Refined Data Analysis Provides Clinical Evidence for Central Nervous System Control of Chronic Glaucomatous Neurodegeneration

William E. Sponsel^{1,2,3,4}✉, Sylvia L. Groth⁵✉, Nancy Satsangi⁶✉, Ted Maddess⁴✉, and Matthew A. Reilly¹✉

¹ Department of Biomedical Engineering, University of Texas at San Antonio, San Antonio, TX, USA

² Rosenberg School of Optometry, University of the Incarnate Word, San Antonio, TX, USA

³ Baptist Medical Center WESMDPA Glaucoma Service, San Antonio, TX, USA

⁴ Australian Research Council Centre of Excellence in Vision Science, Canberra, Australia

⁵ University of Minnesota Medical School, Minneapolis, MN, USA

⁶ University of Texas Health Science Center–San Antonio, San Antonio, TX, USA

Correspondence: William Eric Sponsel, Suite 306 Madison Square Building, 311 Camden St., San Antonio, TX 78215, USA. e-mail: sponsel@earthlink.net

Received: 15 December 2013

Accepted: 15 March 2014

Published: 6 May 2014

Keywords: Refined data analysis; glaucoma; neuroprotection; neurodegeneration; visual fields; perimetry

Citation: Sponsel WE, Groth SL, Satsangi N, et al. Refined data analysis provides clinical evidence for central nervous system control of chronic glaucomatous neurodegeneration. *Trans Vis Sci Tech.* 2014;3(3):1, <http://tvstjournal.org/doi/full/10.1167/tvst.3.3.1>, doi:10.1167/tvst.3.3.1

Purpose: Refined data analysis was performed to assess binocular visual field conservation in patients with bilateral glaucomatous damage to determine whether unilateral visual field loss is random, anatomically symmetric, or nonrandom in relation to the fellow eye.

Methods: This was a case-control study of 47 consecutive patients with bilaterally severe glaucoma; each right eye visual field locus was paired with randomly selected coisopteretic left eye loci, with 760,000 (10,000 complete sets of 76 loci) such iterations performed per subject. The potential role of anatomic symmetry in bilateral visual field conservation was also assessed by pairing mirror-image loci of the paired fields. The mean values of the random coisopteretic and the symmetric mirror pairings were compared with natural point-for-point pairings of the two eyes by paired *t*-test.

Results: Mean unilateral thresholds across the entire visual field were 18.9 dB left and 19.9 dB right (average 19.4), 4 dB lower than the better of the naturally paired concomitant loci of 23.4 dB ($P < 10^{-15}$). A remarkable natural tendency for conservation of the binocular visual field was confirmed, far stronger than explicable by random chance or anatomic symmetry ($P < 0.0001$), and reaffirmed by subsequent prospective simultaneous binocular visual field retesting of an arbitrary subset ($n = 16$) of the study population ($P < 0.0001$).

Conclusions: Refined data analysis of paired visual fields confirms the existence of a natural optimization of binocular visual function in severe bilateral glaucoma via interlocking fields that could be created only by central nervous system (CNS) involvement.

Translational Relevance: Integrated bilateral visual field analysis should better define actual visual disability and more accurately reflect the functional efficacy of current ocular and future CNS-oriented therapeutic approaches to the treatment of glaucoma. Glaucomatous eyes provide a highly accessible paired-organ study model for developing therapeutics to optimize conservation of function in neurodegenerative disorders.

Introduction

Functional patterns of chronic glaucomatous visual field loss have generally been considered the presentation of progressive axonal degeneration

arising in functionally independent eyes. A central tenet of perimetry is that scotomata respecting the horizontal axis are of ocular or optic nerve origin, while those respecting the vertical meridian are of chiasmal or postchiasmal origin. Recent basic science

studies suggest, however, that glaucomatous neurodegeneration may be under central nervous system (CNS) control. Studies of DBA/2 mice report a form of distal dieback of retinal ganglion cell axons projecting to the superior colliculus (SC) in glaucoma.^{1,2} The dieback is preceded by damaged axoplasmic transport and results in brain-derived neurotrophic factor-mediated astrocyte activation³ and reactive gliosis⁴ within the SC. The resulting damage can be sectoral and asymmetric between eyes.² Evidence of dieback is less clear in primate lateral geniculate nucleus, but both cell death^{5,6} and shrinkage^{5,7} have been reported early in experimental primate glaucoma. Microglial activation⁸ and reactive gliosis⁹ are also reported in primate models, as is neurodegeneration from optic nerve to cortex in human glaucoma.¹⁰ Excellent reviews of this topic area are available.^{11,12} Thus, there is some evidence for mechanisms that could support central control of binocular visual field patency in late glaucoma. One clear manifestation of such central control of glaucomatous neurodegeneration would be evidence that the brain actually helps conserve the best possible binocular field by preserving complementary islands of vision in the two eyes in a manner that could not possibly happen by chance or as a consequence of offsetting symmetric bilateral anatomic weaknesses in the paired eyes.

This study thus investigated whether the typically erratic asymmetry of binocular visual field loss of chronic glaucoma patients might, paradoxically, provide new statistical evidence for direct involvement of the CNS. Applying the presumptive null hypothesis that glaucoma progresses independently in each eye, we discovered the converse, that the brain coordinates glaucomatous progression, maximizing residual binocular visual function suggestive of bilaterally coordinated focal neurodegeneration. The result is a highly statistically unlikely tessellation of islands of monocular function that tend to preserve an intact binocular visual field.

