Evidence for Widespread Structural Brain Changes in Glaucoma: A Preliminary Voxel-Based MRI Study

Alice L. Williams,[1] John Lackey,[3] Sheryl S. Wizov,[1] Tao Ming Thomas Chia,[4] Srinivas Gatla,[1] Mark L. Moster,[2] Robert Sergott,[2] George L. Spaeth,[1] and Song Lai[3]

[1]William A. and Anna V. Goldberg Glaucoma Service, Wills Eye Institute, Philadelphia, Pennsylvania
[2]Department of Neuro-ophthalmology, Wills Eye Institute, Philadelphia, Pennsylvania
[3]Department of Radiology, Thomas Jefferson University, Philadelphia, Pennsylvania
[4]Thomas Jefferson University School of Medicine, Philadelphia, Pennsylvania

Correspondence: Song Lai, University of Florida Department of Radiation Oncology, CTSI Human Imaging Core at the McKnight Brain Institute, 1149 South Newell Drive, LG-112A, PO Box 100015, Gainesville, FL 32610-0015; songlai@ufl.edu.

Submitted: January 29, 2013
Accepted: June 24, 2013

Citation: Williams AL, Lackey J, Wizov SS, et al. Evidence for widespread structural brain changes in glaucoma: a preliminary voxel-based MRI study. *Invest Ophthalmol Vis Sci*. 2013;54:5880–5887. DOI: 10.1167/iovs.13-11776

Purpose. To investigate structural brain changes in patients with glaucoma.

Methods. High-resolution T1-weighted anatomical brain magnetic resonance images (MRI) were collected in 15 patients with glaucoma of varying severity and in 15 age-, race-, and sex-matched controls. Exclusion criteria included neurological disease, another disorder which could affect the visual field, and a score of less than 25 on the mini-mental status examination. The scans were analyzed with an automatic volumetric MRI technique to measure the volumes of 93 structures in each brain. Analyses of covariance with age as a covariate were carried out to identify structures that differed significantly between the two groups (i.e., glaucoma versus normal control). The volumes of all brain structures in the group of 15 glaucoma patients were also correlated with clinical measures of disease severity. Linear multivariate regression analyses were conducted to determine the significance of these relationships.

Results. Five structures differed significantly between the two groups ($P < 0.05$). These structures included the right and left inferior occipital gyri and the right middle occipital gyrus, right inferior temporal gyrus, and right occipital lobe white matter. Interestingly, all of these structures were larger in the glaucoma group than in the control group. Within the group of glaucoma patients, 38% of all brain structures had independent associations between decreasing volume and more severe disease in multivariate regression analysis.

Conclusions. These results suggest that patients with glaucoma undergo widespread and complex changes in cortical brain structure and that the extent of these changes correlates with disease severity. (ClinicalTrials.gov number, NCT01303939.)

Keywords: glaucoma, structural MRI, voxel-based morphometry

Glaucoma is the most common cause of irreversible blindness worldwide.[1] It encompasses a group of disorders which are characterized by progressive degeneration of the optic nerve and a corresponding pattern of visual field loss. Glaucoma shares some clinical similarities with central nervous system (CNS) neurodegenerative disorders as well as common mechanisms of neuronal death.[2] These similarities have stirred interest in the conception of glaucoma as a neurodegenerative disorder. A series of studies, including both radiologic and pathologic evidence from experimental and human glaucoma, have lent significant weight to this paradigmatic shift by establishing the fact that optic nerve degeneration is associated with atrophy of the optic chiasm, optic tracts, and the lateral geniculate nucleus.[3–6]

Recent advances in neuroimaging have permitted investigations into the structural integrity of more distant portions of the visual system. Diffusion tensor imaging studies have demonstrated that the optic radiations are smaller in glaucoma patients than in age-matched controls and that the extent of degeneration in these structures correlates with disease severity.[7–11] Investigators have also begun to apply voxel-based morphometry techniques to assess the brain cortex in patients with glaucoma. These studies have demonstrated that neural degeneration in glaucoma extends to the primary visual cortex and that loss of cortical volume and function corresponds to the location of visual field deficits.[9,12–15]

It is possible that neurodegeneration in glaucoma spreads beyond the primary visual cortex. The primary visual cortex has extensive connections to visual association cortices in the occipital and temporal lobes. It also has widespread connections to other areas in the brain, such as the hippocampus, amygdala, cerebellum, and frontal and parietal lobes, where visual input is integrated with other sensory information. In addition to a putative anatomic basis, there is clinical evidence that distant neuronal populations may be affected by neurodegeneration in glaucoma. Such neuroanatomical changes may contribute to the increased instance of central nervous system problems including psychiatric illness, depression, loss of hand-eye coordination, and abnormalities of balance, which have been observed in patients with glaucoma.[16] Finally, extensive brain changes have been documented in both early and adult-onset blind patients.[17,18] It is possible that these structural changes begin before the onset of complete visual deprivation due to blindness. The purpose of the present study was to

investigate the nature and extent of structural brain changes in patients with glaucoma. The thesis of our study was that neural degeneration may spread throughout the visual system in glaucoma and that this degeneration is related to the severity of retinal ganglion cell loss.

Materials and Methods

This study was approved by the Institutional Review Boards in Wills Eye Institute and Thomas Jefferson University. It was registered at ClinicalTrials.gov (number NCT01303939) and adhered to all tenets of the Declaration of Helsinki. Written consent was obtained from each participant after explanation of the nature and possible consequences of the study.

