Peripheral Resolution for Achromatic and SWS Gratings in Early to Moderate Glaucoma and the Implications for Selective Ganglion Cell Density Loss

Raymond O. Beirne, Joanne F. J. Logan, Margarita B. Zlatkova, Simon J. A. Rankin, Shaban Demirel, and Roger S. Anderson

PURPOSE. To investigate whether there is significant selective reduction in short-wavelength-sensitive (SWS) ganglion cell density in early to moderate glaucoma.

METHODS. Peripheral achromatic resolution acuity (an indirect measure of the underlying midget ganglion cell density) and peripheral chromatic resolution acuity under conditions of blue cone isolation (an indirect measure of the underlying small bistratified ganglion cell density) were measured at 13º eccentricity in four oblique meridians in 15 eyes (mean age, 64.6 ± 9.6 years) with early to moderate glaucoma. The results from the subjects with glaucoma were compared with those in a group of 17 age-matched normal eyes (mean age, 62.5 ± 6.6 years).

RESULTS. Mean achromatic resolution acuity across the four locations was significantly lower in the subjects with glaucoma than in the normal subjects (2.92 vs. 4.01 cyc/deg). Mean chromatic resolution acuity across the four locations was also significantly lower in the subjects with glaucoma than the normal subjects (0.78 vs. 0.99 cyc/deg). There was no selective loss of mean SWS acuity in the subjects with glaucoma. Individual location analysis revealed that the chromatic–achromatic resolution ratio was not significantly different in the subjects with glaucoma who had early glaucomatous damage when compared with the normal subjects. The chromatic–achromatic resolution ratio was lower than normal at certain locations in certain individuals with early glaucoma.

CONCLUSIONS. The results indicate that there is no evidence of significant selective reduction in global SWS ganglion cell density in early to moderate glaucoma. However, there may be selective loss of SWS ganglion cell density at individual locations in individual eyes. (Invest Ophthalmol Vis Sci. 2003;44: 4780–4786) DOI:10.1167/iovs.02-1072

The ability to isolate and measure psychophysically the functional responses from specific subsets of retinal ganglion cells has led to widespread investigations of this kind, in the hope of finding improved detection methods for open-angle glaucoma. Of particular interest in this large body of research is the selective light sensitivity loss of the short-wavelength system in the early stages of the disease, which has resulted in the development and implementation of clinical tests such as short-wavelength automated perimetry (SWAP; for a review, see Sample), which measures the light increment sensitivity of the blue pathway that carries the response from the short-wavelength-sensitive (SWS) cones. This pathway is mediated by the small group of “blue-on” ganglion cells (comprising only 5% to 10% of the total ganglion cell population) which are commonly referred to by their morphologic appearance as the small-field, bistratified ganglion cell. This selective chromatic light sensitivity loss can be supported by two main theories of ganglion cell loss in early glaucoma. First, the notion of selective death of certain ganglion cell subtypes, whereby ganglion cells with specific physical and functional properties, such as those that carry responses from the short-wavelength system, may preferentially die early in the disease process, would provide one explanation. Histologic evidence of selective damage to ganglion cells with larger cell bodies and axon diameters (which would include small bistratified cells) early in the disease process, would lend weight to this argument, but is disputed by other recent reports. However, this apparent selective loss of SWS ganglion cells may merely be the result of reduced redundancy. Within this scenario, deficits in a subpopulation such as the SWS-driven pathway (or any other sparse population), which under white-on-white stimulation could be compensated for by cells from another population, remain exposed under SWS-isolating conditions. Evidence has been presented that several visual functions are affected in early glaucoma and that damage does not appear to be exclusively selective for the SWS ganglion cell subpopulation early in the disease. In view of these alternative theories, further psychophysical evidence for the existence or nonexistence of a selective reduction in the number of small bistratified ganglion cells in early to moderate glaucoma would be useful in understanding the disease and the development of methods for early diagnosis.