Methods

Institutional Review Board (IRB)/Ethics Committee approval was obtained for this Health Insurance Portability and Accountability Act-compliant cross-sectional study, which was fully adherent to the tenets of the Declaration of Helsinki. All available records for patients with bilateral chronic progressive glaucoma in the IRB-sanctioned San Antonio, Texas, glaucoma subspecialty clinic were assessed, and all

patients meeting the inclusion criteria are included in this analysis. Inclusion criteria were (1) perimetric experience (two or more prior visual fields) and reliability (false-positive and false-negative rates both < 25%) with moderate or severe visual field loss in both eyes using Humphrey Visual Field Analyzer II (Carl Zeiss Meditec, Dublin, CA) and 30-2 SITA (Swedish Interactive Threshold Algorithm)¹³ full-threshold scoring criteria (see below);¹⁴⁻¹⁶ (2) visual acuity $\geq 20/80$ in both eyes; (3) with severe excavatory optic neuropathy (cup-to-disc ratio ≥ 0.75 in both eyes); and (4) bilaterally stable intraocular pressure in both eyes in the range 6 to 16 mm Hg.

Briefly outlined, the study design is as follows:

1. Objective stable glaucoma bilateral severe and moderate visual field loss chart data screening;
2. Criteria met: Document bilateral visual field (VF) data, mean deviation, and pattern standard deviation, and calculate maximal concomitant threshold values in both eyes;
3. Perform refined data analysis with 10,000 iterations of optionally equivalent bilateral coisopteric outcome for each subject;
4. Perform bilateral absolute symmetry analysis for each of the 74 points on the Humphrey visual field 30-2 full-threshold VF analysis in both eyes; and
5. Calculate the paired *t*-test *P* values for all comparisons (i.e., mean right and left eye versus computed and actual bilateral binocular VF values).

Details of each step are described further below.

Severe visual field loss was defined as a mean defect worse than -12 dB, and/or 37 or more points depressed at or below 5%, and/or 20 or more below 1%, and/or a glaucomatous scotoma with one or more pericentral loci at 0 dB or two such loci at or below 15 dB. Moderate visual field loss was defined as having a mean defect between -12 and -6 dB, and/or 18 to 36 points depressed at or below 5%, and/or 10 to 19 points depressed at or below 1%, and no points in the central 5° at 0 dB, and no pericentral hemifield pairs at or below 15 dB.

All eyes were tested with best refractive lens correction in place during a single perimetric session. A subgroup of the patients ($n = 16$) also underwent binocular testing with both eyes simultaneously open, using the same corrective lenses in trial frames modified to fit beneath the field analyzer forehead rest. All patients with evidence of ptosis underwent perimetric testing with the upper lid taped to the brow to avoid lid artifact. Visual fields from the larger

cohort of 47 subjects were acquired during standard clinical testing over a 4-year period, while the retesting of 16 of these patients was carried out prospectively (at the suggestion of Douglas Anderson) between the first peer-reviewed presentation of this phenomenon at the annual meeting of the American Glaucoma Society in San Francisco in March, 2013, and its subsequent presentation at the annual meeting of the Association for Research in Vision and Ophthalmology in Seattle in May of that year. All 47 subjects were invited for bilateral and simultaneous binocular 30-2 retesting, and all those able to attend during that time interval were included in the analysis.

It has been established that the binocular visual field can be predicted by appropriate pairing of directly corresponding (concomitant) loci of the individual right and left eye visual fields.¹⁷ For the present statistical analysis, to assess the randomness of the contribution of each eye to binocular visual function, each left eye Humphrey 30-2 visual field locus was paired with (α) its actual corresponding (concomitant) right eye locus, or (β) multiple random coisopterical right eye loci, all of equal eccentricity from fixation (Fig. 1). This was performed in a sequential manner choosing one random coisopterical left eye locus for each right eye locus until all 76 were paired, repeating this process 10,000 times for all 47 paired visual fields. The higher of the two paired light sensitivity threshold values for all 76 loci within the central 30° for all subjects were then generated, for actual contralateral concomitant pairings and for physiologically balanced alternative pairings, using combinations α and β above. As an additional exercise to estimate the very best field pairing that could be obtained from the two eyes, the very highest value combination of all 10,000 randomized field pairings was also determined for each of the 47 subjects. The different mean and the maximum light attenuation threshold results obtained for each subject were compiled to provide means of each for all 47 subjects. The results for each patient were fitted with an extreme value probability density function. Composite means for the study population were then compared by paired *t*-test.

In order to investigate the potential contribution of anatomic symmetry, additional comparisons were also made pairing each left eye visual field locus with its horizontal mirror-image locus from the right eye (χ). The rationale for this extra analysis was that if one optic nerve had a propensity for axonal loss inferotemporally, for example, then the nerve of the

fellow eye might reasonably be expected to have a similar tendency. In such an instance, each eye might be expected to develop a superonasal visual field defect. With both eyes open these could mutually offset one another, resulting in a full binocular visual field. To identify the extent of any such passive anatomic compensation, probability distribution comparisons were performed to determine to what extent such passive bilateral symmetric offset might account for any observed optimization of binocular visual function. Three-dimensional (3-D) heat maps of the higher paired threshold value projected binocular visual field were created for all subjects for combinations α , β , and χ , to compare with one another and with their associated individual right and left eye 3-D projections. All computations were carried out using MATLAB v7.13 (The Mathworks, Inc., Natick, MA) in the University of Texas at San Antonio Department of Biomedical Engineering. It should be emphasized that all probability calculations presented are the result of comparisons of the final refined data compilations of each of the 47 individuals in the study, and there is no statistical retreatment of any nonindependent variables in this analysis.