Study Population

Fifteen patients with glaucoma were recruited from the Wills Eye Institute Glaucoma Service (mean age, 66.1 years; range, 50–82; 10 men, 5 women). Fifteen controls matched for age, race, and sex were recruited from among the patients' family members and the Wills Eye staff (mean age, 65.6 years; range, 49–81; 10 men, 5 women). Exclusion criteria included another disorder which could affect the visual field, a score of less than 25 on the mini-mental status examination, and any neurological deficit such as a history of stroke, dementia, traumatic brain injury, psychiatric disorder, or any other condition involving the CNS. Patients were also excluded according to standard magnetic resonance imaging (MRI) exclusion criteria such as claustrophobia, ferromagnetic implants or pacemakers, and inability to lie still for the MRI acquisition time.

Ophthalmic Examination

All participants underwent a complete ophthalmic examination including visual acuity, intraocular pressure (IOP) measurement by Goldmann applanation tonometry, slit-lamp biomicroscopy, and visual fields assessment with a 24-2 SITA-standard automated perimeter (Humphrey field analyzer; Carl Zeiss Meditec, Inc, Dublin, CA). The glaucoma patients were all familiar with standard automated perimetry, having undergone at least two previous visual field examinations during the course of their routine glaucoma management. All patients were also given the National Eye Institute Visual Functioning Questionnaire (VFQ-25), which was administered as previously described.[19]

Glaucoma was defined as characteristic optic nerve damage on slit-lamp examination (defined as a definite notch in the neuroretinal rim or absence of neuroretinal rim not the result of another known cause) with corresponding glaucomatous visual field deficits (defined as a cluster of 3 or more points on pattern deviation plot depressed below the 5% level, at least 1 of which is depressed below the 1% level; odds ratio (OR) corrected pattern standard deviation (SD)/pattern SD significant at a P value of <0.05; OR glaucoma hemifield test "Outside Normal Limits").[20] All controls had normal optic discs, no visual field deficits, and normal IOP (<21 mm Hg).

MRI Data Acquisition

All MRI scanning was carried out with a 3.0-T whole-body clinical MRI system (Achieva; Philips Medical Systems, Best, The Netherlands) equipped with a Quasar Dual high-performance gradient system capable of on-axis (x, y, and z) peak gradient of 80 mT/m and 200 mT/m/ms slew rate and an 8-channel sensitivity-encoding (SENSE) head coil. High-resolution (1-mm^3 isotropic voxel) three-dimensional (3D) T1-weighted MP-RAGE MRI images were collected from each subject (TR/TE = 6.7 ms/3.3 ms; acquisition matrix, 256 × 256; field of view = 256 mm; 176 contiguous slices of 1-mm thickness; number of signal average = 1; acquisition time = 5 min 38 sec).

Image Processing

Each 3D high-resolution T1-weighted anatomic image dataset was analyzed using a robust automatic volumetric analysis technique which combines a fully automated spatial normalization approach, hierarchical attribute matching mechanism for elastic registration (dubbed HAMMER),[21] in conjunction with a tissue mass-preserving deformation mechanism, regional analysis of volumes examined in normalized space (RAVENS).[22]

The first step was rigid alignment to the anterior commissure–posterior commissure plane, followed by semi-automated removal of skull and cerebellar tissues. The images were then segmented into three tissue types: gray matter (GM), white matter (WM), and ventricles (VN). These segmented images were registered to the common brain atlas by using high-dimensional image warping to create tissue density maps for GM, WM, and VN. These maps are also called RAVENS maps.

From the RAVENS maps, the HAMMER technique generated measurements of the sizes of 93 brain structures. These 93 structures were labeled in the template brain. The tissue mass-preserving deformation mechanism in the RAVENS method allowed for linearly translating the average density of each labeled structure in the RAVENS map into a measure of the size of that specific structure in the individual subject's brain (in cubic millimeters). The RAVENS maps are the results of elastic registration of original brain regions to the standard template while preserving the original tissue volumes. Therefore, regional volumetric measurements and comparisons were performed via measurements and comparisons of the respective RAVENS maps.

Data Analysis

Two analyses were carried out: a group comparison to identify structures whose volumes differed significantly between the glaucoma patients and controls and a within-group analysis to determine whether significant correlations existed between the volumes of the brain structures and disease severity for the glaucoma patients. The main outcome measure was the absolute volume of each brain structure. The secondary outcome measure was the relative volume, which was calculated by dividing the absolute volume of each brain structure by that individual's total brain volume.

For the group comparison, the mean volume and SD of each brain structure was calculated for both groups. An analysis of covariance (ANCOVA) with age as a covariate was carried out to identify structures that differed significantly between the glaucoma patients and controls. The ANCOVA has the ability to compare group means while accounting for confounding variables, such as age. Although the groups were well matched for demographic characteristics, brain volumes are so highly dependent on age, they must be taken into account as a confounding variable in any brain morphometric analysis.

For within-group analysis, the volume of each brain structure for the glaucoma patients was correlated with clinical measures of disease severity including the Disc Damage Likelihood Scale (DDLS) and the Glaucoma Staging System (GSS). Linear multivariate regression analyses with age as a covariate were conducted to determine the significance of these relationships. The DDLS and GSS are validated measures of optic nerve and visual field damage, respectively. The DDLS

Investigative Ophthalmology & Visual Science

incorporates disc size and neuroretinal rim width, including focal narrowing of the rim, to quantify glaucomatous damage to the optic nerve.[23] It grades optic nerve damage on a scale of 1 to 10 with 10 representing the most severe damage. The GSS incorporates global indices and pointwise parameters to determine the stage of visual field damage.[20] The GSS grades visual field damage on a scale of 0 to 5 with 5 representing the most severe damage.

