising tool to investigate the neural substrates of cognitive deficits that affect survivors of childhood cancer. However, therapy-induced vasculopathy may alter the blood oxygen level dependent response (BOLD) and confound the interpretation of fMRI studies in this population. In a cross-sectional study of long-term survivors (mean time since diagnosis = 5.4 ± 2.3 years) of leukemia and brain tumor, we found that the BOLD response in the primary visual cortex (V1) to photic stimulation was qualitatively normal, but the post-stimulus undershoot was deeper and more prolonged in patients than in controls[1]. Here we report preliminary results from an ongoing longitudinal fMRI study of children being treated for medulloblastoma, a common childhood brain tumor that occurs primarily in the posterior fossa. Therapy for medulloblastoma consists of maximal resection, craniospinal radiation, and chemotherapy. Our objective in this analysis was to evaluate the acute effect of craniospinal radiation on the BOLD response in V1.

Methods

Subjects: The study was approved by our institutional Office of Human Subjects Protection, and all subjects gave written informed consent to participate. So far, of 17 patients enrolled (age 10.6 ± 1.2 years at the first fMRI), 13 have completed fMRI after surgical tumor resection (TP1), 10 at the completion of radiation therapy (TP2, mean TP2-TP1 = 2.7 ± 2.3 months), and 5 after completion of chemotherapy at (TP3, mean TP3-TP2 = 7.3 ± 0.5 months). ***MRI:*** 1.5T Siemens Symphony scanner. Single shot T2* weighted EPI (TR = 2.06 sec, TE = 50 msec, FOV =192 mm, matrix =64x64, slice thickness = 5 mm, bandwidth = 1954 Hz/pixel) for fMRI data acquisition. ***Visual stimulation*** was a reversing (8 Hz) black-white checkerboard, and the paradigm included four 30-sec blocks in which the stimulus was on for 2 sec; and three 40-sec blocks in which the stimulus was on for 16-sec. ***Data Analysis:*** SPM2 (http://www.fil.ion.ucl.ac.uk/spm/) was used. Images were realigned before voxel based statistical analysis. The thresholds for estimate activation volume were $p = 0.001$ (uncorrected) and 5 voxels ($p < 0.01$ corrected). The average time course of activated ROI in the primary visual cortex was obtained using MarsBar toolbox for SPM2 (http://marsbar.sourceforge.net/).

Results

There was a significant decrease in the BOLD signal and the detected volume of activation after radiation therapy. For the 10 patients who successfully completed the fMRI at TP1 and TP2, the peak BOLD signal decreased by 50% for the shorter (2 sec) stimulus and by 40% for the longer (16 sec) stimulus (Fig. 1). The detected volume of activation decreased by 70%, from 455 ±113 to 126 ± 67 (Fig. 2). These changes between TP2 and TP1 were statistically significant ($p = 0.01$ for BOLD peak and $p = 0.008$ for activated voxels, paired 2-sample t-test). Data from the small number of patients at TP3 suggests that the BOLD response was still depressed 7 months after the completion of radiation therapy (data not shown).

Discussion and Conclusions

Based on control data from our previous study (1), the BOLD response was normal in this cohort of medulloblastoma patients prior to radiation therapy. Furthermore, our data from long-term survivors of medulloblastoma suggest that the BOLD response will recover to essentially normal levels by about one year after the completion of all therapy. Therefore, the changes in BOLD response that we observed reflect either an acute effect of radiation therapy or a more slowly evolving reaction to disease, surgery, and therapy. As accrual to this protocol continues we will evaluate the BOLD response in V1 in relation to patient specific radiation dosimetry, to other functional neuroimaging data (perfusion, diffusion tensor, morphometry, cognitive fMRI), and to neuropsychological testing results. We anticipate that this comprehensive evaluation will yield important insights into the neural substrates of the cognitive sequella of medulloblastoma therapy.

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References: 1. Zou, P., et al., NeuroImage 2004 (in press).

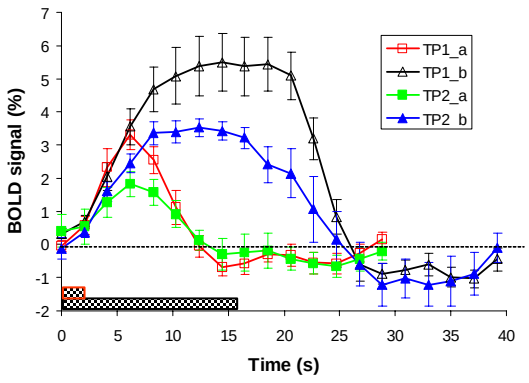

Fig 1. BOLD response to the shorter (2 sec) and longer (16 sec) visual stimuli before (TP1) and after (TP2) radiation.

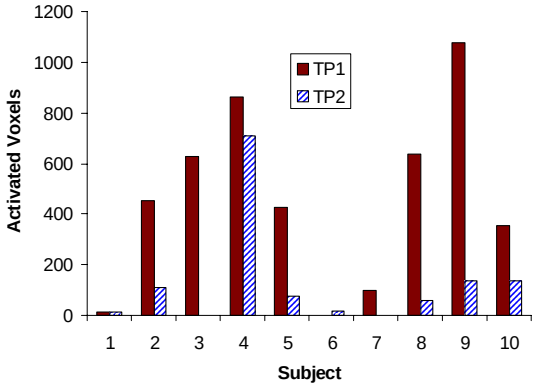

Fig 2. Total number of activated voxels in V1 before (TP1) and after (TP2) radiation .