Results

This study evaluated all 47 adult patients meeting the inclusion criteria. Their mean age was 73 ± 2 (SEM) years. Thirty were female, and 17 were male. Their mean cup-to-disc ratio values were 0.84 ± 0.02 in the right eye and 0.86 ± 0.01 in the left. Their mean Humphrey 30-2 MD and PSD values were -13.72 and 10.70 , respectively, for left eyes and -12.24 and 10.26 for right eyes (see Table 1). The age, sex, and all right and left eye MD and PSD values for all 47 subjects are provided in Table 2. Twenty-three subjects had severe visual field loss in both eyes, 9 had moderate loss in both eyes, and 15 had severe loss in one eye and moderate loss in the other. Eighty-eight percent of patients had undergone successful glaucoma surgery in either or both eyes,¹⁸ stabilizing intraocular pressure bilaterally. Many of the clinical subjects qualifying for the present study were participants in a recently published surgical study¹⁸ who collectively demonstrated very stable and low postoperative glaucoma medication use and IOP values, as well as very high intervisit Humphrey 30-2 stability and reproducibility. All six correlation coefficients (*R*) for comparisons of MD and PSD at 6, 12, and 18 months versus presurgical baseline values in that

Figure 1. Specimen visual field pairs and analytical algorithm. Grayscale (*above*) and pairing algorithm (*below*) representations of Humphrey 30-2 visual field plots. The four grayscale visual field plots show the paired right and left eye visual fields of 4 of the 47 study subjects with clinically stable bilaterally severe chronic glaucoma. Note the complementarity of the patterns of the focal areas of visual loss and visual conservation between the paired eyes, providing compensation when both eyes are used together to view the binocular visual field. The pairing algorithm used matched each of the 76 loci in the left visual field (*lower left*) with (α) the corresponding locus of the right visual field (red), (β) any one randomly selected point from among those equidistant from central fixation (teal), and (γ) the precise mirror-image locus (orange).

study were clustered around 0.9 (range, $R = 0.863$ – 0.957).

The mean intraocular pressure among participants in the present study was 10.1 ± 0.5 mm Hg in the right eye and 11.6 ± 0.6 mm Hg in the left. Only 27% of subjects were receiving any topical ocular hypotensive therapy in either eye with the clinical intent of enhancing IOP reduction. No oral ocular hypotensive agent was in use by any subject. Fifty-seven percent of subjects were prescribed topical carbonic anhydrase

inhibitor eye drops with the intent of augmenting ocular vascular perfusion.¹⁹

Figure 1 presents several select examples of paired visual fields that show a readily apparent nonrandom inverse tendency for focal zones of visual loss in one eye to be seen well by the fellow eye. Note that in these individuals, the alternating positive and negative complementarity between the right and left eye visual fields results in a much more normal binocular field than could be predicted by chance. The examples

Table 1. Mean Right and Left Eye Humphrey 30-2 MD and PSD Global Index Values (Mean Deviation and Pattern Standard Deviation From the Perimetry Printouts) With Associated Standard Errors for All Right and Left Eyes of Consecutive Patients With Clinically Stabilized Bilateral Moderate to Severe Visual Field Loss ($n = 47$) and for the Subset of These Patients Retested Prospectively With Their Right Eye, Left Eye, and Simultaneous Binocular Visual Field Test Mean MD and PSD and Standard Error Values ($n = 16$)

	Right Eye	Left Eye	Binocular
Full data set, $n = 47$			
Mean of mean deviation values (SEM)	−12.24 (0.78)	−13.72 (0.67)	-
Mean pattern standard deviation (SEM)	10.26 (0.46)	10.70 (0.46)	-
Binocular subset, $n = 16$			
Mean of mean deviation values (SEM)	−12.98 (1.2)	−15.38 (1.7)	−7.99 (1.1)
Mean pattern standard deviation (SEM)	11.09 (0.8)	10.44 (0.9)	7.73 (1.0)

shown were chosen because they make the “jigsaw” phenomenon fairly obvious at a glance. Other individuals in the study had significant loss in the same quadrant or hemifield in both eyes, making bilateral compensatory effects far less obvious on cursory inspection of the fields. All patients were included in the statistical analysis. Figure 2 shows an example of a patient with bilateral severe visual field loss who clearly does not demonstrate the jigsaw phenomenon. This 84-year-old female, whose data were included in both the $n = 47$ and $n = 16$ prospective analyses, had coexisting diabetes and systemic hypertension. Her severe bilateral concentric loss overlaps extensively in the peripheral field of both eyes; and the MD of the binocular field is actually worse than either eye on its own, despite taping of both upper lids to prevent ptosis during testing. It is nevertheless intriguing that during that testing she dynamically expanded the functionally more important inferior binocular field while sacrificing binocular function superiorly.