Finally, brain volumes were also correlated with the peripheral vision subscale scores and composite scores for the VFQ-25. Linear multivariate regression analyses with VFQ-25 score as the dependent variable and with age, GSS score, and brain volume as the independent variables were conducted to determine the significance of these relationships.

No correction for multiple comparisons was used. Traditional voxel-by-voxel analyses involve thousands of comparisons and thus necessitate statistical correction. Because our analysis dealt with whole structures only, 93 comparisons were made, and given the preliminary nature of the investigation, no correction for this relatively small number of comparisons was necessary.

Results

Baseline clinical characteristics for all participants are listed in Table 1. Specific diagnoses for the glaucoma group included primary open-angle glaucoma (POAG, 12 subjects), pigmentary glaucoma (1 subject), and combinations of POAG with neovascular glaucoma (1 subject) and POAG with pseudoexfoliation glaucoma (1 subject).

Group Comparison

Of the 93 brain structures whose absolute volumes were compared by analysis of covariance, 5 differed significantly between the two groups (Table 2). All of these structures were larger in the glaucoma group, with volumetric gains ranging from 13% to 30% over the control value. These structures were all components of the visual association cortex.

Total brain volume was also larger in the glaucoma group, although this difference did not reach significance ($P = 0.15$). To further explore the relationship between total brain volume and observed group differences, we also compared the relative volumes between the two groups. Of the five structures whose absolute volumes were larger in the glaucoma group, two were also significantly larger in the analysis of covariance for relative volumes (Table 2). The other three structures did not reach significance in this comparison (right middle occipital gyrus, $P = 0.07$; right inferior occipital gyrus, $P = 0.08$; and right occipital lobe white matter, $P = 0.12$).

We also divided the glaucoma patients into an early disease group (mean DDLS <5; $n = 5$) and a moderate/advanced disease group (mean DDLS >5; $n = 10$). In the early disease group, 21 brain structures were larger in the glaucoma patients than in controls. No structures in this group were smaller in the glaucoma patients. In the moderate/advanced disease group, only three structures (left inferior occipital gyrus, right middle occipital gyrus, and right superior occipital gyrus) were larger in the glaucoma patients, while two structures (right superior frontal gyrus and corpus callosum) were smaller (Table 3).

Associations With Disease Severity

There were many independent associations between absolute brain volume and disease severity. Interestingly, even though the glaucoma patients had several structures that were larger than those of the controls and a trend toward larger total brain volume, the correlations were consistently negative, in that brain volume decreased with more severe disease. Of the 93 brain structures, 35 (38%) had independent associations between decreasing volume and more severe disease in multivariate regression analysis (Table 4). These structures were widespread throughout the brain but most had some association with the visual system. No structure had a significant correlation of increasing volume with more severe disease.

There were also many independent associations between relative brain volume and clinical severity. Most of these associations were similar to those with absolute volume, in that, relative volume decreased with more severe disease. However some structures exhibited an opposite correlation, that is, of increasing relative volume with more severe disease (Table 5).

Table 1. Baseline Clinical Characteristics

Characteristic	Glaucoma	Control
Age, y	66.1 ± 11.2	65.6 ± 11.3
Sex, male/female	10/5	10/5
Race		
African American	3	3
Caucasian	12	12
Visual acuity, logMAR		
Right eye	0.21 ± 0.36	0.01 ± 0.08
Left eye	0.12 ± 0.22	0.03 ± 0.10
GSS score		
Right eye	2.6 ± 1.8	0
Left eye	2.9 ± 1.5	0
DDLS		
Right eye	6.6 ± 2.2	2.3 ± 1.2
Left eye	6.2 ± 2.4	2.2 ± 1.1
IOP, mm Hg		
Right eye	12.7 ± 3.3	13.3 ± 2.2
Left eye	12.9 ± 3.4	13.0 ± 2.7
Duration of disease, y	11 ± 6.4	0
Duration of treatment, y	8.8 ± 6.4	0
Surgical intervention	8 (53%)	0

Values are means ± SD. DDLS, disc damage likelihood score; GSS, Glaucoma Staging System; IOP, intraocular pressure.

Associations With Patient-Reported Visual Disability

Last, we examined the relationship between brain volume and patient-reported visual disability, as measured by the peripheral vision subscale score and composite score of the VFQ-25. Linear multivariate regression analyses with VFQ-25 score as the dependent variable and with age, GSS score, and brain volume as the independent variables were conducted to determine the significance of these relationships. Although 7 structures had strong correlations with one of the VFQ-25 scores ($r > 0.5$), none reached significance in multivariate regression. In most of these models, GSS score was independently associated with VFQ-25 score (Table 6).

