The purpose of this study was to use functional magnetic resonance imaging (fMRI) to investigate the response of the visual cortex to unilateral primary open-angle glaucoma (POAG). Specifically, we assessed whether regions of V1 and V2 with lost input from the glaucomatous eye had a greater response to input from the nonaffected fellow eye. Nine participants with unilateral POAG causing paracentral visual field defects and four controls participated in the study. We found no evidence for an increased response to the fellow eye in glaucoma-affected regions of the visual cortex; however, in agreement with previous studies, there was a pronounced, retinotopically localized reduction of activation in both the primary (V1) and extrastriate visual cortex (V2), when participants viewed through their glaucomatous eye. Our results suggest a remarkable level of stability within the adult primary and extrastriate visual cortex in response to unilateral neurodegeneration of the optic nerve.

Introduction

Glaucoma is a leading cause of blindness that is predicted to affect over 80 million people by the year 2020 (Quigley & Broman, 2006). Glaucoma causes a loss of retinal ganglion cells (RGC), which results in scotomas within the visual field of the affected eye (Medeiros et al., 2013; Weinreb & Khaw, 2004). There is increasing evidence that the neurodegenerative effects of glaucoma are not restricted to the retina and optic nerve, but extend to the brain (Boucard et al., 2009; Graham & Klistorner, 2013; Gupta & Yücel, 2007a; Yücel & Gupta, 2008). For example, it has been reported that glaucoma decreases cell density and metabolic activity within the lateral geniculate nucleus (LGN) of the thalamus and the primary visual cortex, possibly due to trans-synaptic neural degeneration (Crawford, Harwerth, Smith, Mills, & Ewing, 2001; Vickers et al., 1997; Yücel & Gupta, 2008; Yücel, Zhang, Weinreb, Kaufman, & Gupta, 2003). Consistent with this idea, structural changes indicative of cell loss have been found within the visual cortex of human patients with glaucoma using both histological (Gupta, 2006) and neuroimaging techniques (Boucard et al., 2009; Hernowo, Boucard, Jansonius, Hooymans, & Cornelissen, 2011). However, it is currently unclear whether the loss of afferent neural input caused by glaucoma results in functional changes within the human visual cortex. This is an important issue as it relates to our understanding of the visual deficits experienced by glaucoma patients and to the broader issue of neuroplasticity within the adult human visual cortex.

Due to the orderly retinotopic mapping of the visual field across the surface of the primary and extrastriate visual cortex (Dougherty et al., 2003; Engel, Glover, & Wandell, 1997; Wandell, Dumoulin, & Brewer, 2007), it is possible to precisely relate specific retinal locations to their corresponding representations within the visual cortex.
cortex. Using this approach, it has been suggested that monocular and binocular focal retinal lesions in adult primates result in changes to the receptive fields of cells at the borders of the lesion projection zone (LPZ; the area of cortex corresponding to the lesioned retinal location) in the primary visual cortex (Baseler, Gouws, & Morland, 2009; Gilbert & Wiesel, 1992; Heinen & Skavenski, 1991; Kaas et al., 1990; Schmid, Rosa, Calford, & Ambler, 1996). It should be noted that this effect is not universally accepted and may reflect the presence of existing long range connections rather than changes in the size of receptive fields (Botelho, Ceriatte, Soares, Gattass, & Fiorani, 2012; Calford et al., 2005; Wandell and Smirnakis, 2009). A number of functional magnetic resonance imaging (fMRI) studies of humans with macular degeneration have also found evidence for remapping of the visual cortex whereby regions of the cortex within the LPZ became responsive to visual stimuli falling upon undamaged regions of the retina (Baker, Dilks, Peli, & Kanwisher, 2008; Baker, Peli, Knouf, & Kanwisher, 2005; Schumacher et al., 2008). The interpretation of these findings has been disputed. Specifically it has been proposed that the functional activation within the LPZ is due to an unmasking of task-dependent feedback signals from higher cortical areas and not due to low-level changes in cortical function (Liu et al., 2010; Masuda, Dumoulin, Nakadomari, & Wandell, 2008). In addition, a complete absence of visual field remapping has recently been reported in groups of participants with age-related or juvenile macular degeneration (Baseler et al., 2011). Therefore it is still unclear whether functional plasticity occurs within the adult human visual cortex following peripheral damage to the visual system. Further, the human studies conducted in this area to date have focused primarily on macular degeneration, which affects photoreceptors in the retina. The effects of neurodegenerative diseases of the optic nerve such as glaucoma on visual cortex plasticity have not yet been investigated using fMRI. This is important as neurodegeneration is common to a large number of neurological disorders and therefore understanding the impact of neurodegeneration on the visual cortex could provide information that is relevant to understanding the impact of neurodegeneration on the brain in general (Gupta and Yücel, 2007a).

