Spatial Summation Properties for Magnocellular and Parvocellular Pathways in Glaucoma

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PURPOSE. To examine the spatial summation properties for the magnocellular (M) and parvocellular (P) visual pathways in participants with glaucoma and approximately age-matched controls in central and midperipheral retinal eccentricities.

METHODS. Contrast discrimination thresholds were measured for six different stimulus array sizes, using steady- and pulsed-pedestal paradigms designed to measure function of the M and P pathways, respectively. This study involved 15 participants with glaucoma and 17 approximately age-matched controls. All participants completed trials foveally and at 12.5° eccentricity. The peripheral stimulus location for each glaucoma participant was within a quadrant of early visual field loss, and locations were matched for the control group.

RESULTS. The glaucoma group demonstrated significantly elevated thresholds compared with the control group ($F_{(1,30)} = 16.29; P < 0.001$). Thresholds were also significantly dependent on the stimulus sizes, testing location, and pedestal condition. Data obtained for the steady-pedestal paradigm were fit with an exponential decay function, whereas the pulsed-pedestal data were fit with a linear function, demonstrating different spatial summation properties for the M and P pathways, consistent with previous studies using this methodology. Analyses of the curve parameters obtained from the curve fits indicated no significant difference in the shape of the curves between glaucoma and control participants.

CONCLUSIONS. Although spatial summation properties are different for presumed M- and P-mediated pathways, the underlying spatial summation properties associated with these pathways are similar in the control and glaucoma participants in this study, centrally and midperipherally. (Invest Ophthalmol Vis Sci. 2009;50:1221–1226) DOI:10.1167/iovs.08-2517

Glaucoma is an insidious disease, characterized functionally by a progressive loss of visual field due to neural damage, and is one of the leading causes of blindness in the developed world. Consequently, substantial research effort has been directed toward determining the earliest changes that result from this disease with the aim of identifying affected persons as early as possible in the disease process. Recent evidence from pri-

mate experimentally induced glaucoma shows that some of the earliest structural changes in glaucoma are likely to be to the dendritic trees of retinal ganglion cells. Parasol and midget retinal ganglion cells show a simplification of dendritic architecture before cell death in response to elevated intraocular pressure. Reduced dendrite length and surface area will presumably decrease the level of innervation by more distal retinal neurons. Associated neurophysiology demonstrates alterations of spatial and temporal processing in such neurons compared with those in normal eyes.

If similar changes occur in human glaucoma, alterations of functional aspects of spatial and temporal processing may arise early in the disease process. Changes in contrast processing early in glaucoma are present in magnocellular (M) and parvo-
cellular (P) systems (incorporating responses from the parasol and midget retinal ganglion cell systems, respectively). Original interest in the study of M and P systems derived from the suggestion that the M system might be preferentially susceptible to glaucoma, however, more recent convergent evidence from histology and psychophysics demonstrates damage to both systems.

One possible functional consequence of changes to the dendritic architecture of parasol and midget retinal ganglion cells in early glaucoma is an alteration of spatial summation properties. Spatial summation is classically studied by observing the rate of improvement in sensitivity that results as stimulus area is increased. Classically, this improvement is described in terms of Ricco’s law, Piper’s law, and Pieron’s law. Ricco’s law refers to full summation—results when tiny stimulus areas are used—and can be largely accounted for by the optical point-spread function of the eye. Piper’s law refers to square root summation, and Pieron’s law refers to cube root summation. Such summation is presumed to reflect averaging at a cortical level. Eventually, for large enough stimulus areas, threshold is independent of test area. If the receptive field coverage of the ganglion cell network changes in early glaucoma, it is possible that alterations in spatial summation characteristics for small stimuli may result. It is also possible that reorganization of spatial properties beyond the retina might arise as ganglionic damage can extend beyond retinal ganglion cells into the lateral geniculate nucleus and the primary visual cortex.

In this study, we used the steady- and pulsed-pedestal contrast-discrimination methods of Smith et al. to explore the effect of increasing stimulus area on contrast discrimination thresholds within the presumed M and P pathways in glaucoma. These tasks briefly present luminance increments on luminance pedestals. In the steady-pedestal paradigm, a contrast-discrimination judgment is made after adapting to the pedestal luminance. However, in the pulsed-pedestal paradigm, adaptation is to the background. The adaptation-induced contrast gain and temporal summation properties of these paradigms are different and have been shown to be consistent with those of the M pathway for the steady-pedestal paradigm and the P pathway for the pulsed-pedestal paradigm. Smith et al. demonstrated different spatial summation properties for the steady- and pulsed-pedestal paradigms. These psychophysical functions do not relate to the spatial properties of single cells in the respective networks. Rather, the different functions arise from differences in the manner in which informa-

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tion is averaged spatially. An advantage of adopting this paradigm is that the test phase of the stimulus presentation is identical for the steady (presumed M) and pulsed (presumed P) tasks; the only difference was in the adaptation phase. Our laboratory has previously used these tasks to demonstrate that contrast discrimination was reduced in glaucoma in the M and P pathways. The purpose of the present study was to further explore the findings of Smith et al. and to examine spatial summation properties for steady- and pulsed-pedestal paradigms in midperipheral vision and in glaucoma.

