

Structural, Metabolic and Functional Relationships between the Eye and the Brain in Glaucoma using Multimodal MRI and Optical Coherence Tomography

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Target Audience: Clinicians and scientists interested in translational use of MRI and MRS to study ophthalmic disease in the brain.

Purpose: Glaucoma is a neurodegenerative disease of the visual system. Although recent reports indicate the involvement of the visual brain in addition to the eye, the causes and pathogenesis of glaucoma in the human visual brain and their relationships with glaucoma progression in the eye remain largely unknown. This study aimed to use a noninvasive MRI exam to investigate neurophysiological alterations in the visual cortex associated with glaucoma, and to associate brain MRI findings with clinical ophthalmic imaging assessments.

Methods: *Subject Recruitment:* We recruited 22 subjects after obtaining informed written consent, and categorized them into 6 control subjects, 7 early glaucoma subjects and 9 advanced glaucoma subjects according to the American Glaucoma Society coding system. *MRI Protocol:* MR images were collected on a 3T Siemens Allegra scanner. To measure activation in the visual cortex, each subject underwent two fMRI scans (one for each eye). The subjects focused on a fixation cross while they were presented with 8Hz hemifield checkerboard patterns that alternated between the upper and lower visual fields with each trial. The stimuli were presented in a block paradigm with 12 seconds of rest and 12 seconds of stimulus repeated for 12 trials. Functional MR images were collected with a single-shot gradient echo EPI pulse sequence with the following parameters: TR/TE=2000/26 ms, FOV=20.5 cm, 104x104 imaging matrix, and twenty-eight contiguous 3 mm thick slices to cover the entire occipital lobe. In addition, 1H-MRS data were collected from a 20x25x30 mm³ voxel centered about the calcarine sulcus using a STEAM sequence. *Data Analysis:* For fMRI data, we calculated activation maps for each subject using a combination of in-house software and SPM8 subroutines. Images underwent slice timing correction and realignment, were normalized to MNI space, masked with a subject specific gray matter mask, and smoothed with a Gaussian kernel (FWHM=5 mm). The time course of each voxel was fitted with a general linear model (GLM) with predictors including the stimuli paradigms (one predictor for each the upper and lower field stimuli) convolved with a canonical hemodynamic response function, the temporal derivative of those predictors, motion parameters obtained during realignment, and a constant. BOLD % change maps (one for each combination of eye and field) were calculated by dividing the coefficient of the stimulus paradigm predictor by the coefficient of the constant term. A one sample t-test for each of the upper and lower visual field stimuli for the left eye is shown in Figure 1 (thresholded at an FDR corrected p<0.05). Since glaucoma subjects each have a unique visual field deficit, data were summarized within a region of interest (ROI) that was the intersection of a subject specific gray matter mask, regions of significant positive BOLD response across all subjects for a given field (seen in Fig. 1), and Brodmann area (BA) 17 (primary visual cortex). For each subject, four measures of activation were measured corresponding to each possible combination of eye and field. *Metabolic and structural measurements:* For 1H-MRS, peak integrals from the visual brain were determined using Siemens' Syngo MR software for comparison with brain functions in BOLD-fMRI. In addition, the regional averages of clinical spectral-domain optical coherence tomography (OCT) measurements of macular retinal ganglion cell/inner plexiform layer (RGCL+IPL) thickness were obtained in each eye of the same patients for comparison with brain fMRI results. *Statistical analysis:* Differences between groups were tested by MANOVA. Post hoc t-tests were used to detect pairwise group differences. Correlations were tested using a GLM to control for eye, visual field and differences between subjects. FDR corrected p values of less than 0.05 were considered significant.