With regard to glaucoma, a number of studies have shown that regions of the primary visual cortex corresponding to glaucoma-affected areas of the retina show a reduced BOLD (blood-oxygen-level dependent) response when patients view visual stimuli during fMRI (Duncan, Sample, Weinreb, Bowd, & Zangwill, 2007b; Qing, Zhang, Wang, & Wang, 2010). This indicates that fMRI is sensitive to the loss of visual function experienced by these patients. However, the question of whether remapping of cortical function occurs in patients with glaucoma remains an area of debate. Our aim was to build upon this previous work by using fMRI to assess whether regions of cortex within the LPZ responded differently to input from the fellow eye (non-glaucomatous eye) than regions of visual cortex outside of the LPZ. Differential responses would indicate functional changes within the LPZ that are sufficiently pronounced to affect processing of information from the fellow-eye. We have adopted the term “lesion projection zone” to be consistent with previous work.

Although the issue of functional changes in the primary and extrastriate visual cortex has not previously been addressed in humans, data from primate models of unilateral glaucoma support two different predictions. Lam, Kaufman, Gabelt, To, and Matusbara (2003) found a number of neurochemical changes in the primary visual cortex of monkeys with unilateral glaucoma, which would be highly conducive to functional plasticity. These changes occurred in both glaucomatous and fellow eye ocular dominance columns and included evidence for a reduction in GABA (gamma-aminobutyric acid) mediated inhibition. If the reduction in inhibition is most pronounced in regions most affected by glaucoma, a greater functional response to fellow eye input would be expected within the LPZ than for other areas of the cortex with preserved binocular input and greater inhibition. An increased functional response to fellow eye stimulation within the LPZ would also be consistent with the effects of long-term monocular deprivation that results in a potentiation of neural responses to the nondeprived eye (Crozier, Wang, Liu, & Bear, 2007; Sawtell et al., 2003; Smith, Heynen, & Bear, 2009).

On the other hand, Yücel et al. (2003) found that unilateral glaucoma caused loss and shrinkage of LGN neurons connected to the fellow eye in a primate model. This suggests that unilateral glaucoma is associated with a loss of cortical inputs from both eyes, possibly due to transsynaptic neurodegeneration, whereby transport of specific growth factors and other key metabolites is blocked or hindered (Almasieh, Wilson, Morquette, Cueva Vargas, & Di Polo, 2012; Gupta & Yücel, 2007b). If this is the case, it follows that the functional response within the LPZ may be reduced for both eyes relative to other regions of the cortex that have not yet been measurably affected by glaucoma.

We also investigated whether any glaucoma-related functional changes within the primary visual cortex extend to extrastriate visual area V2. To the best of our knowledge, the effect of glaucoma on the functional responses of extrastriate visual areas in humans has not previously been investigated.