Discussion

Our results show that in comparison to healthy controls, patients with glaucoma have volumetric gains in several structural components of the visual association cortex. These volumetric gains are more widespread in early disease, where 20% of all brain structures were larger in the glaucoma group. In moderate/advanced disease, only three structures (left

Investigative Ophthalmology & Visual Science

Table 2. Brain Structures Which Differed Significantly Between the Glaucoma and Control Groups

Structure	Glaucoma	Control	*P* Value
Absolute volumes, mm^3			
Inferior occipital gyrus L	3067 ± 903	2302 ± 357	0.005
Inferior temporal gyrus R	10,574 ± 4209	7375 ± 2453	0.017
Middle occipital gyrus R	3609 ± 831	2939 ± 758	0.029
Occipital lobe white matter R	19,863 ± 3325	17,317 ± 2732	0.030
Inferior occipital gyrus R	1130 ± 268	906 ± 281	0.034
Relative volumes			
Hippocampal formation L	0.0046 ± 0.001	0.0050 ± 0.000	0.020
Inferior occipital gyrus L	0.0037 ± 0.001	0.0029 ± 0.001	0.021
Inferior temporal gyrus R	0.0124 ± 0.004	0.0092 ± 0.003	0.024
Cerebellum R	0.00016 ± 0.000	0.00024 ± 0.000	0.036

Data are mean volumes ± SD.

inferior occipital gyrus, right middle occipital gyrus, and right superior occipital gyrus) were larger in the glaucoma patients, while two structures (right superior frontal gyrus and corpus callosum) were smaller. We have also shown that 38% of all brain structures have significant correlations between decreasing volume and more severe disease. Considered together, these data suggest that patients with glaucoma may have volumetric gains in some structures early in disease, but that brain volumes decrease toward and in some cases below control volumes as the disease progresses.

Strengths of our study include the exclusion of any adults with cognitive impairment as well as the matching of glaucoma and control groups by demographic characteristics which may influence brain volume. Limitations of our study include its small sample size and cross-sectional observational design. Larger and especially longitudinal cohort studies are needed to confirm these observations and to determine their time course in regard to the progression of optic nerve damage in glaucoma. A larger study would also provide more refined data, as many structures trended toward but did not reach significance in both our group comparison and within-group clinical correlation. Finally, a larger sample size might also explain why some group differences were unilateral in nature. Unilateral brain changes are a common finding in preliminary volumetric investigations, but it is not known whether they are related to imprecise data with small sample sizes or have some biological basis.

Table 3. Brain Structures Which Differed Significantly Between the Glaucoma and Control Groups, by Disease Stage

Structure	Glaucoma	Control	*P* Value
Early group			
Brain stem	21,535 ± 2257	10,886 ± 2613	<0.001
Medial front-orbital gyrus L	2131 ± 199	1287 ± 205	<0.001
Middle temporal gyrus R	27,078 ± 3436	18,042 ± 1672	0.002
Medial front-orbital gyrus R	2540 ± 254	1929 ± 180	0.007
Lateral occipitotemporal gyrus R	8505 ± 1161	6187 ± 415	0.008
Temporal lobe WM R	60,744 ± 5430	48,275 ± 7429	0.008
Anterior limb of internal capsule R	10,923 ± 2015	5623 ± 2296	0.012
Frontal lobe WM L	81,286 ± 3015	67,657 ± 7651	0.013
Frontal lobe WM R	87,346 ± 6168	72,144 ± 7585	0.016
Cuneus R	4354 ± 364	3336 ± 514	0.019
Inferior temporal gyrus R	14,658 ± 2949	9204 ± 1670	0.020
Insula L	6498 ± 538	5335 ± 609	0.028
Globus pallidus L	1569 ± 173	1243 ± 181	0.029
Parahippocampal gyrus R	3892 ± 455	2760 ± 683	0.03
Superior temporal gyrus L	14,138 ± 1248	11,394 ± 1445	0.031
Insula R	6631 ± 673	5475 ± 506	0.038
Medial frontal gyrus L	9713 ± 1259	8045 ± 575	0.048
Cuneus L	3913 ± 591	2832 ± 622	0.048
Corpus callosum	12,919 ± 1563	10,036 ± 1617	0.048
Middle frontal gyrus L	16,613 ± 1911	13,277 ± 1804	0.049
Medial frontal gyrus R	11,632 ± 1991	9400 ± 950	0.049
Moderate/Advanced Group			
Middle occipital gyrus R	3528 ± 514	2694 ± 566	0.004
Superior frontal gyrus R	7451 ± 988	9105 ± 1300	0.008
Superior occipital gyrus R	4901 ± 644	4000 ± 707	0.014
Inferior occipital gyrus L	3067 ± 859	2219 ± 368	0.017
Corpus callosum	10,388 ± 1161	11,558 ± 1142	0.048

Data are mean volumes ± SD (mm^3). L, left; R, right; WML, white matter left; WMR, white matter right.

Investigative Ophthalmology & Visual Science

Table 4. Correlation Coefficients (*r*) and *P* Values for Structures With Significant Relationships Between Absolute Brain Volume and Disease Severity