**METHODS**

**Participants**

Fifteen participants with primary open-angle glaucoma (POAG) and 17 approximately age-matched controls participated. Participants with glaucoma were 51 to 87 years of age (mean, 71 ± 8 years), and controls were 56 to 75 years of age (mean, 67 ± 5 years). There was no significant difference in mean age between these groups (t = 1.84; P = 0.08); however, the range was slightly more restricted in the control group.

All participants were required to have best-corrected visual acuity of 6/7.5 or better and to have refractive errors less than ± 5.00 diopter (D) sphere and ± 2.00 D astigmatism. Participants were required to be free from systemic disease known to affect visual function. Those in the glaucoma group were required to have an ophthalmological diagnosis of POAG and to be free from other ocular disease. For the purposes of this study, the visual field loss of each glaucoma subject was documented on a perimeter (M700; Medmont, Camberwell, Australia). Visual fields were classified according to Mills et al. (modified for use with the Medmont perimeter) and all participants with glaucoma were classified as having early visual function loss. All control participants were required to have normal findings in a comprehensive eye examination, which included visual fields (Medmont perimeter), slit lamp biomicroscopy, ophthalmoscopy of the macula and optic nerve, and optic nerve head imaging (Heidelberg Retinal Tomograph, version 3.0; Heidelberg Engineering, Heidelberg, Germany). Intraocular pressure measured with applanation tonometry was less than 21 mm Hg for all controls. Each participant provided written informed consent before participation, in accordance with a protocol approved by our institutional human research ethics committee and in accordance with the tenets of the Declaration of Helsinki.

**Stimuli and Equipment**

Test stimuli were similar to those used by Smith et al. and are presented in Figure 1. Stimuli were generated (ViSaGe; Cambridge Research Systems Ltd., Kent, UK) with custom software (Matlab 7; Mathworks, Natick, MA) and presented on a γ-corrected, 21-inch monitor (resolution, 1264 × 947 pixels; frame rate, 75 Hz; G520 Trinitron; Sony, Tokyo, Japan). Participants viewed the monitor monocularly from a distance of 50 cm using a chin and forehead rest, with refractive correction for the viewing distance if required. Only one eye of each participant was tested. In the glaucoma cohort, if both eyes were potentially eligible to be included, one eye was chosen at random. For the controls, eyes were chosen to match the glaucoma group so that the overall number of left and right eyes tested was balanced between groups. Participants used a button box to indicate their responses (model CB6; Cambridge Research Systems).

The test array consisted of four squares separated by gaps of 10 minarc. The height and width of each square within the four-square array was varied between 0.125° and 4°. A central (10 minarc) black fixation dot was used for larger test arrays, whereas four diagonal lines that extended beyond the outer corners of the four-square array provided a fixation target for the two smallest test arrays. Contrast discrimination thresholds (the ability to discriminate an increment in luminance of one of the four squares) were measured for arrays with six square widths: 0.125°, 0.25°, 0.5°, 1°, 2°, and 4°.

The steady-pedestal stimulus consisted of a four-square pedestal, with a luminance of 19.02 cd/m² presented continuously throughout the experiment, within a background luminance of 12 cd/m². The luminance of one of the four squares was incremented for 26.7 ms during the test trial. For the pulsed-pedestal condition, a fixation marker alone was continuously presented against the screen background of 12 cd/m². In this condition, the four squares were simultaneously presented only during the 26.7-ms test presentation. Three of the squares had the pedestal luminance, and one square had the pedestal luminance plus a luminance increment.

Participants were tested foveally and at a peripheral location. The peripheral location was placed so that the center of the four-square array was located 12.5° on a 45° diagonal line from the fovea. The peripheral location for the glaucoma group was chosen such that it
was placed in a quadrant of reduced visual field sensitivity. The peripheral testing location for the control group was chosen to match that of the glaucoma group. As in the McKendrick and Badcock study, the size of the squares was increased to assess an approximately equal number of ganglion cells foveally and peripherally because of the reduced retinal ganglion cell density with eccentricity from the fovea. For peripheral testing, the height and width of each of the squares was scaled by 1.73°, and the gap between the squares could be incremented in luminance (those marked with an “x”), so that these could be presented at the same retinal eccentricity.