Figure 3 provides a 3-D projection heat map set for one specimen visual field pair, with results obtained by the actual natural focal pairings of all 74 visual field loci (α) and the mean of 10,000 randomized isopterically equivalent pairings using the same left eye visual field data (β). Note in this instance that the latter physiologically balanced pairings would render an improved but still severely defective binocular visual field, while the actual natural pairings render a binocular field that approaches normal.

Numerical analysis of the entire study population reaffirms the general strength of this tendency. Figure 4 and Table 3 illustrate and summarize the statistical findings from the full study group ($n = 47$; 94 eyes).

Among these eyes, the mean threshold value across the entire visual field (74 loci) was 18.9 dB for left eyes and 19.9 dB for right eyes (average 19.4), 4 dB lower than the better of the naturally paired concomitant loci (α) at 23.4 dB ($P < 10^{-15}$). This mean threshold value (α) for concomitant direct pairings was significantly higher than was attainable from the same eyes when pairing was performed using the randomized coisopterically equivalent options (β), which yielded 21.9 dB ($P < 10^{-12}$). The natural bilateral overlay pairings (α) provided function levels within 0.3 dB of the mean of the very highest of the 47 individual results among the 470,000 randomized pairings used to calculate β values. Mirror-image pairings, in contrast, were statistically indistinguishable from the randomized coisopteric pairings.

Simultaneous binocular visual field testing carried out prospectively among the returning subset of 16 of the 47 patients confirmed that concomitant testing with both eyes open produced results essentially equivalent to the higher light attenuation threshold value of all 74 naturally paired bilaterally concomitant loci (α) of the individual right and left visual fields. These subjects comprised 10 individuals with severe visual field loss in both eyes, 2 with moderate loss in both eyes, and 4 with a mixture thereof (Fig. 5, Table 4). Paired t -test values showed a highly significant 6.2-dB difference between the binocular Humphrey 30-2 global index MD (-7.97 ± 1.1 dB) and the mean of the right and left MD values (-14.18 ± 1.3 dB; see Table 1) obtained on retesting immediately beforehand among this cohort ($P < 0.0001$). The mean difference between the randomized mean paired right and left visual field values and the true measured binocular values among this prospectively retested subgroup was 1.6 dB ($P < 0.005$). The

Table 2. Age, Sex, and Right and Left Eye Mean Deviation and Pattern Standard Deviation Values for the 47 Subjects, Confirming the Bilateral Severity of the Humphrey 30-2 Visual Field Loss Among the Study Population (the Arbitrary Subset of 16 Subjects Able to Return During a 2-Month Interval for Repeat Right and Left Eye Retesting and Simultaneous Binocular 30-2 Visual Field Testing Is Shown)

Age	Sex	Right Eye MD	Right Eye PSD	Left Eye MD	Left Eye PSD	Repeat Binocular VF Field and Repeat R/L
72	M	-11.50	10.89	-14.55	13.96	
49	M	-9.28	4.34	-14.14	10.94	X
75	F	-14.84	15.51	-20.54	13.47	X
80	M	-5.09	3.38	-6.86	8.64	
66	M	-12.96	9.82	-17.87	9.64	
12	F	-18.10	13.32	-14.21	14.46	
72	M	-16.83	14.24	-21.12	12.15	
69	M	-17.49	14.21	-21.65	14.22	X
65	F	-13.86	9.57	-7.46	5.30	
77	F	-6.82	6.65	-8.42	8.19	X
48	F	-15.14	10.75	-10.53	9.50	
57	F	-13.44	14.97	-10.51	10.88	
83	F	-9.67	12.75	-16.86	12.14	
64	M	-14.98	13.96	-8.81	5.47	X
75	F	-8.17	10.36	-13.66	11.89	
84	F	-9.92	13.14	-20.77	11.67	
77	F	-4.05	7.11	-12.85	10.73	X
83	M	-9.06	10.74	-5.50	2.75	X
53	M	-7.42	5.46	-12.26	10.45	
81	F	-18.05	7.23	-22.02	8.17	
78	M	-16.26	10.01	-11.92	9.75	
91	M	-11.59	9.52	-16.72	12.63	
89	M	-8.92	6.65	-13.45	7.82	
78	F	-23.13	10.16	-15.89	14.74	
87	F	-6.73	6.63	-11.65	13.15	X
72	M	-17.90	12.42	-14.22	11.66	
63	M	-8.95	5.35	-12.54	11.04	
89	M	-13.51	10.41	-9.45	8.76	
84	M	-9.57	7.74	-7.42	4.13	
81	M	-8.60	5.44	-15.00	9.60	
57	F	-19.48	12.81	-14.49	13.39	
63	F	-4.50	8.55	-12.40	15.04	
99	F	-13.91	11.08	-19.62	10.62	
50	F	-11.35	10.53	-7.89	8.62	
76	F	-10.66	7.00	-15.75	7.06	
73	F	-21.58	13.16	-20.98	13.02	
61	F	-18.91	12.44	-20.75	16.36	X
96	F	-19.66	14.22	-15.72	11.31	
61	F	-11.67	12.50	-11.19	15.37	X
76	M	-17.16	11.80	-10.11	9.66	X
88	F	-7.63	5.63	-10.78	10.50	
61	M	-9.36	10.87	-12.86	12.02	X

Table 2. Continued.

