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Arterial spin labeling fMRI measurements of decreased blood flow in primary visual cortex correlates with decreased visual function in human glaucoma

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ABSTRACT

Purpose: Altered metabolic activity has been identified as a potential contributing factor to the neurodegeneration associated with primary open angle glaucoma (POAG). Consequently, we sought to determine whether there is a relationship between the loss of visual function in human glaucoma and resting blood perfusion within primary visual cortex (V1).
Methods: Arterial spin labeling (ASL) functional magnetic resonance imaging (fMRI) was conducted in 10 participants with POAG. Resting cerebral blood flow (CBF) was measured from dorsal and ventral V1. Behavioral measurements of visual function were obtained using standard automated perimetry (SAP), short-wavelength automated perimetry (SWAP), and frequency-doubling technology perimetry (FDT). Measurements of CBF were compared to differences in visual function for the superior and inferior hemifield.
Results: Differences in CBF between ventral and dorsal V1 were correlated with differences in visual function for the superior versus inferior visual field. A statistical bootstrapping analysis indicated that the observed correlations between fMRI responses and measurements of visual function for SAP ($r = 0.49$), SWAP ($r = 0.63$), and FDT ($r = 0.43$) were statistically significant (all $p < 0.05$).
Conclusions: Resting blood perfusion in human V1 is correlated with the loss of visual function in POAG. Altered CBF may be a contributing factor to glaucomatous optic neuropathy, or it may be an indication of post-retinal glaucomatous neurodegeneration caused by damage to the retinal ganglion cells.

1. Introduction

The glaucomas, the second leading cause of worldwide blindness, are a group of progressive optic neuropathies that are characterized by a gradual loss of retinal ganglion cells and a progressive neurodegeneration of the optic nerve. Left untreated, there can be irreversible vision loss and eventual blindness. Although elevated intraocular pressure is a leading risk factor, the pathophysiology of the neuronal degeneration of the glaucomas remains unknown. Several factors other than altered intraocular pressure have been identified as potentially contributing to the disease (Weinreb & Khaw, 2004), including alterations in ocular perfusion and alterations in the ocular and systemic microcirculation (Harris, 2009).

In addition to the retinal ganglion cells, the glaucomas also can have damage to post-retinal mechanisms, including the lateral geniculate nucleus of the thalamus (LGN) and the primary visual cortex (V1). Neuronal degeneration of the LGN and activity changes in V1 have been discovered using experimental models of glaucoma in primates (Crawford et al., 2000, 2001; Vickers et al., 1997; Weber et al., 2000; Yucel et al., 2000, 2001, 2003). Metabolic activity is also greatly reduced within V1 ocular dominance columns that receive input from the glaucomatous eye (Brooks et al., 2004; Crawford et al., 2000, 2001).

Neuroimaging methods have been used to monitor glaucomatous changes in human brain morphology and function *in vivo* (Duncan, 2010). Studies using traditional MRI methods (e.g., T1-weighted imaging) have reported a decrease in the volume of anatomically distinct visual areas including the optic nerve, LGN, and V1 in human glaucoma (Boucard et al., 2009; Brodsky, Glasier, & Creel, 1993; Fujita et al., 2001; Gupta et al., 2009; Iwata et al., 1997; Kashiwagi, Okubo, & Tsukahara, 2004; Kitsos et al., 2009; Lagreze et al., 2009). Diffusion tensor imaging has also been used to measure glaucomatous degeneration of the optic nerve (Garcia, de Bazelaire, & Alsop, 2005; Xu et al., 2008). While anatomical imaging techniques have proven useful for quantifying cortical thickness and volume in post-retinal structures, these methods are limited because they cannot measure neuronal function or blood flow, which may be better indicators of the neuropathology of the glaucomas. Furthermore, anatomical techniques are not ideal for comparing cortical data to visual function data because regions of interest within visual cortex can only be localized

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reliably using functional activity. fMRI, on the other hand, can be used to localize regions of interest throughout V1 (Duncan et al., 2007a, 2007b), which is important considering the variability of visual areas between individuals (Duncan & Boynton, 2003).

While the traditional blood oxygen level dependent (BOLD) fMRI technique is preferred for defining regions of interest in the brain based on neuronal activity, it is difficult to measure glaucomatous neurodegeneration using BOLD. Visual stimulation must be used to elicit neuronal activity in BOLD experiments. Therefore, it is difficult to differentiate whether a reduction in the cortical fMRI signal of glaucoma patients is due to cortical neurodegeneration or damage to the optic disk. Furthermore, the BOLD technique measures the relative change in neuronal activity associated with two brain states, and therefore BOLD does not directly measure ischemic injury in quantitative units.

Arterial spin labeling (ASL) is a non-invasive MRI method that measures absolute CBF in ml/100 g/min (Detre et al., 1992). ASL can measure resting CBF in the absence of visual stimulation. Compared to the BOLD technique, ASL demonstrates less inter-subject variability, and ASL tends to be more robust in the presence of baseline vascular changes (Aguirre et al., 2002; Brown et al., 2003; Stefanovic et al., 2006; Tjandra et al., 2005; Wang et al., 2003). It also has been suggested that the ASL signal may be more localized to brain parenchyma than BOLD (Kim, 1995; Luh et al., 2000). Therefore, ASL is a better choice for measuring the resting perfusion state of brain tissue in human glaucoma.