	Mean DDLS		Mean GSS	
Optic Pathway Structures	***r***	***P* Value**	***r***	***P* Value**
Thalamus L	−0.607	**0.014**	−0.563	**0.003**
Cuneus gyrus L	−0.764	**0.002**	−0.662	**0.007**
Cuneus gyrus R	−0.820	**<0.001**	−0.622	**0.017**
Lingual gyrus L	−0.755	**<0.001**	−0.582	**0.001**
Lingual gyrus R	−0.571	**0.024**	−0.296	0.125
Other Brain Structures				
Middle temporal gyrus R	−0.882	**<0.0001**	−0.689	**0.006**
Temporal pole R	−0.871	**<0.0001**	−0.662	**0.004**
Lateral occipitotemporal gyrus R	−0.792	**<0.001**	−0.636	**0.001**
Globus pallidus L	−0.803	**<0.001**	−0.615	0.018
Temporal lobe WM R	−0.758	**0.001**	−0.643	0.014
Precuneus L	−0.764	**0.002**	−0.662	0.007
Occipital pole L	−0.736	**0.003**	−0.715	0.001
Frontal lobe WM R	−0.711	**0.004**	−0.391	0.086
Perirhinal cortex R	−0.717	**0.004**	−0.598	0.011
Perirhinal cortex L	−0.714	**0.004**	−0.407	0.138
Lateral occipitotemporal gyrus L	−0.678	**0.005**	−0.339	0.105
Medial occipitotemporal gyrus R	−0.696	**0.006**	−0.520	**0.034**
Frontal lobe WM L	−0.680	**0.006**	−0.500	**0.023**
Middle temporal gyrus L	−0.675	**0.008**	−0.444	0.069
Superior occipital gyrus L	−0.500	0.06	−0.663	**0.01**
Corpus callosum	−0.648	**0.012**	−0.536	**0.021**
Inferior temporal gyrus R	−0.648	**0.013**	−0.483	0.061
Superior temporal gyrus L	−0.602	**0.024**	−0.571	**0.015**
Temporal pole L	−0.606	**0.016**	−0.580	**0.032**
Precentral gyrus R	−0.629	**0.016**	−0.499	0.059
Middle frontal gyrus L	−0.585	**0.026**	−0.604	**0.021**
R superior temporal gyrus	−0.569	**0.033**	−0.491	**0.026**
Entorhinal cortex L	−0.549	**0.028**	−0.240	0.46
Globus pallidus R	−0.587	**0.028**	−0.292	0.219
Amygdala R	−0.560	**0.038**	−0.489	**0.032**
Superior frontal gyrus R	−0.570	**0.034**	−0.385	0.155
Occipital lobe WM L	−0.522	**0.037**	−0.350	0.251
Anterior limb of internal capsule R	−0.541	**0.039**	−0.524	0.058
Medial front-orbital gyrus L	−0.545	**0.045**	−0.349	0.131
Temporal lobe WM L	−0.527	**0.049**	−0.402	0.156

Significant values are in boldface type. DDLS, disc damage likelihood score; GSS, Glaucoma Staging System.

Group Comparison

The structures which were significantly larger in the glaucoma group (right inferior temporal gyrus, right middle occipital gyrus, right occipital lobe white matter, and right and left inferior occipital gyri) contribute to higher-order processing of visual information. They are all components of the ventral stream (the "what" pathway) of the visual system, which functions in identification and classification of visual stimuli.[24] Two other preliminary studies have found volumetric gains in the visual association cortices of glaucoma patients.[25,26] These studies investigated small cohorts of patients with mostly advanced glaucoma by using different voxel-based approaches. In addition to their findings in the visual association cortices, they identified several other cortical regions of increased or decreased gray matter volume, as was seen in our moderate/advanced group. Other whole-brain analytical approaches have also found evidence for distant cortical changes. Dai et al.[27] have demonstrated altered functional connectivity between the primary visual cortex and several components of the association cortices, while two other authors have found evidence for decreased structural integrity of several white matter tracts beyond the visual pathway.[28] An early observational study by Ong et al.[29] also found that patients with low tension glaucoma have thinning of the corpus and genu of the corpus callosum. The corpus callosum is the largest white matter structure in the brain and was also atrophied in our moderate/advanced group. Although there are many areas of overlap, all of the whole-brain analyses summarized here have identified different sets of brain structures as being significantly different from their respective control groups. Variations in patient populations, disease stage, radiological and statistical approaches likely account for these differences. Large longitu-

Table 5. Correlation Coefficients (*r*) and *P* Values for Structures with Significant Positive Relationships Between Relative Brain Volume and Disease Severity

	Mean DDLS		Mean GSS	
Structure	***r***	***P* Value**	***r***	***P* Value**
Hippocampus L	0.639	0.007	0.653	0.013
Hippocampus R	0.533	0.029	0.688	0.008
Cerebellum L	0.554	0.040	0.540	0.041

DDLS, disc damage likelihood score; GSS, Glaucoma Staging System.

Table 6. Structures With Strong Correlations Between Absolute Brain Volume and Peripheral Vision Subscale or Composite Scores on the VFQ-25

Structure	Peripheral Vision Score		Composite Score	
	Volume	Mean GSS	Volume	Mean GSS
Cuneus gyrus R	0.44 (0.95)	−0.71 (**0.02**)	0.56 (0.86)	−0.89 (<**0.001**)
Middle temporal gyrus R	0.46 (0.81)	−0.71 (**0.02**)	0.55 (0.58)	-0.89 (<**0.001**)
Perirhinal cortex R	0.41 (0.81)	−0.71 (**0.02**)	0.60 (0.19)	−0.89 (<**0.01**)
Cuneus gyrus L	0.61 (0.43)	−0.71 (0.07)	0.58 (0.83)	−0.89 (<**0.01**)
Lateral occipitotemporal gyrus R	0.59 (0.44)	−0.71 (0.14)	0.50 (0.79)	−0.89 (<**0.01**)
Lingual gyrus L	0.60 (0.24)	−0.71 (0.22)	0.47 (0.50)	−0.89 (<**0.01**)

Values are *r* (*P* value). Significant values are in boldface type. GSS, Glaucoma Staging System.

dinal studies will be necessary to provide definitive indications of which brain structures are altered during the course of the glaucomatous disease process.