To demonstrate a selective loss psychophysically, it is necessary to have test procedures that not only isolate and stimulate the desired ganglion cell subsets separately to compare differences in their performance, but also yield results which are dependent on the density of the corresponding ganglion cell subpopulations. To this end, we decided to use the well-researched technique of peripheral grating resolution acuity. Whereas resolution of achromatic gratings in central vision is limited by the optics of the eye, whereby spatial frequencies higher than the sampling density of the retina do not pass through, grating resolution in peripheral vision is limited by the density of the retinal neurons that sample the optical image and not by the quality of the optics. It is therefore often referred to as sampling limited. The hallmark of a sampling-limited task in peripheral vision is the observation of aliasing, where a grating stimulus with a mean luminance

From the 1Vision Science Research Group, School of Biomedical Sciences, University of Ulster at Coleraine, Northern Ireland, United Kingdom; the 2Department of Ophthalmology, Queens University and The Royal Group of Hospitals, Belfast, Northern Ireland, United Kingdom; and 3Discoveries in Sight, Devers Eye Institute, Portland, Oregon. Supported by Project Grant 056655 from the Wellcome Trust. Submitted for publication October 21, 2002; revised March 4 and July 1, 2003; accepted July 17, 2003.

Disclosure: R.O. Beirne, None; J.F.J. Logan, None; M.B. Zlatkova, None; A.J. Jackson, None; S.J.A. Rankin, None; S. Demirel, None; R.S. Anderson, None.

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Corresponding author: Raymond O. Beirne, Vision Science Research Group, School of Biomedical Sciences, University of Ulster, Cromore Road, Coleraine, Northern Ireland BT52 1SA, UK, r.beirne@ulster.ac.uk.
equivalent to the surround can be detected but not resolved, often masquerading as a grating of lower spatial frequency and frequently with a different orientation. This results in two different measurable spatial thresholds: a detection threshold and a resolution threshold. Whereas peripheral grating detection is limited by the receptive field size of the retinal ganglion cells, peripheral resolution acuity is limited by the spacing of the individual ganglion cells. Thibos et al., presented convincing evidence that for high contrast, stationary achromatic gratings, it is the density of the retinal ganglion cells that project to the parvocellular layers of the lateral geniculate nucleus (referred to as “midget” ganglion cells) that is the limiting factor in resolution acuity. Using density estimates of these cells (which comprise ~80% of the total ganglion cell population), measurements of achromatic grating resolution closely match expected values. Therefore, measurements of achromatic grating resolution in peripheral vision can be used to give indirect estimates of the underlying retinal midget ganglion cell density. This provides an excellent method of estimating localized midget ganglion cell density in a disease such as glaucoma, and sampling-limited resolution acuity has been shown to be successful and reliable for assessing subjects with glaucoma. Because of the sampling-limited nature of the task, peripheral achromatic resolution acuity has the advantage of being relatively unaffected by large amounts of optical defocus. Which is a source of error in conventional white-on-white perimetry, adding further weight to its clinical utility.

A recent study investigating the factors that limit the resolution of short-wavelength gratings in peripheral vision found that under the correct conditions this task is also sampling limited. By using the conventional method of SWS cone isolation—adequate saturation of the long- and medium-wavelength receptors with a bright yellow adapting background—it was found that, beyond a certain retinal illuminance, resolution acuity reaches a plateau where it is mediated by the SWS system and the task is sampling limited. This was evidenced by a superiority of detection acuity over resolution acuity with an accompanying chromatic aliasing zone where, similar to achromatic acuity, chromatic gratings at their own resolution limit often appear as splotchy chromatic patches rather than as a veridical perception. Peripheral acuity measurements of SWS-isolating gratings closely match those predicted by using estimates of density of the aforementioned group of ganglion cells which receive their input from the SWS cones—the small bistratified ganglion cells. Hence, resolution measurements for SWS-isolating gratings in peripheral vision give indirect estimates of the density of the blue-yellow subset of ganglion cells. As with achromatic peripheral resolution acuity, SWS-isolating grating resolution is not adversely affected by moderate optical defocus (up to 3 D in the periphery) and, more important, is robust to the effects of moderate simulated and age-related lens yellowing, which has an adverse effect on short-wavelength light sensitivity both with age and with age-related cataract. Thus, as with achromatic resolution acuity measurements for midget ganglion cell density, short-wavelength resolution acuities should provide a very useful method of estimating localized small bistratified ganglion cell density in diseases such as glaucoma.