We recruited participants with glaucoma resulting in localized para-foveal monocular visual field defects and used established retinotopic mapping techniques to
identify the LPZ of the glaucomatous eye in V1 and V2 (Dougherty et al., 2003; Engel et al., 1994; Sereno et al., 1995; Wandell et al., 2007). We then presented the participants with central field (16°) dynamic checkerboard stimuli under monocular viewing conditions and recorded the functional response within the LPZ and a closely matched control area corresponding to a healthy region of retina. Stimulus contrast was modulated to putatively target parvocellular (high contrast) and magnocellular (low contrast) cortical inputs (Albrecht & Hamilton, 1982; Hess, Li, Lu, Thompson, & Hansen, 2010; Shapley & Hugh Perry, 1986). The group results showed no evidence for either an increased or decreased response within the LPZ for fellow eye viewing. In addition, we found that stimulation of the glaucomatous eye evoked a weak but measurable functional response within the LPZ. In a preliminary analysis we found that the eccentricity mapping of these LPZ responses did not differ systematically between the fellow and glaucomatous eyes, suggesting that they were not a result of remapping. However, the use of visual stimuli optimized for receptive field mapping will be required to fully address this question in future studies. As a whole, our results indicate considerable stability of the adult human primary and extrastriate visual cortex in response to unilateral glaucoma.

### Table 1. Clinical details.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age</th>
<th>Sex</th>
<th>Eye</th>
<th>Most affected hemifield</th>
<th>HFA 24-2</th>
<th>OCT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MD</td>
<td>Mean rim area (mm²)</td>
<td>Mean rim volume (mm³)</td>
</tr>
<tr>
<td>P1</td>
<td>71</td>
<td>M</td>
<td>ODGl</td>
<td>Superior</td>
<td>-10.6</td>
<td>12.1</td>
</tr>
<tr>
<td>P2</td>
<td>76</td>
<td>M</td>
<td>ODGl</td>
<td>Normal</td>
<td>-0.7</td>
<td>2.1</td>
</tr>
<tr>
<td>P3</td>
<td>74</td>
<td>M</td>
<td>ODGl</td>
<td>Superior</td>
<td>-14.2</td>
<td>12.4</td>
</tr>
<tr>
<td>P4</td>
<td>72</td>
<td>M</td>
<td>ODGl</td>
<td>Superior</td>
<td>-9.7</td>
<td>12.5</td>
</tr>
<tr>
<td>P5</td>
<td>80</td>
<td>M</td>
<td>ODGl</td>
<td>Normal</td>
<td>-2.2</td>
<td>1.9</td>
</tr>
<tr>
<td>P6</td>
<td>59</td>
<td>M</td>
<td>ODGl</td>
<td>Normal</td>
<td>-0.4</td>
<td>1.2</td>
</tr>
<tr>
<td>P7</td>
<td>65</td>
<td>M</td>
<td>ODGl</td>
<td>Superior</td>
<td>-2.3</td>
<td>8.3</td>
</tr>
<tr>
<td>P8</td>
<td>72</td>
<td>F</td>
<td>ODGl</td>
<td>Superior</td>
<td>-11.4</td>
<td>14.6</td>
</tr>
<tr>
<td>P9</td>
<td>54</td>
<td>M</td>
<td>ODGl</td>
<td>Superior</td>
<td>-12.2</td>
<td>8.5</td>
</tr>
</tbody>
</table>

**Notes:** Values outside of the normal range are indicated in bold. M: male; Gl: glaucomatous eye; Fl: fellow eye; HFA: Humphrey Field Analyser; MD: mean deviation; PSD: pattern standard deviation; HRT: Heidelberg retinal tomography; OCT: optical coherence tomography; RNFL: retinal nerve fiber layer; GCL: ganglion cell layer.

### Methods

**Participants and clinical measures**

Of 1,650 patients screened, nine (eight male and one female, mean age 70 years, SD = 8.7, Table 1) had unilateral primary open angle glaucoma (defined as a unilateral, reproducible visual field defect and characteristic glaucomatous optic nerve head changes) that met the inclusion criteria. The inclusion criteria required a unilateral visual field loss that (a) was of at least 10 dB mean deviation, (b) was within the central 20° of the visual field, (c) was at least 10 dB of the visual field, (d) had been present for a minimum of 3 years over at least five consecutive visits, and (e) did not preclude stable fixation with the affected eye. Patients also had to be willing to undergo both structural and functional MRI testing with no contraindications for MRI, be older than 18 years, have best corrected visual acuity of 20/40 or better, and refractive error within ± 5 diopters (D) sphere and ±3 D cylinder.