The objective of this study was to compare ASL fMRI measurements of CBF from V1 to standard measures of visual function in human primary open angle glaucoma, the most prevalent of the glaucomas.

2. Methods

2.1. Subjects

Participants with primary open angle glaucoma (POAG) were selected from the ongoing longitudinal Diagnostic Innovations in Glaucoma Study (DIGS), conducted at the Hamilton Glaucoma Center at the University of California at San Diego (UCSD). The DIGS study is prospectively designed to assess structure and function in glaucoma. Informed consent was obtained from all participants after the nature and procedures of the study were explained. The Institutional Review Board of the University of California at San Diego approved the study, which follows the tenets of the Declaration of Helsinki.

2.1.1. Inclusion criteria for DIGS

Participants underwent complete ophthalmologic examinations including slitlamp biomicroscopy, intraocular pressure measurement, and dilated stereroscopic fundus examination. Simultaneous stereoscopic photographs were obtained for all participants and had to be of adequate quality for the subject to be included. All participants had open angles, a best corrected acuity of 20/40 or better, a spherical refraction within and inclusive of ±5.0 D (transposition allowed), and cylinder correction within ±3.0 D. A family history of glaucoma was allowed.

2.1.2. Exclusion criteria for DIGS

We excluded all participants with non-glaucomatous secondary causes of elevated intraocular pressure (IOP) (e.g., iridocyclitis, trauma), other intraocular eye disease, other diseases affecting the visual field (e.g., pituitary lesions, demyelinating diseases, HIV+ or AIDS, or diabetic retinopathy), with medications known to affect visual field sensitivity, or with problems other than glaucoma affecting color vision (as assessed by the Farnsworth D-15 color vision test).

2.1.3. For this report

Glaucomatous optic neuropathy was defined for this report based on the appearance of a glaucomatous optic disk and by a repeatable abnormal SAP result in at least one eye. Ten participants with reliable visual field results on three tests of visual function were included from DIGS. Reliable visual fields were defined as $\leqslant$25% false positives, false negatives, and fixation losses. Participants also had a statistically significant superior–inferior visual hemifield asymmetry on at least two consecutive tests in one eye for SAP, as indicated by the Glaucoma Hemifield Test in the StatPac analysis package included with the visual field analyzer (Carl Zeiss Meditec, Dublin, CA). All tests of visual function were done in randomized order and completed within a 3-month period. Participants were also screened for standard MRI exclusion criteria: no conditions/medications known to affect cerebral metabolism, no metal in the body that could not be removed, and no history of claustrophobia. Participants were selected on the basis of consecutive visual field testing using the Glaucoma Hemifield Test and not MR imaging.

2.2. Evaluation of stereophotographs

Evaluation of stereophotographs has been described in detail elsewhere (Sample et al., 2006). Evaluation of structural damage to the optic disk was based on assessment of simultaneous stereoscopic optic disk photographs (Nidek Stereo Camera Model 3-DX, Nidek Inc, Palo Alto, CA). Two experienced graders evaluated the photographs, and each grader was masked to the subject's identity, the other test results, and the other grade. All included photographs were judged to be of good quality. Discrepancies between the two graders were resolved either by consensus or by a third experienced grader. Glaucomatous optic disks were defined as having either asymmetric vertical cup-to-disk ratio >0.2, rim thinning, notching, excavation, disk hemorrhages, or nerve fiber layer defects.

2.3. Psychophysical tests of function

Visual fields were collected using SAP, SWAP, and FDT. Details of these tests have been presented previously (Boden et al., 2005; Martinez, Sample, & Weinreb, 1995; Racette & Sample, 2003; Racette et al., 2008; Sample et al., 2006). All measurements were conducted within the central 30° of the visual field and required fixation by the participant. Proper refraction was provided for each device. All tests required a 3 mm or larger pupil. Dilation was used if necessary. Lids of eyes with potential ptosis were taped to reduce artifacts. The untested eye was occluded with an eye patch.

2.3.1. SAP

SAP utilizes a small (0.47°), 200-ms flash of white light as the target presented on a dim background (10 cd/m^2 or 31.5 asb). The target was randomly presented to 54 locations within the central 24° of visual field using a Humphrey Visual Field Analyzer II (Carl Zeiss Meditec, Dublin, CA), which used the 24-2 protocol (software version 3.4.7) and the Swedish Interactive Thresholding Algorithm (SITA) testing algorithm. The two locations just above and below the blind spot were not included in the analysis.

2.3.2. SWAP

SWAP was measured with the same perimeter, software version, and protocol as SAP-SITA. SWAP utilizes a 440 nm, narrow band, 1.8° target at 200-ms duration on a bright 100 cd/m^2 yellow