By measuring peripheral resolution for SWS-isolating gratings and achromatic gratings in patients with early to moderate glaucoma and comparing this to a group of age-matched normal subjects, we wanted to know whether there is a selective reduction in SWS-driven acuity in early-stage glaucoma. In that no evidence has been found of selective loss of small bistratified cells with age by using this method, any selective loss is likely to be pathologic rather than age related. This will provide us with further psychophysical evidence for the existence or nonexistence of a significant selective loss of small bistratified ganglion cells in early to moderate glaucoma.

**Methods**

**Subjects**

Subjects with glaucoma were recruited from a specialist ophthalmology outpatient clinic in a large regional teaching hospital. The patients had either primary open-angle glaucoma (POAG) or normal-tension glaucoma (NTG) and were all under the care of a specialist consultant ophthalmologist. None of the subjects had any other eye disease, with visual acuity better than 20/40 (Snellen). Refractive errors lay within ±6 D spherical equivalent and less than 2 D cylinder. There was no obvious central color vision defect on testing with Ishihara or City University color tests.

All subjects were deemed to be in the early to moderate stages of the disease, as defined by having characteristic glaucomatous field loss with mean defect (MD) of better than −7 dB (mean, −2.6 dB, range, −2.1 to −6.9 dB) on testing with the C24-2 program of the Humphrey Field Analyzer II (HFA II; Carl Zeiss Meditec, Dublin, CA) in combination with either baseline increased intraocular pressure (more than 21 mm Hg by Goldmann tonometry) and/or glaucomatous neuropathy of the optic nerve head. All were judged to have minimal lens opacity on examination by slit lamp biomicroscopy.

In all, 15 eyes (8 right eyes [RE], 7 left eyes [LE]) of 15 different subjects with glaucoma (mean age, 64.6 ± 9.6 years) who met the criteria of being in the early to moderate stages of the disease underwent achromatic and chromatic resolution acuity testing. In those subjects who had bilateral disease, the eye with the least MD loss was chosen as the study eye. Of these 15 eyes, 10 had POAG (mean age, 63.9 ± 10.7 years) and 5 NTG (mean age, 66.0 ± 5.5 years). The results from the subjects with glaucoma were compared with those in an age-matched group (t = 0.74, P = 0.47) of 17 normal eyes (17 RE; mean age, 62.5 ± 6.6 years) of 17 subjects. Normal subjects were recruited from the staff and patients of an optometry clinic. All were deemed to have normal vision (20/20+ Snellen or better), normal central color vision (Ishihara and City University color tests), and no history of eye disease or ocular surgery. As in the subjects with glaucoma, all normal subjects had refractive errors within ±6 D spherical equivalent and less than 2 D cylinder.

The study adhered to the tenets of the Declaration of Helsinki with full ethical approval for the study being obtained from the relevant review bodies. Informed written consent was obtained from all subjects before participation.

**Apparatus and Stimuli**

We designed a resolution perimeter capable of measuring achromatic and chromatic peripheral grating resolution acuity at different locations in the visual field. The resolution perimeter, based on a previous experimental design for studies that required SWS system isolation, is a self-contained device that can measure both achromatic and chromatic resolution acuity easily and interchangeably as follows (see Fig. 1).

**Chromatic and Achromatic Acuity**

All the stimuli were generated by a visual stimulus generator (VSG2/3; Cambridge Research Systems, Rochester, UK) and were displayed on a gamma-corrected high-resolution monitor (500PS; Sony, Tokyo, Japan). The monitor had a frame rate of 100 Hz, a pixel resolution of 1024 × 768 and a screen size of 30 × 40 cm².