Age	Sex	Right Eye MD	Right Eye PSD	Left Eye MD	Left Eye PSD	Repeat Binocular VF Field and Repeat R/L
70	F	−11.14	12.85	−10.42	13.33	X
71	F	−14.62	13.34	−6.71	7.56	
76	F	−9.99	14.20	−14.70	12.38	X
84	F	−16.43	7.27	−16.97	7.74	X
63	M	−9.65	13.17	−9.81	5.85	X

difference between the means of the very best of the 10,000 coisopterics randomized combinations of individual right and left visual fields and the natural bilateral pairings (α) was only 0.25 dB, in favor of the best-of-10,000 ($P = 0.02$). Remarkably, however, the mean difference between these optimal pairings and actual measured (simultaneous) binocular visual fields was statistically indistinguishable (0.4 dB in favor of the binocular field, $P = 0.93$); both of these were >5 dB higher than the means of the right and left fields, and >2 dB higher than the mean of 10,000 randomized coisopterics pairings (β) or mirror-image pairings (χ).

Discussion

These analyses indicate that chronic glaucomatous neurodegeneration is mediated not by random degradation in isolated eyes but by an integrated process that attempts to maximize the binocular visual field. Such interlocation of focally asymmetric defects

implies direct brain involvement. This model also explains a classic metabolic paradox: the clinical tendency for conservation of the temporal crescent in end-stage glaucoma, even after central vision has been lost. In all other quadrants, distally located axons in the retinal periphery are among the first area to disappear in chronic glaucoma. The protracted conservation of the most distal nasal ganglion cells makes little sense in general physiologic terms, but makes great sense in a bilaterally coordinated system in which ganglion cell perseverance is under CNS-mediated optimization of the binocular visual field, since these are the axons that support temporal peripheral visual field, obscured throughout adult life for the fellow eye by the profile of the nose.

Although many of the published data suggest control by cortical mechanisms, we cannot rule out control by the SC since the best evidence for dieback is for the SC.^{1,2} Due to decussation, each primate SC represents a hemifield and almost all SC cells are binocular.^{20,21} Functional magnetic resonance imaging studies confirm this in humans.^{22,23} The two SCs

Figure 2. An example of paired and binocular fields that did not demonstrate the “jigsaw phenomenon.” Left eye (A), right eye (B), and simultaneous binocular (C) Humphrey 30-2 visual field plots from an 84-year-old female with open-angle glaucoma and coexisting diabetes and systemic hypertension. This patient’s diabetes was nonproliferative, and she had never undergone laser treatment. Perimetric testing of individual right and left eyes and for the simultaneous binocular visual field was carried out with the relevant upper lids taped to the brow to avoid ptosis artifact.

Figure 3. Example of pairing algorithm outcomes and associated 3-D heat maps. Left and right Humphrey 30-2 visual field pair for one subject (grayscale 2-D, *above*) and associated set of heat maps (colored 3-D, *below*). Note that the lower left composite applying the better of each of the 76 loci (α) arising naturally for the two eyes has a much less pathologic binocular visual field loss than the composite derived from isopterically equivalent randomly selected points (β) at the *lower right*. The probability that the mean logarithmic global light sensitivity threshold was the same for pairings (α) and (β) among all 47 subjects was $<10^{-4}$. The mean global threshold for (α) was 23.4 and for (β) was 21.8 dB.

are also interconnected in humans, providing a possible substrate for coordinating binocular visual field patency across the vertical meridian.²⁴ Certainly some higher cortical functions, such as visual attention, are in part mediated via the SC.²⁵ It may be that processing in the thalamic lateral geniculate is responsible for this effect. The lateral geniculate is a bilateral structure that includes six layers: layers 2, 3, and 5 receive information from the ipsilateral eye while layers 1, 4, and 6 receive it from the

contralateral eye. Locations in adjacent layers correspond to visually concomitant areas of each retina. It has been shown that when there is damage to one optic nerve, compensatorily higher light sensitivity is developed to adjacent layer input in the lateral geniculate from the fellow eye.²⁶ Focal axonal injury in one eye appears to be accompanied by increased activity in the contralateral retinal glia and geniculate layers receiving concomitant visual information from the fellow noninjured eye.^{26–29} One factor could be

Figure 4. Mean thresholds for monocular and paired visual field outcomes. Histogram showing global mean threshold values ($n = 47$) with associated standard errors of the mean (SEM) for left (a) and right eye (b) Humphrey 30-2 visual fields, and for both eyes overlying the higher of the 76 concomitant right and left eye using (c) the pairings of each left locus with any alternate randomly selected coisopteric right values (repeated for all 76 loci $\times$ 10,000 iterations for each of the 47 eyes), (d) each left locus with its precise mirror-image symmetric locus, and (e) the natural left/right pairings. The actual observed fields provide the highest conjoint sensitivity.

that adjacent geniculate layers share the same vascular supply, so loss of axons from one eye may be accompanied by increased availability of nutrients to, and more rapid clearance of catabolites from, the immediately adjacent contralateral eye synapses. Focally coordinated bilateral compensation of this kind may be a major factor in the conservation of the binocular visual field in patients with chronic progressive glaucoma. Whether some neuroprotective feature is required, or whether only a form of winner-takes-all control determining which eye undergoes programmed cell death, remains unclear. There may even be a role for neuroplastic neuroregeneration. Identification of causal mechanisms that regulate this phenomenon might suggest new treatment options.