Exclusion criteria were unreliable visual field measurements (fixation loss, false negative, and false positive errors >25%), unstable fixation with the glaucomatous eye and the presence of any other disorders that may affect vision. In particular, patients were excluded if there was a history of amblyopia,
uveitis, or intraocular surgery (except uncomplicated cataract surgery), diabetes, and ocular diseases possibly affecting the peripapillary area (such as large peripapillary atrophy). Patients were also excluded if there was evidence of any media opacities that prevented good quality imaging and any retinal (including macular) or neurologic disease other than glaucoma, which could confound the evaluations. Finally, patients were excluded if any visual field defects were identified in the fellow eye.

Visual field testing was performed monocularly with a Humphrey Visual Field Analyzer (HFA, Carl Zeiss Meditec, Dublin, CA) using the 24–2 Swedish interactive thresholding algorithm (SITA). Full refractive correction was provided. Results were compared to the HFA normative database. Glaucomatous optic nerve head changes were defined as an asymmetric vertical cup-to-disk ratio of 0.2, rim thinning, notching, excavation, disc hemorrhages, or nerve fiber layer defects. All participants underwent complete ophthalmologic examination including slit-lamp biomicroscopy, gonioscopy, intraocular pressure, dilated stereoscopic fundus examination, stereophotography of the optic nerve heads, and ocular imaging with a spectral domain optical coherence tomography (OCT, Cirrus HD-OCT; Carl Zeiss Meditec) and scanning laser ophthalmoscopy with Heidelberg retinal tomography (HRT, HRT-3 Eye Explorer software version 1.5.1.0; Heidelberg Engineering, GmbH, Heidelberg, Germany; Table 1). All participants were required to have normal visual fields and optic nerve head appearance in the fellow eye.

The retinal nerve fiber layer (RNFL) parameters provided by the OCT system were average RNFL thickness within a 3.4 mm diameter circular region centered on the optic nerve head (ONH) and temporal, superior, nasal, and inferior quadrant RNFL thicknesses. Only good quality scans with signal strength $>7$ and the absence of motion and blinking artifacts and segmentation failures were analyzed.

Fixation stability was measured using a ViewPoint EyeTracker PC-60 HMD infrared eye tracking system (Arrington Research, Scottsdale, AZ). Each eye was assessed individually (the nonviewing eye was occluded with an eye patch) while participants viewed the stimuli used during scanning. All participants were able to maintain fixation within 2° of a central fixation point with either eye.

Four control participants (one female, mean age 59 years, $SD = 8.2$) with no history of visual or neurological defects were also scanned to confirm that monocular retinotopic mapping results were comparable between the two eyes in the absence of glaucoma.

This study adhered to the declaration of Helsinki and was approved by institutional ethics review boards. All participants provided informed written consent.

**Visual stimuli**

Participants took part in two scanning sessions. The first involved retinotopic mapping and the second involved central visual field stimulation using counterphase checkerboard stimuli.

Standard wedge and ring stimuli were used for retinotopic mapping (Sereno et al., 1995). Following Li, Lu, Tjan, Dosher, and Chu (2008) the wedge and ring stimuli were constructed from high contrast (100%) checkerboards counterphasing at 8 Hz (Figure 1). The wedge stimulus had a radius of 8°, a width of one-eighth of a circle and rotated in a clockwise direction around a central fixation point at a rate of 9.4°/s. A full sweep of the visual field took 38.4 s (32 TRs) and each scanning run contained 12 sweeps. The ring stimulus was scaled for width in order to factor in cortical magnification with the widest part of the stimulus (2.4°) occurring at the periphery (Harvey & Dumoulin, 2011). The ring stimulus expanded from the center and covered the viewable region of the visual field in 24 seconds (20 TRs). Each scan consisted of 14 expansions each separated by 4.8 s (4 TRs) of blank fixation.