Isolation of the SWS system was achieved by selective chromatic adaptation using a broadband yellow adapting background above 530 nm (Commission Internationale de l’Eclairage [CIE] x = 0.51, y = 0.48; luminance 600 cd/m² at the eye) designed to render medium- and long-wavelength-sensitive cones insensitive to the short-wave-
length stimuli. This provided adequate retinal illuminance to ensure that resolution of the short-wavelength stimulus would involve a sampling-limited task mediated by the SWS-cone pathway, as confirmed in a previous study. All luminance and spectral measurements were made with a colorimeter (PR650 Spectrascan; PhotoResearch, Inc., Chatsworth, CA). The bright yellow background was produced by placing a long-wavelength pass yellow filter (Schott OG530; Edmund Optics Ltd., York, UK) in front of the lens of a halogen globe. The yellow light was then projected, from a position perpendicular to the monitor, through a white diffusing screen toward a beam splitter angled at 45°. The halogen globe and yellow filter were contained in a light-tight box in the white diffusing screen, insuring minimal stray light. The observer viewed the monitor straight ahead through the beam splitter, allowing the adapting background to cover a greater area than the monitor at all times. The beam splitter and monitor were contained in a light-tight box, except for an aperture for the subject to view the screen (Fig. 1).

The circular patches of short-wavelength sinusoidal grating stimuli (5° diameter, 90% contrast) were generated on the color monitor placed 0.74 m from the subject. This patch size ensured that at least two full cycles would be displayed, even at very low acuities. The SWS gratings, which were generated using only the blue gun of the monitor (CIE x = 0.147, y = 0.07), had the same mean luminance as the blue surround of the screen (0.9 cd/m² mean luminance). Gratings were presented within a sharp-edged disc, as this presentation form does not affect SWS resolution acuity over the range of spatial frequencies measured. The gratings were presented with their center at 13° eccentricity from a central fixation target in one of four oblique meridians (35°, 145°, 215°, and 325°).

For achromatic resolution acuity measurements the subject maintained the same viewing position as before with the halogen globe turned off. Patches of green-on-green sinusoidal grating stimuli that were contained in a 2D Gaussian window to avoid any edge effect (spread parameter f = 2°, 90% contrast), were generated in the same manner as before using only the green gun of the monitor (CIE x = 0.294, y = 0.616) and had the same mean luminance (40 cd/m²) as the green surround. At least six grating cycles were displayed within 2 σ of spatial spread, and therefore the effect of stimulus size on acuity was negligible. These achromatic gratings were presented at the same four locations used for the chromatic gratings.

Psychophysical Procedure

Subjects’ pupils were dilated with 1% tropicamide (Chauvin Pharmaceuticals, Romford, UK) to achieve sufficiently high retinal illumination to ensure complete isolation of the SWS-driven system for measuring chromatic peripheral grating resolution acuity. Pupil dilation also attempted to reduce any confound owing to different pupil sizes in older subjects, with dilated pupil size measuring between 5 and 8 mm.

After an initial 5-minute practice period, peripheral achromatic resolution acuity was measured, followed by a short rest period before peripheral chromatic resolution was measured. Each subject was given 2 minutes to adapt to the background and another practice period to become familiar with the task. Subjects sat with the chin on a chin rest and viewed the gap between two vertically aligned squares (0.4° size, 0.6° offset, 0° meridian) to maintain central fixation. For each task the subjects were optically corrected for the distance of the screen, including compensation for defocus due to chromatic aberration and the cycloplegic effects of the mydriatic. The nontested eye was patched.

Stimuli were presented randomly in each of the four oblique locations. The procedure involved a two-alternative, forced-choice (2AFC) orientation identification task in which the grating was oriented obliquely at 135° (to the left) or at 45° (to the right). This removed any cue to orientation, which may have biased the results if horizontal and vertical gratings were used. The subject had to press one of two buttons to register a response. There was an audible tone between each presentation and the subject was encouraged to respond to each stimulus even if it involved guessing. Target presentation time was 1 second (0.3 rise time, 0.3 decay), and resolution threshold was estimated with a three-up/one-down staircase procedure in which three correct responses resulted in a 10% increase in stimulus spatial frequency, and one incorrect response resulted in a 10% decrease in stimulus spatial frequency. Gratings were initially presented supra-threshold to the expected resolution acuity, as determined within the practice period. Thirty presentations were made for each location, and this resulted in an average of three to four reversals for each location. Resolution threshold for each location was calculated as the mean of the reversal values. The testing time was approximately 7 minutes per eye, with testing for chromatic gratings taking slightly longer than for achromatic gratings.
RESULTS