The size of the jigsaw piece of any part field may be proportional to the ocular dominance column width projected into visual space. The column width would

likely constrain binocular interaction for any mechanism based on cortical plasticity. This idea could be tested in experimental glaucoma in primates, where the column width in various primates and humans is related to the cortical magnification and disparity information.

Many innovative investigations on apparent anterograde CNS associations with optic neuropathy^{30–38} preceded the landmark Vanderbilt laboratory studies revealing retrograde effects from the brain to the eye in chronic glaucoma.¹ This present study provides strong clinical evidence that the brain exerts bilaterally coordinated direct influences on ganglion cell function and viability to maximize the binocular visual field in patients with advanced chronic glaucoma. As far as we are aware, aside from the Vanderbilt report in *Proceedings of the National Academy of Sciences U S A*, this phenomenon has not been previously recog-

Table 3. Comparative Mean Threshold Differences and Associated Paired *t*-Test *P* Values for Consecutive Patients, Comparing Mean Threshold Compilations From Right and Left Eye Humphrey 30-2 SITA Full-Threshold Visual Fields (*N* = 47)

	Randomized Bilateral Mean Threshold (<i>P</i> Value)	Mirrored Bilateral Threshold (<i>P</i> Value)	Overlaid Bilateral Mean Threshold (<i>P</i> Value)	Best of 10,000 Random Pairings (<i>P</i> Value)
Left eye mean threshold	2.8 dB* (<i><</i> 0.0001)	2.9 dB* (<i><</i> 0.0001)	4.4 dB* (<i><</i> 0.0001)	4.8 dB* (<i><</i> 0.0001)
Right eye mean threshold	2.0 dB* (<i><</i> 0.0001)	2.0 dB* (<i><</i> 0.0001)	3.5 dB* (<i><</i> 0.0001)	3.9 dB* (<i><</i> 0.0001)
Randomized bilateral mean threshold		0.04 dB (0.6)	1.6 dB* (<i><</i> 0.0001)	1.9 dB* (<i><</i> 0.0001)
Mirrored bilateral threshold			1.5 dB* (<i><</i> 0.0001)	1.9 dB* (<i><</i> 0.0001)
Overlaid bilateral mean threshold				0.3 dB* (<i><</i> 0.0001)

* Significant values *P* < 0.05.

nized. Further investigation into this process might help provide insights into possible intrinsic functional compensation mechanisms at work in other bilateral neurodegenerative disorders. Chronic glaucoma is an age-related disease that shares strong homology with

the neurodegenerative cellular biology of Alzheimer's.^{39–42} Both age-related disorders progress bilaterally, involving both eyes and both cerebral hemispheres, respectively, and each disorder exhibits focally asymmetric neurodegeneration. It is possible

Figure 5. Mean thresholds for monocular and paired visual field outcomes and actual simultaneous binocular visual fields. Histogram showing global mean threshold values (*n* = 16) with associated standard errors of the mean (SEM) for left (a) and right eye (b) Humphrey 30-2 visual fields, and for both eyes overlying the higher of the 76 concomitant right and left eye using (c) the pairings of each left locus with any alternate randomly selected coisopterical right values (repeated for all 76 loci $\times$ 10,000 iterations for each of the 47 eyes), (d) each left locus with its precise mirror-image symmetric locus, (e) the natural left/right pairings, and (f) the actual simultaneous binocular visual fields.

Table 4. Comparative Mean Threshold Differences and Associated Paired *t*-Test *P* Values for Consecutive Patients, Comparing Left and Right Eye Compilations and Same-Session Binocular Humphrey 30-2 SITA Full-Threshold Visual Fields (*N* = 16)

	Randomized Bilateral Mean Threshold (<i>P</i> Value)	Mirrored Bilateral Threshold (<i>P</i> Value)	Overlaid Bilateral Mean Threshold (<i>P</i> Value)	Best of 10,000 Random Pairings (<i>P</i> Value)	Simultaneous Binocular Mean Threshold (<i>P</i> Value)
Left eye mean threshold	1.8 dB* (0.001)	1.8 dB* (0.0004)	3.2 dB* (<0.0001)	3.4 dB* (<0.0001)	3.4 dB* (<0.0001)
Right eye mean threshold	4.1 dB* (<0.0001)	4.2 dB* (<0.0001)	5.5 dB* (<0.0001)	5.7 dB* (<0.0001)	5.7 dB* (0.0001)
Randomized bilateral mean threshold		0.04 dB (0.8)	1.4 dB* (<0.0001)	1.6 dB* (<0.0001)	1.6 dB* (0.005)
Mirrored bilateral threshold			1.3 dB* (0.0001)	1.6 dB (<0.0001)	1.6 dB* (0.008)
Overlaid bilateral mean threshold				0.3 dB* (0.02)	0.2 dB (0.7)
Best of 10,000 random pairings					0.04 dB (0.9)

* Significant values $P < 0.05$.

that analogous mechanisms for conserving functionality via asymmetric, focally compensating programmed neuroprotective processing might help conserve maximum global functioning in both glaucoma and Alzheimer's. The exquisite accessibility and bilateral sequestration of paired eyes provides an intricate input and response system for placebo-controlled intra-subject CNS studies with high statistical power, unfettered by the enormous statistical dilutional effects of interindividual variability.⁴³

There are limitations to the present study. It is clear that much additional work will be required to elucidate the actual neurophysiologic basis for this phenomenon, and refined data analyses of visual fields from patients with subclinical and mild glaucomatous visual field loss are now essential. If similar findings arise in such individuals, detection of such bilateral compensation at a subclinical stage might facilitate the early characterization and timely treatment of chronic glaucoma before more severe permanent neuronal damage can occur.