A broadband checkerboard stimulus counterphased at 8 Hz was used for central visual field stimulation (Figure 2). This stimulus consisted of 0.25 cpd (cycles per degree) checks and subtended 18° by 16° of visual angle. Checkerboards of low (5%), medium (25%), and high (80%) contrast were displayed for 20 s (10 TRs) separated by 20 s of mean luminance blank fixation following a block design. Each contrast was repeated three times within a scanning session and the sequence of contrast presentation was randomized.

Throughout all scans, participants viewed a central fixation mark that changed from an “X” to an “O,” and vice versa, at unpredictable intervals. The participants had to signal each change with a button press. Visual stimuli were generated using Psykinematix version 1.3 (KyberVision, Montreal, Canada) and were presented on a gamma-corrected MRI-compatible TFT–LCD monitor (Invivo, Gainesville, FL) positioned at the head-end of the scanner bore and viewed via a front-surface mirror mounted on the head-coil. MRI-compatible corrective lenses were provided, to ensure best-corrected vision for the viewing distance. Participants viewed monocularly with a tight-fitting eye patch covering the nonviewing eye. The viewing eye was alternated between scans.

**Data acquisition**

Scanning was conducted on a 3.0 Tesla Philips Achieva scanner (Eindhoven, The Netherlands) equipped with an eight-channel head coil. Each session began with the acquisition of a T1-weighted 3D turbo
field-echo anatomical volume (1000 ms inverted prepulse, 1 x 1 x 1 mm voxel resolution, 180 sagittal slices, 2.7 ms TE, 5.9 ms TR, 80° flip angle). In the first session, four functional datasets were then acquired; one polar angle (wedge stimulus, 366 volumes) and one eccentricity (ring stimulus, 414 volumes) map for each eye. Functional data were acquired using a T2*-weighted gradient echo EPI sequence (TR = 1.2 s, TE = 30 ms, flip angle = 65°, voxel resolution 2.5 x 2.5 x 2.5 mm). Each volume consisted of 20 coronal slices oriented perpendicular to the calcarine sulcus and covering the whole occipital lobe.

In the second session an additional four functional datasets (two datasets per eye) were collected while participants viewed the checkerboard stimuli. A T2*-weighted gradient echo, EPI sequence (TR = 2.0 s, TE = 30 ms, flip angle = 90°, voxel resolution 3.0 x 3.0 x 3.0 mm) was used to acquire 190 volumes, constructed from 39 axial slices oriented parallel to the calcarine sulcus.

**Data analysis**

Data were analyzed using Brain Voyager (Brain Innovation B.V., Maastricht, The Netherlands). The anatomical MRI images were transformed to Talairach space and each hemisphere was inflated and flattened using automated segmentation procedures. Each stage of this process was subject to visual inspection and manual correction where necessary. Functional data were high-pass filtered, slice-time corrected, motion corrected, and coregistered to the anatomical data using subroutines within BrainVoyager.

Retinotopic mapping data were analyzed using linear correlation analysis to identify the preferred stimulus position within the visual field for each voxel. The data were then viewed on the flattened representation of the occipital lobe to reveal polar angle and eccentricity maps for each hemisphere. The boundaries between visual areas V1, V2, V3, V3A, and V4 were identified as phase reversals in the polar map.
identified as reversals in the preferred position for the wedge stimulus running approximately parallel to the representation of the horizontal meridian within the calcarine sulcus with V3A having a full-field representation (Wandell et al., 2007). Lesion projection zones (LPZ) were identified for one hemisphere of each participant (the hemisphere with the greater visual field deficit) by superimposing the polar angle maps for each eye (thresholded at $r > 0.3$) on the flattened cortical surface. Each LPZ was apparent as a “hole” in the glaucomatous eye map relative to the fellow eye map (Figure 3). LPZ regions of interest (ROIs) were readily identifiable in V1 and V2 for all participants. Control ROIs were generated by mirroring the LPZ ROIs into a visual quadrant with no visual field deficits in order to match the corresponding LPZ ROI for eccentricity and polar-angle.