Results and Discussion: MANOVA revealed significant group-wise differences in BA 17 as shown in the left panel of Figure 2 (p<0.01). Both the control and early glaucoma groups exhibited significantly greater activation than the advanced glaucoma group (p<0.01). No significant differences were observed between the control and early glaucoma groups, suggesting that alterations in the response of the BA 17 to visual stimulation occur only at high levels of disease severity. Furthermore, the BOLD response within BA 17 was significantly correlated with retinal RGCL+IPL thickness in the eye as assessed by clinical ophthalmic

imaging using OCT (Figure 2 middle panel, p<0.05), as well as with the ratio of N-acetylaspartate to creatine measured by 1H-MRS, which is typically considered a measure of neuronal integrity (right panel of Figure 2, p<0.01). Collectively, these results reproduce the finding that glaucoma affects brain function in the visual cortex as assessed by fMRI, and further demonstrate that a significant relationship exists between brain function and metabolism and clinical ophthalmic measures of glaucoma severity.

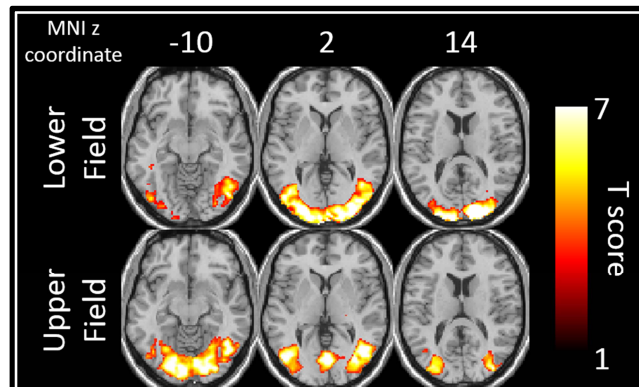


Figure 1. Sample BOLD fMRI activation maps showing results of one sample t-tests for the left eye visual stimulation (thresholded at an FDR corrected p<0.05). Note that upper visual field stimulation activated predominantly the ventral visual cortex while lower visual field stimulation activated predominantly the dorsal visual cortex.

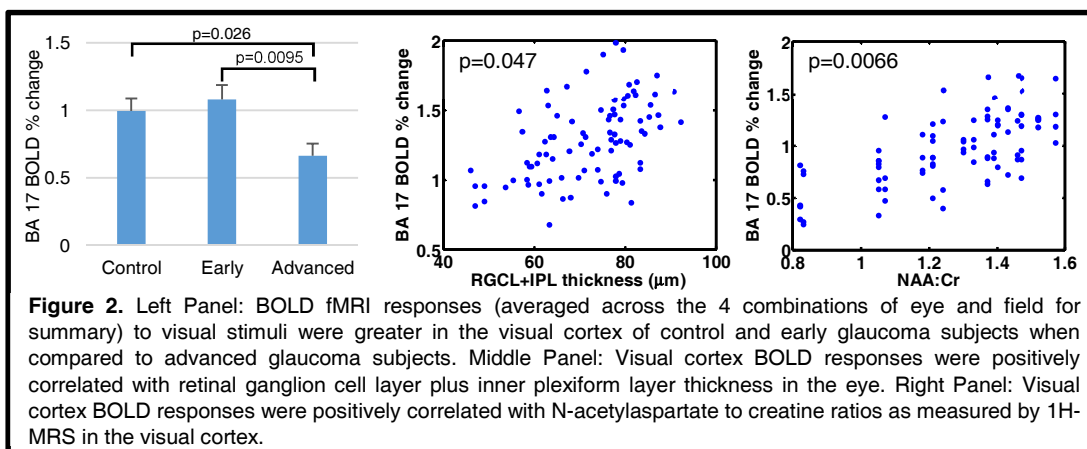


Figure 2. Left Panel: BOLD fMRI responses (averaged across the 4 combinations of eye and field for summary) to visual stimuli were greater in the visual cortex of control and early glaucoma subjects when compared to advanced glaucoma subjects. Middle Panel: Visual cortex BOLD responses were positively correlated with retinal ganglion cell layer plus inner plexiform layer thickness in the eye. Right Panel: Visual cortex BOLD responses were positively correlated with N-acetylaspartate to creatine ratios as measured by 1H-MRS in the visual cortex.