These findings should be of some comfort to glaucoma sufferers, and of considerable assistance to clinicians in their management of patients with progressive glaucoma. It would be helpful if future perimeters could be designed to facilitate the performance of both integrated bilateral visual field analysis

and simultaneous binocular testing. This would help better define each patient's actual functional visual disability and more accurately reflect the functional efficacy of current ocular and future CNS-oriented therapeutic approaches.

Acknowledgments

Presented in part at the annual meetings of the American Glaucoma Society in San Francisco March 1, 2013, the Association for Research in Vision and Ophthalmology in Seattle May 8, 2013, and the American Academy of Ophthalmology in New Orleans November 18, 2013.

All authors contributed significantly to the preparation of this manuscript. WES devised the concept for the paper. The theory was discussed with Stuart J. McKinnon of the Duke University Department of Ophthalmology, MAR, TM, and SLG to assist in elucidating the details of the theory. NS gathered the visual fields, and NS, WES, and SLG all input the data. MAR ran the statistical analysis of the field data. MAR created the graphs and figures. The draft manuscript was written by WES and SLG, with subsequent additions, revisions, and editing by all the

coauthors. TM, SLG, and WES performed literature searches.

Disclosure: **W.E. Sponsel**, None; **S.L. Groth**, None; **Nancy Satsangi**, None; **T. Maddess**, None; **M.A. Reilly**, None

References

1. Crish SD, Sappington RM, Inman DM, Horner PJ, Calkins DJ. Distal axonopathy with structural persistence in glaucomatous neurodegeneration. *Proc Natl Acad Sci U S A*. 2010;107:5196–5201.
2. Schlamp CL, Li Y, Dietz JA, Janssen KT, Nickells RW. Progressive ganglion cell loss and optic nerve degeneration in DBA/2J mice is variable and asymmetric. *BMC Neurosci*. 2006;7:66.
3. Crish SD, Dapper JD, MacNamee SE, et al. Failure of axonal transport induces a spatially coincident increase in astrocyte BDNF prior to synapse loss in a central target. *Neuroscience*. 2013;229:55–70.
4. Zhang S, Wang H, Lu Q, et al. Detection of early neuron degeneration and accompanying glial responses in the visual pathway in a rat model of acute intraocular hypertension. *Brain Res*. 2009;1303:131–143.
5. Weber AJ, Chen H, Hubbard WC, Kaufman PL. Experimental glaucoma and cell size, density, and number in the primate lateral geniculate nucleus. *Invest Ophthalmol Vis Sci*. 2000;41:1370–1379.
6. Yucel YH, Zhang Q, Gupta N, Kaufman PL, Weinreb RN. Loss of neurons in magnocellular and parvocellular layers of the lateral geniculate nucleus in glaucoma. *Arch Ophthalmol*. 2000;118:378–384.
7. Yucel YH, Zhang Q, Weinreb RN, Kaufman PL, Gupta N. Atrophy of relay neurons in magnocellular and parvocellular layers in the lateral geniculate nucleus in experimental glaucoma. *Invest Ophthalmol Vis Sci*. 2001;42:3216–3222.
8. Imamura K, Onoe H, Shimazawa M, et al. Molecular imaging reveals unique degenerative changes in experimental glaucoma. *Neuroreport*. 2009;20:139–144.
9. Sasaoka M, Nakamura K, Shimazawa M, Ito Y, Araie M, Hara H. Changes in visual fields and lateral geniculate nucleus in monkey laser-induced high intraocular pressure model. *Exp Eye Res*. 2008;86:770–782.
10. Gupta N, Ang LC, Noel de Tilly L, Bidaisee L, Yucel YH. Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex. *Br J Ophthalmol*. 2006;90:674–678.
11. Calkins DJ. Critical pathogenic events underlying progression of neurodegeneration in glaucoma. *Prog Retin Eye Res*. 2012;31:702–719.
12. Calkins DJ. Age-related changes in the visual pathways: blame it on the axon. *Invest Ophthalmol Vis Sci*. 2013;54:ORSF37–ORSF41.
13. Bengtsson B, Olsson J, Heijl A, Rootsen H. A new generation of algorithms for computerized threshold perimetry, SITA. *Acta Ophthalmol Scand*. 1997;75:368–375.
14. Sponsel WE, Ritch R, Stamper R, et al. Prevent Blindness America visual field screening study. The Prevent Blindness America Advisory Committee. *Am J Ophthalmol*. 1995;120:699–708.
15. Sponsel WE, Arango S, Trigo Y, Mensah J. Clinical classification of glaucomatous visual field loss by frequency doubling perimetry. *Am J Ophthalmol*. 1998;125:830–836.
16. Budenz DL, Rhee P, Feuer WJ, McSoley J, Johnson CA, Anderson DR. Comparison of glaucomatous visual field defects using standard full threshold and Swedish interactive threshold algorithms. *Arch Ophthalmol*. 2002;120:1136–1141.
17. Crabb DP, Viswanathan AC, McNaught A, Poinoosawmy D, Fitzke FW, Hitchings RA. Simulating binocular visual field status in glaucoma. *Br J Ophthalmol*. 1998;82:1236–1241.
18. Sponsel WE, Groth SL. Mitomycin-augmented non-penetrating deep sclerectomy: preoperative gonioscopy and postoperative perimetric, tonometric and medication trends. *Br J Ophthalmol*. 2013;97:357–361.
19. Sponsel WE, Harrison J, Elliott WR, Trigo Y, Kavanagh J, Harris A. Dorzolamide hydrochloride and visual function in normal eyes. *Am J Ophthalmol*. 1997;123:759–766.
20. Cynader M, Berman N. Receptive-field organization of monkey superior colliculus. *J Neurophysiol*. 1972;35:187–201.
21. Lane RH, Allman JM, Kaas JH, Miezin FM. The visuotopic organization of the superior colliculus of the owl monkey (*Aotus trivirgatus*) and the bush baby (*Galago senegalensis*). *Brain Res*. 1973;60:335–349.
22. DuBois RM, Cohen MS. Spatiotopic organization in human superior colliculus observed with fMRI. *NeuroImage*. 2000;12:63–70.
23. Limbrick-Oldfield EH, Brooks JC, Wise RJ, et al. Identification and characterisation of midbrain