Procedure
The pulsed- and steady-pedestal paradigms were investigated in separate runs. All procedural details for each paradigm were identical except for the initial preadaptation. Participants were required to adapt for 1 minute to the background and the pedestal for the steady condition or to the background alone for the pulsed condition. Two temporal alternatives could be presented to the participant for each trial, and the observer was instructed that one square would appear brighter or darker than the other three on one of these intervals. The participant had to choose which interval contained the “odd square” (two-interval, forced-choice). A schematic representation of a trial is presented in Figure 1 (right). Each of the two intervals coincided with an auditory signal that indicated the intervals. The square of different luminance was presented randomly in either the first or the second interval. The second interval was presented 500 ms after the first. Incorrect response resulted in a 25% increase. Staircases commenced as required.

Thresholds were determined with a three-down, one-up staircase in which three successive correct responses led to a 25% decrease in the luminance increment of the test stimuli on the following trial; every incorrect response resulted in a 25% increase. Staircases commenced at a clearly visible luminance increment level. Each staircase was terminated after four reversals, with the staircase result calculated as the mean of the last two reversals. Two staircases were completed concurrently within each run, and the final contrast sensitivity estimate was calculated as the mean result of the two staircases.

A separate test run was conducted for each of the six array sizes, location (foveal and 12.5° eccentricity) and pedestal condition (steady and pulsed). The order of trials was randomized between participants. Participants completed practice trials to familiarize themselves with the requirements of the task. Participants completed trials over two sessions of approximately 2 hours in duration, with rest breaks permitted as required.

Results
Figure 3 compares the performance of the control and glaucoma groups for the steady- and pulsed-pedestal paradigms. Median log luminance increment thresholds for each group are plotted as a function of the log area of an individual test square. The median was used because the results were not normally distributed. Data are presented as a function of the log area of a single square of the array because the discrimination task involved identification of the different square. Figures 3a and 3c show data for the steady-pedestal paradigm, and Figures 3b and 3d show data for the pulsed-pedestal paradigm. The upper panels (Figs. 3a, 3b) show data for stimuli viewed foveally, and the lower panels (Figs. 3c, 3d) present peripheral data. Filled to be less problematic than changes in the eccentricity of the incremented square. No feedback regarding the accuracy of the response was provided.
symbols represent data from the control group, and open symbols represent the glaucoma group data.

Repeated-measures ANOVA (within factors: location, pedestal-paradigm, stimulus size; between factor: experimental group) of the log data showed that the thresholds for the glaucoma group were significantly elevated compared with the control group \( (F_{1,30} = 16.29; P < 0.001) \). In other words, the glaucoma participants performed significantly more poorly than the controls. As noted earlier, though every attempt was made to match participants between groups by age, the age range was slightly more restricted in the control group. To determine whether the significant elevation in threshold for the glaucoma group was an age-related artifact, Spearman correlations were conducted between age and thresholds obtained for each condition. All correlations were nonsignificant, implying that the significant elevation in threshold was not age related.

Thresholds were significantly elevated when stimuli were presented peripherally \( (F_{1,30} = 80.14; P < 0.001) \) and were significantly different for stimulus size \( (F_{2,27,68} = 51.78; P < 0.001) \) and between pedestal-paradigms \( (F_{1,30} = 66.66; P < 0.001) \). As expected, performance was significantly reduced in peripheral vision compared with central vision. As can be observed in Figure 3, thresholds were dependent on the size of the stimuli and the pedestal paradigm, such that thresholds were elevated for smaller test squares and for the pulsed-pedestal paradigm.

The two-way interaction between the testing location and the group was significant \( (F_{1,30} = 4.48; P < 0.05) \). However, the two-way interaction between the pedestal-paradigm and group was not significant \( (F_{1,30} = 3.65; P = 0.07) \), nor was the interaction between stimulus size and group \( (F_{2,27,68} = 0.85; P = 0.44) \). This implies that the difference between groups depended on the testing location and not the pedestal paradigm or the size of the stimulus. Inspection of Figure 3 reveals larger differences between control and glaucoma groups in the periphery than in the fovea. Potential differences between groups in the shapes of the threshold-area functions are explored.