Increased volume may be a sign of neuronal injury, such as cellular swelling or microglial activation.[30,31] Conversely, increased volume may indicate enhanced neuronal function or cortical plasticity. There is growing evidence that the adult brain is capable of undergoing extensive reorganization in response to sensory deprivation and that anatomical changes may accompany these functional adaptations. Several studies have linked increased cortical volume to enhanced task performance in both sensually deprived and normal human subjects,[17,32] and recent laboratory experiments have found evidence for increased dendritic arborization and diversion of axonal tracts as substrates for these functional changes.[33] In the blind, many studies have demonstrated that the visual association cortices are recruited for diverse functions including tactile, auditory, and linguistic tasks.[34,35]

Our data suggest that these changes may develop in patients with glaucoma before complete blindness ensues. A definite time course for neuronal plasticity has never been established, although there is evidence that functionally relevant cortical reorganizations can occur quite rapidly, on the order of several days.[36] Moreover, it is difficult to determine the duration of the glaucomatous disease process in each patient. Glaucoma typically progresses slowly, with even the most severe cases requiring an average of 25 years to progress from normal vision to complete blindness.[37] Additionally, the agreement between clinical examinations which establish disease severity and pathologic assessments of retinal ganglion cell loss is poor in early disease. In fact, there is almost no correlation between the two metrics when retinal ganglion cell loss is below 50%.[38] Thus, even a patient with "early" glaucoma may have significant neuronal losses and these losses may have been present for many years, allowing ample time for cortical reorganization.

It is not surprising that we found no volumetric deficits among the structures of the optic pathway, as has been established in prior reports.[3,5,9,13,25,26] Those studies used highly specific pathologic or voxel-by-voxel–based MRI analyses. Because our technique measures entire brain structures, it would be expected to miss small, localized volumetric differences. The lateral geniculate nucleus, for example, comprises only a minor portion of the thalamus. Our analysis of the entire thalamus could thus fail to detect a small change in this substructure. On the other hand, our approach has the ability to detect diffuse changes in structural volume which may not be significant enough to be distinguished at the level of a single voxel. This may explain why one previous whole-brain voxel-based analysis failed to detect widespread cortical change in glaucoma.[39] Results from both approaches must be considered in concert to gain a complete understanding of structural brain changes in this disorder.

Disease stage is another consideration which may account for the findings in our study. Most prior reports have studied patients with advanced glaucoma, as these individuals would be expected to have the most extensive neurodegenerative changes. Our patient cohort, in contrast, had many patients with early disease and on average only moderately advanced glaucoma. The clinical correlations found in our study indicate that the average disease stage of the patient group under investigation will greatly influence the results of any between-group volumetric comparisons. Study cohorts with more advanced disease may have more volumetric deficits while cohorts with early disease may have more volumetric gains as compared to a group of matched controls. Given the complex relationships between disease stage and structural volume found in our study, it is also possible that some brain structures undergo concomitant gains and losses of cortical volume, with the ratio of these changes differing by brain region, disease stage, and other factors which may influence rates of cortical degeneration and reorganization.

Associations With Disease Severity

The correlations of decreasing cortical volume as disease progresses are consistent with prior studies, but our data indicate that these changes are more widespread than previously shown. Although the correlations found in our study cannot establish a causal relationship, they do suggest that cortical atrophy may be a progressive process that begins in early disease and worsens as it progresses to blindness. This atrophy may develop in reaction to the progressive deprivation of visual input, may spread from adjacent degenerated structures via trans-synaptic degeneration, or it may develop independently in widely separated neuronal populations throughout the brain. Given the widespread changes found in our study and the similarities between glaucoma and other neurodegenerative disorders, this conception of glaucoma as a more global degenerative process affecting the optic nerve and other brain structures independently deserves further investigation.[2,40,41] Other groups have found evidence of widespread cerebral abnormalities in glaucoma including microvascular disease,[8,29,42] decreased mean and peak middle cerebral artery blood flow,[43,44] and white matter hemorrhages.[45] Each of these factors has been associated with cortical atrophy in the normal elderly or cognitively impaired population.[46,47]

From a statistical standpoint, it is remarkable that nearly 40% of all brain structures exhibited correlations of decreasing volume with more severe disease. Voxel-based measurements of whole brain structures have an inherent degree of variability, due to registration errors and the multifactorial determinants of brain volume.[48] Clinical measures of disease severity for glaucoma are even more variable due to the inherent subjectivity of these examinations.[49,50] Typical correlations of the DDLS with visual field metrics range from 0.39 to 0.62.[23] Our cohort had better, although still imperfect, consistency

between these two measurements, with correlations between the DDLS and GSS scores ranging from 0.77 to 0.87. Thus, for some structures, the correlations between brain volume and disease severity were stronger than those between the disease severity metrics themselves.

The only exceptions to the widespread correlations of decreasing cortical volume with disease severity were the left cerebellum and the right and left hippocampi. These structures had significant correlations of increasing relative volume with more severe disease, although the absolute volumes of these structures had no correlative relationship to disease severity (Table 5). While this finding should be confirmed by a more specific region-of-interest analysis, it is interesting to note that both the cerebellum and the hippocampi are larger in the blind as compared to sighted controls.[18] Increased hippocampal volume may also have a functional correlate in superior spatial navigation skills.[17] In the absence of any significant correlations for absolute volume, however, it is impossible to draw any firm conclusions regarding the clinical import of these observations. Correlations of increasing relative volume in the face of stagnant absolute volume may indicate that these structures are increasing in volume at a level below the sensitivity of this study, or that they are merely maintaining volume while many other structures across the brain atrophy.