Achromatic and chromatic resolution acuities were included for all locations tested, apart from those with absolute scotomas (total deviation [TD] more than −25 dB HFA II C24-2 in the location being tested) or where a true acuity threshold could not be established because performance fell below the operating range of the instrument. This resulted in 57 values for achromatic and chromatic resolution acuity from the subjects with glaucoma and 66 values from the normal subjects.

For the normal subjects, two-way ANOVA on log-transformed data, with location and test type (achromatic or chromatic) as factors, showed no significant effect of location on acuity measurements \(F(3,124) = 0.96, P = 0.413\), and no significant interaction was found between location and test type \(F(3,124) = 0.73, P = 0.533\). This was in agreement with a previous study showing that location did not have a statistically significant effect on achromatic or chromatic acuity at any age.43 This previous study had a power of 80% to detect an effect size of 0.2 standard deviations, which would be considered a small effect size by convention.41 This allowed us to average the resolution acuities across the four different locations for each subject.

Two-way ANOVA on log-transformed data, with subject type (glaucoma or normal) and test type (achromatic or chromatic) as factors showed that the subject type had a significant effect on resolution acuity \(F(1,60) = 12.1, P = 0.001\) as did the test type \(F(1,60) = 225.8, P < 0.001\). No significant interaction was found between these factors \(F(1,60) = 0.004, P = 0.95\). Therefore, both the mean achromatic and chromatic acuities in the subjects with glaucoma (2.92 and 0.78 cyc/deg, respectively) were significantly lower than in the normal subjects (4.01 and 0.99 cyc/deg, respectively) showing the 95% confidence limits (±1.96 SEM).

The relationship between the mean TD for a particular location and the corresponding achromatic acuity at that location was a weak one (Fig. 4). For locations that would be classified as having early to moderate HFA field loss (up to 7 dB mean TD), there was a wide range in achromatic acuity, from close to that of the mean normal value to very low values. In those subjects with significant mean TD (greater than 7 dB) for a particular location, achromatic acuities were lower than mean normal acuities. There were no locations with a significantly lower mean TD value (greater than 7 dB) that also had an acuity the same as the mean normal acuity.

The relationship between the mean TD for a particular location and the corresponding chromatic acuity at that location was similar to the achromatic case (Fig. 5). At locations in the early to moderate stages of the disease (up to 7 dB mean TD), there was a wide range in chromatic acuities, some close to the mean chromatic normal acuity and others very low. In those locations where the mean TD became significant (greater than 7 dB), the chromatic acuity was lower than the mean normal acuity. There was only one location that had a significant mean TD and still had a chromatic acuity above mean normal. It can be seen that the spread of acuities was larger for locations and possibly selective sparing at others.

Figure 2. Mean achromatic (●) and mean chromatic (○) acuity across the four locations for both the normal subjects (4.01 and 0.99 cyc/deg, respectively) and the subjects with glaucoma (2.92 and 0.78 cyc/deg, respectively) showing the 95% confidence limits (±1.96 SEM).

Figure 3. Typical TD plot of a subject with glaucoma, obtained in an HFA C24-2 test (Carl Zeiss Meditec, Dublin, CA), showing how mean TD values were calculated for the locations where resolution acuity was measured. A mean TD was calculated using the values recorded from the points on the HFA II plot that would correspond to, or close to, where the grating would fall. The TD values were determined by using the manufacturer’s internal normative database for the HFA II. The mean TD represented nine values from the TD plot for each location, or eight if the location was on the same side as the blind spot (see Fig. 3 for an example).
the chromatic test than for the achromatic test, with acuities ranging from above mean normal right down to values approaching zero. This greater variation in chromatic acuity compared with achromatic acuity in the subjects with glaucoma (which is also evident in the 95% confidence limits in Fig. 2) is an important observation in terms of selective loss of SWS acuity (see the Discussion section).

