Retinotopic-specific changes of cerebral blood flow and grey matter in visual cortex of patients with glaucoma

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Target audience: Those who are interested in clinical applications of perfusion functional imaging and voxel-based morphometry (VBM).

Purpose: Glaucoma is traditionally perceived as an ocular disease. However, accumulating evidence indicates that visual pathway from retina to visual cortex may all be involved in this disease[1, 2]. We have investigated changes in brain cortical structure, cerebral blood flow (CBF) and magnetic resonance spectroscopy (MRS) in the visual cortices of patients with primary open angle glaucoma (POAG) in comparison with age-matched controls.

Methods: Twenty-three POAG patients (14 males; age 47.5±7.6 years) and 26 healthy subjects (17 males; age 48.4±7.5 years; as controls) were scanned on a Siemens Trio Tim 3T scanner (Erlangen, Germany) with written informed consent. A conventional multi-echo 3D MP-RAGE sequence was used to acquire T1-weighted images, which were used as an anatomic reference for VBM analysis[3] [matrix size: 256 × 256, 176 sagittal slices, voxel size: 1.0 x 1.0 x 1.0 mm^3, phase encoding anterior-posterior, TR/TI/TE: 2530/1100/(1.64, 3.5, 5.36, 7.22) ms, flip angle: 7°, bandwidth: 651 Hz/px for all echoes (bipolar readout trajectory), acceleration: 2x GRAPPA (32 ref. lines)]. After 3D structural image acquisition, the subjects were scanned by pulsed continuous arterial spin labeling (pCASL)[3] in rest, monocular and binocular stimulation with black-white checkerboard alternating at 8 Hz, and MRS in rest. The pCASL acquisitions were performed using a single-shot gradient-echo echo-planar imaging (EPI) sequence [matrix: 64 × 64, 20 slices, voxel size: 3.4 × 3.4 × 5.0 mm^3 with 1 mm gap between slice, 7/8 phase partial Fourier, 2x GRAPPA (24 ref. lines), labeling duration: 1650 ms, post labeling delay: 1200 ms, TR/TE: 4000/9.2 ms, flip angle: 90°, bandwidth: 3004 Hz/Px]. Single-voxel 1H-MRS was acquired in occipital pole including both the left and right sides (Fig. 2b upper) (TR/TE: 2000/144 ms, signal averages: 128, single-voxel size: 30 × 15 × 20 mm^3).

The EPI data were preprocessed using Matlab, SPM8, VBM8, marsbar and ASLtbx. For each dataset, EPI images were realigned, coregistrated to structural image, and spatial smoothed. Following the spatial pre-processing, the CBF images were first reconstructed with ASLtbx, and then normalized to the MNI space. The first 2 images were eliminated and the remaining 30 CBF images were averaged into a single image for each condition (rest, monocular or binocular stimulation) for each patient or healthy subject. Lastly, two-sample *t* test with the averaged CBF images between patient and control groups was adapted for detection of the CBF difference. The value of regional CBF (rCBF) was extracted and normalized to the global mean value of the averaged CBF image, followed by a two-sample *t* test of rCBF value to determine the significant difference between the two groups. The 3D structural images were spatially adjusted for VBM analysis [4]. A standard segmentation of gray matter (GM), white matter (WM) and cerebral spinal fluid (CSF) was conducted for each dataset, followed by GM image normalization and spatial smoothing with a 6 mm FWHM Gaussian kernel. A two-sample *t*-test of those smoothed GM images of the two groups was adapted to investigate the change of GM volume in patients compared to the healthy subjects. The MRS data were processed by Syngo™ spectroscopy software package (Siemens Medical Solutions). All peak values (concentrations of each of the measured metabolites) were normalized to that of creatine (Cr) [2]. The same two-sample *t*-test of the normalized concentrations was conducted to compare the difference between the two groups.