Associations With Patient-Reported Visual Disability

The correlations between increasing cortical volume and increasing scores on the VFQ-25 are likely attributable to a confounding variable; namely, the disease severity metrics, which were independently associated with VFQ-25 score in multivariate regression. Despite these negative results, it will be important for future studies to determine what impact these cortical changes may have on visual function and quality of life in glaucoma. Given the high incidence of neurological comorbidities in glaucoma, it would be especially interesting to analyze the relationship between other types of disability and the volumes of their relevant cortical structures.

Acknowledgments

Funding was provided by the Wills Eye Institute and the Glaucoma Service Foundation to Prevent Blindness. These sources had no participation in the collection, analysis, or interpretation of study data.

Disclosure: **A.L. Williams**, None; **J. Lackey**, None; **S.S. Wizov**, None; **T.M.T. Chia**, None; **S. Gatla**, None; **M.L. Moster**, None; **R. Sergott**, None; **G.L. Spaeth**, None; **S. Lai**, None

References

1. Quigley H, Broman A. The number of people with glaucoma worldwide in 2010 and 2020. *Br J Ophthalmol*. 2006;90;262–267.
2. Gupta N, Yücel YH. Glaucoma as a neurodegenerative disease. *Curr Opin Ophthalmol*. 2007;18;110.
3. Gupta N, Ang LC, de Tilly LN, Bidaisee L, Yücel Y. Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex. *Br J Ophthalmol*. 2006;90;674–678.
4. Yücel YH, Zhang Q, Weinreb RN, et al. Effects of retinal ganglion cell loss on magno-, parvo-, koniocellular pathways in the lateral geniculate nucleus and visual cortex in glaucoma. *Prog Retin Eye Res*. 2003;22;465.
5. Kashiwagi K, Okubo T, Tsukahara S. Association of magnetic resonance imaging of anterior optic pathway with glaucomatous visual field damage and optic disc cupping. *J Glaucoma*. 2004;13;189.
6. Chen Z, Wang J, Lin F, et al. Correlation between lateral geniculate nucleus atrophy and damage to the optic disc in glaucoma [published online ahead of print February 19, 2013]. *J Neuroradiol*. doi: 10.1016/j.neurad.2012.10.004.
7. Garaci FG, Bolacchi F, Cerulli A, et al. Optic nerve and optic radiation neurodegeneration in patients with glaucoma: in vivo analysis with 3-T diffusion-tensor MR imaging. *Radiology*. 2009;252;496–501.
8. Engelhorn T, Michelson G, Waerntges S, et al. Diffusion tensor imaging detects rarefaction of optic radiation in glaucoma patients. *Acad Radiol*. 2011;18;764–9.
9. Zikou A, Kitsos G, Tzarouchi L, et al. Voxel-based morphometry and diffusion tensor imaging of the optic pathway in primary open-angle glaucoma: a preliminary study. *Am J Neuroradiol*. 2012;33;128–134.
10. Murai H, Suzuki Y, Kiyosawa M, et al. Positive correlation between the degree of visual field defect and optic radiation damage in glaucoma patients. *Jpn J Ophthalmol*. 2013;57;257–262.
11. Chen Z, Lin F, Wang J, et al. Diffusion tensor magnetic resonance imaging reveals visual pathway damage that correlates with clinical severity in glaucoma. *Clin Experiment Ophthalmol*. 2013;41;43–9.
12. Boucard CC, Hernowo AT, Maguire RP, et al. Changes in cortical grey matter density associated with long-standing retinal visual field defects. *Brain*. 2009;132;1898–1906.
13. Hernowo AT, Boucard CC, Jansonius NM, et al. Automated morphometry of the visual pathway in primary open-angle glaucoma. *Invest Ophthalmol Vis Sci*. 2011;52;2758–2766.
14. Duncan RO, Sample PA, Weinreb RN, et al. Retinotopic organization of primary visual cortex in glaucoma: a method for comparing cortical function with damage to the optic disk. *Invest Ophthalmol Vis Sci*. 2007;48;733–744.
15. Duncan RO, Sample PA, Weinreb RN, et al. Retinotopic organization of primary visual cortex in glaucoma: comparing fMRI measurements of cortical function with visual field loss. *Prog Retin Eye Res*. 2007;26;38.
16. Ramulu P. Glaucoma and disability: which tasks are affected, and at what stage of disease? *Curr Opin Ophthalmol*. 2009;20;92.
17. Fortin M, Voss P, Lord C, et al. Wayfinding in the blind: larger hippocampal volume and supranormal spatial navigation. *Brain*. 2008;131;2995–3005.
18. Leporé N, Voss P, Lepore F, et al. Brain structure changes visualized in early-and late-onset blind subjects. *Neuroimage*. 2010;49;134–140.
19. Mangione CM, Lee PP, Gutierrez PR, et al. Development of the 25-item national eye institute visual function questionnaire. *Arch Ophthalmol*. 2001;119;1050.
20. Mills RP, Budenz DL, Lee PP, et al. Categorizing the stage of glaucoma from pre-diagnosis to end-stage disease. *Am J Ophthalmol*. 2006;141;24–30.
21. Shen D, Davatzikos C. HAMMER: hierarchical attribute matching mechanism for elastic registration. *IEEE Trans Med Imaging*. 2002;21;1421–1439.
22. Davatzikos C, Genc A, Xu D, Resnick SM. Voxel-based morphometry using the RAVENS maps: methods and validation using simulated longitudinal atrophy. *Neuroimage*. 2001;14;1361–1369.
23. Danesh-Meyer H, Gaskin B, Jayusundera T, et al. Comparison of disc damage likelihood scale, cup to disc ratio, and Heidelberg retina tomograph in the diagnosis of glaucoma. *Br J Ophthalmol*. 2006;90;437–441.
24. Mishkin M, Ungerleider LG. Contribution of striate inputs to the visuospatial functions of parieto-preoccipital cortex in monkeys. *Behav Brain Res*. 1982;6;57–77.