The data from the checkerboard stimulus scans were analyzed using a region-of-interest approach. Time series data were extracted from each ROI and normalized to the mean of the blank fixation blocks. The mean BOLD change was then calculated for each block of checkerboard stimulation (six blocks for each of the three contrasts) by averaging the BOLD change values within a 7TR window, starting 3TRs (6 s) after the onset of each block to account for the hemodynamic delay and ending at the offset of the stimulus. Finally, grand average values were calculated for each contrast for each ROI for each participant. These data were then subjected to statistical analyses, which were corrected for multiple comparisons using the false
discovery rate algorithm (Benjamini & Hochberg, 1995).

In a separate preliminary ROI analysis, the data from the expanding ring stimulus were used to compare the representation of eccentricity within the V1 and V2 LPZ and control ROIs for glaucomatous versus fellow eye viewing. Vectors were projected onto the flattened cortical surface of each participant. Each vector ran parallel to the horizontal meridian and passed through the center of either the LPZ or the control ROI (Figure 4). The preferred eccentricity for each voxel intersected by each vector was calculated for glaucomatous eye viewing and fellow eye viewing. For each participant, a plot of fellow eye viewing eccentricities versus glaucomatous eye viewing eccentricities was generated for each ROI (LPZ vs. control) and for each visual area (V1 vs. V2) to assess whether systematic differences existed between the two eyes. In addition, group eccentricity values were plotted as a cumulative distribution for each ROI (LPZ vs. control) for each eye (glaucomatous vs. control) and fitted with a cumulative Gaussian function using a boot-strapping technique available within the Psignifit software package (Wichmann & Hill, 2001).

**Results**

**BOLD change within the primary visual cortex (V1) and extrastriate visual cortex (V2)**

LPZ and control ROIs could be identified for all nine participants with glaucoma and the cortical location of the LPZ ROIs were consistent with the participants’ visual field defects. Individual polar angle maps for each patient are shown in Supplementary Figure 1. No LPZ ROIs could be found in control participants suggesting that the “holes” in the retinotopic maps of participants were due to glaucoma (Supplementary Figure 2). To further support this, no statistically significant difference in activation between the eyes of controls was found for the centrally-presented checkerboard stimuli.

The BOLD changes evoked by the central-field checkerboard stimuli within the LPZ and control ROIs under fellow versus glaucomatous eye viewing conditions (Figure 5) were compared using a three-way within-subjects ANOVA with factors of ROI (LPZ vs. control), Eye (fellow vs. glaucomatous eye), and Contrast (low, medium, and high). Within V1, the
BOLD change differed significantly between the two eyes, $F(1, 8) = 61.4, p < 0.001$, and the two ROIs, $F(1, 8) = 6.9, p = 0.031$, and varied significantly with stimulus contrast, $F(2, 16) = 59.0, p < 0.001$. There was also a significant three-way interaction between ROI, Eye, and Contrast, $F(2, 16) = 14.9, p = 0.002$, indicating that the difference between the two eyes varied with both ROI and Contrast. In order to examine the nature of this three-way interaction, a series of two-way ANOVAs was conducted.