The individual locations in the subjects with glaucoma with less than a 6-dB loss in mean TD would be the glaucomatous locations where we might most expect to find a selective loss of SWS acuity. One-way ANOVA on log-transformed data, with subject type (glaucoma or normal) as the factor showed that there was no significant difference between the individual chromatic-achromatic resolution ratios in these locations (up to 6 dB mean TD) and the individual chromatic-achromatic resolution ratios of the normal subjects ($F_{(1,115)} = 1.49, P = 0.22$). Although acuity for both tests was reduced for the subjects with glaucoma compared with the normal subjects, the ratio of acuity was similar in both, with the mean resolution ratio being 0.27 for each subject type (i.e., those subjects with glaucoma with reduced chromatic acuity generally had similarly reduced achromatic acuity). Using this number of subjects we had a power of 80% to detect an effect size of 0.5 SD, which would be considered a "moderate" effect size by convention. More subjects may have increased the power to detect a smaller effect size, but we believe such a small effect size would then enter the realms of clinical irrelevance. For these ratios the correlation coefficient was not significantly different from zero ($r = -0.04, P = 0.78$) showing that, in general, achromatic, and chromatic acuity decline at the same rate in these early stages of the disease (Fig. 6).

**DISCUSSION**

Evidence that there is no exclusive significant selective loss of 5-cone pathway function in early glaucoma has been presented before. This study provides further evidence to support this theory by comparing the change in small bistratified ganglion cell density (by measuring chromatic grating resolution acuity under conditions of blue cone isolation) to midget ganglion cell density (by measuring achromatic grating resolution acuity) in early to moderate subjects with glaucoma. This study confirms previous findings that peripheral resolution acuity for achromatic gratings is significantly reduced in early glaucoma, implying that the corresponding underlying localized midget ganglion cell density is significantly reduced. The spread of resolution values in the normal group (coefficient of variation [CV] = 27%) reflects the large normal variation in midget ganglion cell density between individuals and also the differences with age that exist within this group. The larger spread within the subjects with glaucoma (CV = 35%) is a combination of the aforementioned intrindividual variations in localized midget ganglion cell density and the differing stages of the disease process displayed by the subjects, ranging from those with a "normal" visual field (MD +2.1 dB, HFA II C24-2) to a "moderate" stage of visual field loss (MD −6.9 dB, HFA II C24-2). The large interindividual variability in normal ganglion cell numbers means that it is entirely possible for a patient with early glaucoma to possess more ganglion cells than a normal subject and consequently to perform better on an acuity task. This can be seen in the bottom left corner of Figure 4 in which there are a number of locations that have achromatic acuities above the normal mean. However, although no location with greater than 7 dB mean TD loss displayed resolution close to the mean in normal subjects, there are numerous locations that had significantly reduced achromatic resolution acuity but normal HFA II C24-2 thresholds. Having stated that our acuity measurements indirectly estimate the underlying ganglion cell density, these findings would be in agreement with a study by Harwerth et al. showing that traditional perimetry does not provide a reliable...
estimate of ganglion cell density loss until a substantial percentage of cells have died.

As expected, this study tells us that peripheral resolution acuity for chromatic gratings is also significantly reduced in early glaucoma, implying that the underlying localized small bistratified ganglion cell population is significantly reduced at this early stage in the disease process. The spread of the resolution values in the normal subjects (CV = 24%) can again be accounted for by the previously stated reasons for differences in achromatic acuity applied to small bistratified cells. However, these intraindividual variations would not fully account for the larger spread of chromatic resolution values in the subjects with glaucoma (CV = 49%). From the bottom left corner of Figure 5 it can be seen that there were several locations that had chromatic acuities above mean normal. As for the achromatic test, there were also numerous locations that had significantly reduced chromatic resolution acuity but normal HFA II C24-2 thresholds.

Although the mean achromatic and mean chromatic acuities were lower in the subjects with glaucoma, there was no significant selective loss of mean SWS acuity. Those subjects with low chromatic acuity generally had low achromatic acuity as well. Therefore, when analyzed globally, the different underlying ganglion cell subpopulations appear to cease functioning with a similar time course at this stage of the disease.