- nuclei using optimised functional magnetic resonance imaging. *NeuroImage*. 2012;59:1230–1238.
24. Tardif E, Clarke S. Commissural connections of human superior colliculus. *Neuroscience*. 2002; 111:363–372.
 25. Knudsen EI. Control from below: the role of a midbrain network in spatial attention. *Eur J Neurosci*. 2011;33:1961–1972.
 26. Luthra A, Gupta N, Kaufman PL, Weinreb RN, Yucel YH. Oxidative injury by peroxynitrite in neural and vascular tissue of the lateral geniculate nucleus in experimental glaucoma. *Exp Eye Res*. 2005;80:43–49.
 27. Yucel Y, Gupta N. Review: glaucoma of the brain: a disease model for the study of transsynaptic neural degeneration. *Prog Brain Res*. 2008; 173:465–478.
 28. Bodeutsch N, Siebert H, Dermon C, Thanos S. Unilateral injury to the adult rat optic nerve causes multiple cellular responses in the contralateral site. *J Neurobiol*. 1999;30:116–128.
 29. Penagis L, Thanos S, Fischer D, Dermon CR. Unilateral optic nerve crush induces bilateral retinal glial cell proliferation. *Eur J Neurosci*. 2005;21:2305–2309.
 30. Dai Y, Sun X, Chen Q. Differential induction of c-Fos and c-Jun in the lateral geniculate nucleus of rats following unilateral optic nerve injury with contralateral retinal blockade. *Exp Brain Res*. 2009;193:9–18.
 31. Macharadze T, Goldschmidt J, Marunde M, et al. Interretinal transduction of injury signals after unilateral optic nerve crush. *Neuroreport*. 2009; 20:301–305.
 32. Weber AJ, Kaufman PL, Hubbard WC. Morphology of single ganglion cells in the glaucomatous primate retina. *Invest Ophthalmol Vis Sci*. 1998;39:2304–2320.
 33. Morgan JE, Uchida H, Caprioli J. Retinal ganglion cell death in experimental glaucoma. *Br J Ophthalmol*. 2000;84:303–310.
 34. Matthews MR. Further observations on trans-neuronal degeneration in the lateral geniculate nucleus of the macaque monkey. *J Anat*. 1964;98: 255–263.
 35. Yucel YH, Kalichman MW, Mizisin AP, Powell HC, Weinreb RN. Histomorphometric analysis of optic nerve changes in experimental glaucoma. *J Glaucoma*. 1999;8:38–45.
 36. Martin KR, Quigley HA, Zack DJ, et al. Gene therapy with brain-derived neurotrophic factor as a protection: retinal ganglion cells in a rat glaucoma model. *Invest Ophthalmol Vis Sci*. 2003;44:4357–4365.
 37. Caleo M, Menna E, Chierzi S, Cenni MC, Maffai L. Brain-derived neurotrophic factor is an anterograde survival factor in the rat visual system. *Curr Biol*. 2000;10:1155–1161.
 38. Riddle DR, Lo DC, Katz LC. NT-4-mediated rescue of lateral geniculate neurons from effects of monocular deprivation. *Nature*. 1995;378:189–191.
 39. Mungas D, Harvey D, Reed BR, et al. Longitudinal volumetric MRI change and rate of cognitive decline. *Neurology*. 2005;65:565–571.
 40. McKinnon SJ. Glaucoma: ocular Alzheimer's disease? *Front Biosci*. 2003;8:1140–1156.
 41. Patton N, Aslam T, MacGillivray T, Pattle A, Deary IJ, Dhillon B. Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures. *J Anat*. 2005;206:319–348.
 42. Frost S, Kanagasingam Y, Sohrabi H, et al. Retinal vascular biomarkers for early detection and monitoring of Alzheimer's disease. *Transl Psychiatry*. 2013;3:e233;doi:10.1038/tp.2012.150.
 43. Sponsel WE, McKinnon SJ. Preface: Special Edition; Neuroprotection and the Eye. *Brain Res Bull*. 2004;62:435–437.