An ANOVA with factors of ROI and Contrast conducted on the fellow eye data revealed a significant main effect of stimulus contrast, $F(2, 16) = 39.3, p < 0.001$; however, BOLD change did not differ reliably between the two ROIs, $F(1, 8) = 0.8, p = 0.4$, and there was no interaction between ROI and contrast, $F(2, 16) = 0.009, p = 0.49$. This indicated that the cortical response to the fellow eye was similar between the LPZ and control regions. The same analysis conducted for the glaucomatous eye data revealed a significant effect of contrast, $F(2, 16) = 38.1, p < 0.001$, and a significant difference between the two ROIs, $F(1, 8) = 13.6, p = 0.006$, consistent with visual field loss. This clearly demonstrates that fMRI is sensitive to the scotoma caused by glaucoma, as previously reported (Duncan, Sample, Weinreb, Bowd, & Zangwill, 2007b; Furuta, Nakadomari, Misaki, Miyauchi, & Iida, 2009; Gupta, 2006). In addition, this analysis demonstrated that the difference in BOLD response between the LPZ and control ROIs varied with stimulus contrast (significant ROI by Contrast interaction, $F(2, 16) = 14.9, p = 0.004$). Post-hoc paired sample $t$ tests revealed that the functional loss was evident for the medium ($t_4 = 3.97, p = 0.004$) and high contrast stimuli ($t_4 = 3.88, p = 0.005$), but was not significant for the low contrast stimulus ($t_4 = 2.65, p = 0.03$, FDR corrected critical $p$ value = 0.02). The same pattern of results was present in V2.

**Eccentricity mapping in V1 and V2**

Although there was a reduction in BOLD change in the LPZ ROIs for glaucomatous eye viewing, considerable residual activation was still evident for the high and medium contrast stimuli (Figure 5). A mixed ANOVA with factors of ROI (LPZ vs. control), Eye (glaucomatous vs. fellow) and Participant (nine participants) conducted on the raw preferred eccentricity values for V1 revealed no significant interaction between ROI and Eye, $F(1, 449) = 1.84, p = 0.18$. Therefore, the eccentricity mapping of responses in the region of both ROIs did not differ significantly between the glaucomatous and fellow eyes for the voxels sampled by our vector-based technique (Figure 4). The relationship between eccentricity mapping for the glaucomatous and fellow eye in the LPZ and control ROIs is shown for three participants in Figure 6. Although the relationship between eccentricity responses for the two eyes was noisier for the LPZ ROI compared to the control ROI, there were no systematic shifts in eccentricity mapping that could be identified consistently across participants. This was consistent with the lack of an interaction in the ANOVA model. The noisier response in the LPZ ROI was likely due to the weaker BOLD response in this region. Figure 7 shows group mean cumulative distributions of preferred eccentricity for each combination of eye and ROI. Again no systematic differences between eyes or ROIs were apparent. The extent of residual activation in V1 or V2 was not correlated with the visual field.

Figure 4. Regions of interest for analyzing the representation of eccentricity. Vectors (white dashed lines) running parallel to the horizontal meridian and passing through the center of either the LPZ (orange dashed line) or the control ROI (green dashed line) were projected onto the flattened representation of the visual cortex for each participant. The preferred eccentricities of the voxels falling along each vector were used to compare the representation of eccentricity within V1 and V2 for glaucomatous versus fellow eye viewing. The dashed black lines show visual area boundaries. The figure shows representative data from participant P1.
Discussion

The effect of unilateral glaucoma on the functional organization of the human visual cortex is currently unknown. However, evidence from primate models suggests that the cortical response to the nonglaucomatous eye may be either (1) increased due to a reduction in GABA-mediated inhibition (Lam et al., 2003) or (2) reduced due to transsynaptic neurodegeneration (Almasieh et al., 2012; Gupta et al., 2007; Yücel et al., 2003). Our aim was to address this question in humans with unilateral POAG using fMRI. This was achieved by comparing the response of retinotopic regions within V1 and V2 that corresponded to the scotoma in the glaucomatous eye (LPZ) and a matched region of intact visual field (control ROI) when participants viewed with each eye.

In agreement with previous work, we found reduced BOLD activation within the LPZ when participants viewed with their glaucomatous eye, indicating that fMRI is sensitive to the effect of glaucoma on visual function (Duncan et al., 2007a; Qing et al., 2010). A comparison between the LPZ and control ROI for fellow eye viewing showed no reliable differences between the ROIs. These effects were seen in both V1 and V2, making this one of the first fMRI studies in

mean deviation scores corresponding to the LPZ region ($p > 0.05$).