When we looked at the ratio of acuity (chromatic to achromatic) at the individual locations with early glaucomatous damage (up to 6 dB mean TD) we found that it was not significantly different from that in the normal subjects. There was no significant change in the resolution ratio in the subjects with glaucoma from those with no HFA II defect through to those with moderate defect (6 dB mean TD). Therefore at individual locations, even though both chromatic and achromatic acuity was reduced in the subjects with glaucoma, there was no significant selective loss of SWS acuity. This is psychophysical evidence that there is no statistically significant selective loss of small bistratified ganglion cell numbers early in the disease process at the locations tested. However, it is also evident that the chromatic acuities in the subjects with glaucoma were more varied than the achromatic acuities when compared with those in the normal subjects. It can be seen that at certain locations chromatic acuity was very low in comparison with achromatic acuity (the resolution ratio was very low; Fig. 6), and these locations may indeed represent areas with selective loss of SWS acuity. It is also evident that chromatic acuity loss in comparison with achromatic acuity at other locations (the resolution ratio was high), indicating a selective sparing of SWS acuity. This suggests that not all eyes and locations (within the same eye) are affected in the same way in the early stages of the disease. Therefore, we cannot rule out selective loss of SWS (and hence small bistratified ganglion cell density) at certain locations in certain individuals in the subjects that we have used.

Even though our results give a good idea of the number of live functioning cells, we have no way of assessing how “sick” the cells may be. When grating resolution acuity is measured using contrast as high as in the present study, cells that are barely alive may still contribute to resolving the grating. It could well be that the small bistratified ganglion cells become selectively sicker sooner than other cells, and this may contribute to their having altered function. This may be what we detect in a clinical test such as SWAP, with that functional alteration being manifest as a selective chromatic increment sensitivity loss. Therefore, it would be interesting to measure achromatic and chromatic resolution acuities at locations from subjects with SWAP defects that are greater than (or not present) on standard automated perimetry. Do these locations with apparent selectively reduced SWS light sensitivity also have a low chromatic-to-achromatic resolution ratio, indicating a selective loss of small bistratified cells, or do they have resolution ratios near the mean (SWS acuity is not selectively reduced) indicating some other mechanism for this reduction in chromatic light sensitivity other than selective cell loss?

The selective ganglion cell loss theory has predominantly relied on anatomic evidence. It must be recognized that the evidence for selective cell death is presented mostly in relation to those ganglion cells that have the largest cell bodies and diameter axons in comparison with the mean. These cells, most often referred to as parasol cells or M cells, generally have larger cell bodies than the small bistratified cells. M cells may indeed be selectively lost in the early stages of the disease, and psychophysical evidence for 42 and against 17,18 this idea has been presented in the past, but they remain notoriously difficult to completely isolate psychophysically. 46,47 The histologic findings of selective damage to these cells in early glaucoma 10,11 have been the subject of much debate, especially in relation to the difficulties and limitations of the original methods used to count such cells. 12-14 Cell shrinkage is cited as the main drawback to these original conclusions, producing an artifact that makes it appear as if the larger diameter cells have been selectively affected, but this has been strongly refuted by the original investigators. 48 It has also been argued that the conclusions of psychophysical studies finding no selective loss of function for a particular ganglion cell subtype are not a valid reason in themselves to refute completely the anatomic findings of selective loss of ganglion cell subtypes by different laboratories. 49

The evidence presented herein and in other studies suggests that the ability to detect early visual field damage in glaucoma by isolation of the SWS mechanisms emanates from something other than the significant preferential cell death in this group of cells. New, alternative theories to the ones presented in this article may account for the apparent greater sensitivity loss of the chromatic system than that of the achromatic system and may help to resolve the discrepancy between the anatomic and psychophysical findings. 50

In any case, our conclusions against significant selective loss of SWS ganglion cells in early to moderate glaucoma, does not negate the validity of selective psychophysical testing targeted at this functional subgrouping, both in the clinic and as a research tool.

Acknowledgments

The authors thank the reviewers for many useful comments.

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