25. Li C, Cai P, Shi L, et al. Voxel-based morphometry of the visual-related cortex in primary open angle glaucoma. *Curr Eye Res*. 2012;37;794–802.
26. Chen WW, Wang N, Cai S, et al. Structural brain abnormalities in patients with primary open-angle glaucoma: a study with 3T MR imaging. *Invest Ophthalmol Vis Sci*. 2013;54;545–554.
27. Dai H, Morelli JN, Ai F, et al. Resting-state functional MRI: Functional connectivity analysis of the visual cortex in primary open-angle glaucoma patients [published online ahead of print March 28, 2012]. *Hum Brain Mapp*. doi:10.1002/hbm.22079.
28. Lu P, Shi L, Du H, et al. Reduced white matter integrity in primary open-angle glaucoma: A DTI study using tract-based spatial statistics. *J Neuroradiol*. 2013;40;89–93.
29. Ong K, Farinelli A, Billson F, et al. Comparative study of brain magnetic resonance imaging findings in patients with low-tension glaucoma and control subjects. *Ophthalmology*. 1995; 102;1632–1638.
30. Rodriguez JJ, Verkhratsky A. Neuroglial roots of neurodegenerative diseases? *Mol Neurobiol*. 2011;43;87–96.
31. Xu H, Chen M, Forrester JV. Para-inflammation in the aging retina. *Prog Retin Eye Res*. 2009;28;348–368.
32. May A. Experience-dependent structural plasticity in the adult human brain. *Trends Cogn Sci*. 2011;15;475–82.
33. Johansen-Berg H. Structural plasticity: rewiring the brain. *Curr Biol*. 2007;17;R141–R144.
34. Merabet LB, Pascual-Leone A. Neural reorganization following sensory loss: the opportunity of change. *Nat Rev Neurosci*. 2009;11;44–52.
35. Voss P, Zatorre RJ. Organization and reorganization of sensory-deprived cortex. *Curr Biol*. 2012;22;R168–R173.
36. Merabet LB, Hamilton R, Schlaug G, et al. Rapid and reversible recruitment of early visual cortex for touch. *PLoS One*. 2008;3; e3046.
37. Heijl A, Bengtsson B, Hyman L, Leske MC. Natural history of open-angle glaucoma. *Ophthalmology*. 2009;116;2271–2276.
38. Harwerth RS, Carter-Dawson L, Shen F, et al. Ganglion cell losses underlying visual field defects from experimental glaucoma. *Invest Ophthalmol Vis Sci*. 1999;40;2242–2250.
39. Dai H, Yin D, Hu C, et al. Whole-brain voxel-based analysis of diffusion tensor MRI parameters in patients with primary open angle glaucoma and correlation with clinical glaucoma stage. *Neuroradiology*. 2013;55;233–243.
40. Wostyn P, Audenaert K, De Deyn PP. Alzheimer's disease-related changes in diseases characterized by elevation of intracranial or intraocular pressure. *Clin Neuroradiol Neurosurg*. 2008;110;101–109.
41. Nucci C, Martucci A, Cesareo M, et al. Brain involvement in glaucoma: advanced neuroimaging for understanding and monitoring a new target for therapy. *Curr Opin Pharmacol*. 2013;13;128–33.
42. Stroman GA, Stewart WC, Golnik KC, et al. Magnetic resonance imaging in patients with low-tension glaucoma. *Arch Ophthalmol*. 1995;113;168.
43. Harris A, Siesky B, Zarfati D, et al. Relationship of cerebral blood flow and central visual function in primary open-angle glaucoma. *J Glaucoma*. 2007;16;159–163.
44. Harris A, Zarfati D, Zalish M, et al. Reduced cerebrovascular blood flow velocities and vasoreactivity in open-angle glaucoma. *Am J Ophthalmol*. 2003;135;144–147.
45. Kitsos G, Zikou A, Bagli E, et al. Conventional MRI and magnetisation transfer imaging of the brain and optic pathway in primary open-angle glaucoma. *Brit J Ophthalmol*. 2009;82; 896–900.
46. Appelman AP, Vincken KL, van der Graaf Y, et al. White matter lesions and lacunar infarcts are independently and differently associated with brain atrophy: the SMART-MR study. *Cerebrovasc Dis*. 2010;29;28–35.
47. Franceschi M, Alberoni M, Bressi S, et al. Correlations between cognitive impairment, middle cerebral artery flow velocity and cortical glucose metabolism in the early phase of Alzheimer's disease. *Dement Geriatr Cogn Disord*. 1995;6;32–38.
48. Bandettini PA. What's new in neuroimaging methods? *Ann NY Acad Sci*. 2009;1156;260–293.
49. Katz J, Congdon N, Friedman DS. Methodological variations in estimating apparent progressive visual field loss in clinical trials of glaucoma treatment. *Arch Ophthalmol*. 1999;117; 1137.
50. Henderer JD, Liu C, Kesen M, et al. Reliability of the disk damage likelihood scale. *Am J Ophthalmol*. 2003;135;44–48.

Investigative Ophthalmology & Visual Science