![Figure 5. BOLD change within the LPZ and control ROIs for V1 and V2. Light bars show BOLD changes for the fellow eye and dark bars for the glaucomatous eye. Solid bars indicate the LPZ ROI and hatched bars the control ROI. Reduced responses were found within the LPZ for the glaucomatous eye. The fellow eye responses did not differ between the two ROIs. Results were consistent for V1 and V2. Error bars show $\pm 1$ standard error of the mean. * $p \leq 0.05$, ** $p \leq 0.01$.]

humans to demonstrate the effects of glaucoma on a higher visual area.

Our results were not consistent with reduced GABA-mediated inhibition of cortical inputs from the fellow eye within the LPZ or with transsynaptic degeneration. Based on our current understanding of the BOLD signal, regions of reduced GABA would be expected to result in a larger BOLD response (Muthukumaraswamy, Edden, Jones, Svettenham, & Singh, 2009), whereas a loss of cells responsive to the fellow eye would result in a decreased LPZ BOLD signal. Our results demonstrated a striking level of stability within the primary and extrastriate cortex, whereby responses to the fellow eye were equivalent within the LPZ and the control ROIs.
The results from our group of patients, therefore, do not support either the cortical degeneration or increased cortical plasticity hypotheses, but rather suggest that when the retina is intact, fellow eye responses within V1 and V2 are similar within the LPZ and control regions. Experimental models of glaucoma have shown that the magnocellular and parvocellular pathways undergo atrophy within the LGN and V1 (Yücel, Zhang, Weinreb, Kaufman, & Gupta, 2001; Yücel et al., 2003). By using varying degrees of contrast in the central field checkerboard stimulation, we intended to provide initial insights into whether either one of these geniculo-cortical pathways was more susceptible to the functional losses caused by glaucoma. Cells in the parvocellular pathway have a low-contrast gain and only saturate at high contrast, whereas cells in the magnocellular pathway have a high-contrast gain and reach saturation at medium contrast (Hess et al., 2010; Kaplan & Shapley, 1986). We found that for the LPZ ROI, the most significant loss of BOLD signal occurred at higher contrasts for glaucomatous eye viewing (Figure 5). This is consistent with a greater functional impairment of the parvocellular pathway. However, manipulating stimulus contrast does not allow for a direct measure of magnocellular versus parvocellular function. Furthermore, the lowest contrast stimulus induced low levels of BOLD response across all ROIs. Together these considerations prevent us from drawing strong conclusions on this point.

We found it interesting to observe that measurable BOLD activity, albeit reduced, was present within the LPZ when participants viewed with their glaucomatous eye. Typically glaucoma progress from peripheral to central areas of the visual field and therefore we wanted to explore whether preferred eccentricity of voxels within the LPZ differed when participants viewed with their fellow versus glaucomatous eye. Specifically, a shift of preferred eccentricities toward the fovea for the glaucomatous eye viewing versus fellow eye viewing for the group of patients as a whole, which suggests a lack of remapping. However, this analysis should be considered as preliminary because our mapping stimuli were not optimized for the estimation of receptive field size and may not have been sensitive enough to reliably distinguish between responses emanating from within the LPZ and those resulting from activation of cortical tissue surrounding the LPZ. Therefore, precise mapping of residual cortical responses in the vicinity of the LPZ will be required to fully understand the origin of these signals. This issue is important, because the possibility of residual cortical activity within an LPZ is directly relevant to the success of retinal prostheses as these devices will rely on the presence of functioning cortical cells even after long periods of visual deprivation (Weiland, Cho, & Humayun, 2011).

**Conclusion**

Our data in a limited number of participants with unilateral POAG do not support the hypothesis that cortical inputs from the fellow eye are subject to decreased inhibition that would be conducive to neural plasticity. Furthermore, we did not find evidence of neurodegeneration affecting cells receiving information from the fellow eye. Rather we found high levels of stability within both the primary and extrastriate visual cortex of patients with unilateral glaucoma.

**Keywords:** fMRI, retinotopic mapping, cortical reorganization, plasticity, optic neuropathy

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