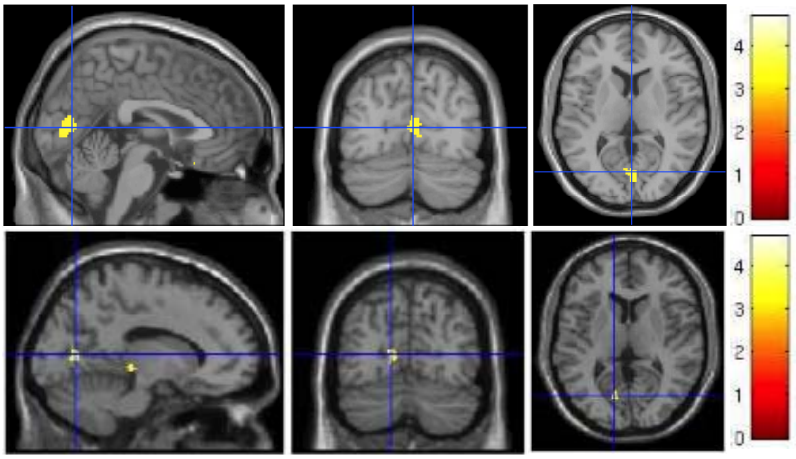

Fig. 1

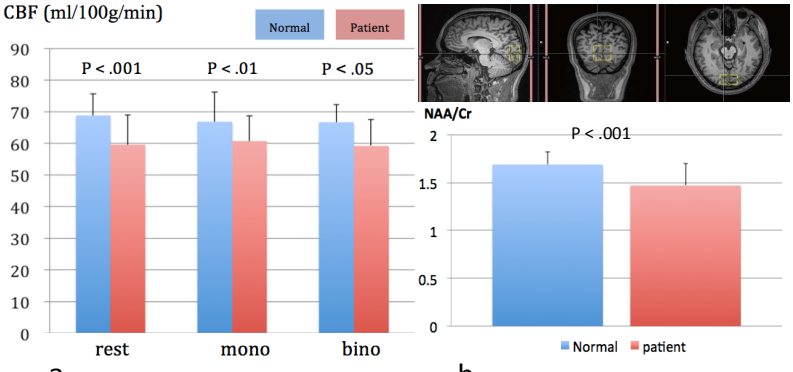

Fig. 2

Results: Figure 1 shows the t-maps ($p < .001$, uncorrected, extend voxel size = 40) of CBF (a) and VBM (b). A convergent result was obtained: rCBF and grey matter volume reductions were observed in peripheral retina projection zones in the visual cortex of glaucoma patients. Figure 2a shows comparison of the rCBF values for the activated region shown in Fig. 1a, while Figure 2b displays comparison of normalized concentrations of N-acetyl-aspartate (NAA/Cr) of single-voxel 1H-MRS. The resting rCBF of the POAG patients was significantly lower than the controls (59.59± 9.44 vs. 68.90±6.82 ml/100g/min, $p < 0.001$). Similarly, rCBF in monocular and binocular stimulation of patients were both significantly lower than the controls (60.72±8.05 vs. 66.84±5.54 ml/100g/min, $p < 0.01$; 59.24±8.27 vs. 66.78±6.18 ml/100g/min, $p < 0.05$). The normalized NAA concentration of patients was significantly lower than the controls, which indicated a similar trend of change in POAG patients in rCBF.

Discussion & Conclusion: Brain changes in glaucoma have not been well understood yet in human subjects. Meanwhile, no sensitive and specific imaging marker has been developed in the diagnosis and following up in clinical patient management. In this study, we have observed differences in blood flow, morphology and metabolites in the visual cortex between POAG patients and age-matched controls. Comparing with controls, the POAG patients showed grey matter volumetric reduction in peripheral retina projection zones in the visual cortex. Whole brain ASL study has shown a local decrease of cerebral blood flow in the same region. These findings suggest a retinotopic-specific neuronal degeneration of visual cortex accompanied by cerebral blood flow insufficiency in glaucoma. This indicates that rCBF and/or VBM may be used as a specific and sensitive marker in assessing brain injury in glaucoma patients. Further, glaucoma patients can be benefited from neuroprotective strategies targeting at entire visual pathway.

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