Data for the pulsed-pedestal paradigm showed a shallow, linear decrease in log threshold with log area. However, data for the steady-pedestal paradigm showed a steeper decrease in threshold with log area for small stimulus sizes, with an asymptote for larger stimulus sizes. This is in accordance with Smith et al.,12 who characterized this relationship using extensive data collected on trained psychophysical observers. The pulsed-pedestal data in Figure 3 were fit with a linear function, and the steady-pedestal data were fit with an exponential decay function. We explored the curve fits. As expected, the average goodness-of-fit data were always higher for the function of choice for each experimental condition in control and glaucoma groups.

The equation for these fits to the steady-pedestal data is

\[
y = y_0 + ae^{-bx},
\]

where \( y_0 \) is the asymptotic value, \( a \) is the value of \( y \) minus the value of \( y_0 \) at \( x = 0 \), \( b \) is the exponential constant for the rate of decay, and \( x \) is the area of the test square. The dashed lines fit to the pulsed-pedestal data are derived from a linear function, and the equation for these fits is

\[
y = y_0 + ax,
\]

where \( y_0 \) is the \( y \)-intercept, \( a \) is the slope of the function, and \( x \) is the area of the test square.

Data obtained from each participant were fit with these functions. Examples for two observers in the control group are shown in Figure 4a, and examples from the glaucoma group are shown in Figure 4b. To determine whether there were any differences in the nature of the threshold area functions between groups, MANOVA was performed to compare the parameters that may affect the shape of the curves fit to each participant’s results for the steady- and pulsed-pedestal conditions for both central and peripheral testing. Given that our previous ANOVA results reported that luminance increment
thresholds were significantly elevated for the glaucoma group, the parameters of interest for this analysis included $a$ (estimate of the slope) from the linear functions fit to the pulsed-pedestal data and $b$ (estimate of the exponential constant for the rate of decay) from the exponential decay functions fit to the steady-pedestal data. For the pulsed-pedestal linear functions, there was no significant difference for the slope of the curve between groups ($F_{(2,29)} = 1.83; P = 0.18$), suggesting that the underlying mechanisms resulting in differences in luminance increment thresholds with increasing stimulus size for the pulsed-pedestal paradigm were not different between the control and glaucoma groups. For the steady-pedestal paradigm, there was no significant difference for the rate of decay of the exponential decay functions between the control and glaucoma groups ($F_{(2,29)} = 1.71; P = 1.96$). These nonsignificant differences in the shape of the curves suggest that the underlying spatial summation properties are not different between groups for the steady-pedestal paradigm.

**DISCUSSION**

In this study, the steady- and pulsed-pedestal tasks of Smith et al.\(^\text{12}\) were used to measure threshold-area functions for the presumed M and P pathways for participants with glaucoma and approximately age-matched controls. Our findings compare well with those of Smith et al.,\(^\text{12}\) demonstrating different spatial summation properties for the M and P pathways and support the suggestion that the tasks are measuring the performance of separate mechanisms. Average thresholds for our glaucoma participants were significantly elevated compared with the control group on both tasks, with significant glaucoma-related effects present across the range of stimulus sizes tested. Consistent with the results of ANOVA, no significant group differences in the functions were observed when the shapes of the threshold-area functions were determined for each of our participants and compared across groups.

Although there has been considerable interest in the usefulness of different perimetric stimulus sizes for the monitoring of glaucoma (see, for example, Sloan,\(^\text{16}\) Wild et al.,\(^\text{17}\) Wood et al.\(^\text{18}\)), to date, there has been limited study directed at determining whether spatial summation properties are altered because of glaucoma. Danheim et al.\(^\text{19}\) found that although light sensitivity was reduced for participants with glaucoma, the spatial and temporal summation curves were similar in shape to those of persons with normal vision.\(^\text{20}\) In contrast, Fellman et al.\(^\text{21}\) interpreted their experimental results as consistent with alterations of spatial summation in glaucoma, but stimulus area-threshold functions were not measured directly in that study.

A motivation for our study arose from reports of simplifications of dendritic architecture before cell death in response to elevated intraocular pressure in animal models of glaucoma.\(^\text{2,3}\) These changes in dendritic architecture are posited as one of the earliest anatomic alterations in the disease process. All glaucoma participants included in our study were classified as having early functional loss according to the staging system of Mills et al.\(^\text{14}\). However, given that substantial loss of retinal ganglion cells can occur before manifest visual field loss,\(^\text{22}\) these participants cannot be considered to represent the earliest disease stages. We chose to use such participants to attempt to include persons early in the disease process but for whom no dispute regarding diagnosis was possible. This study cannot address the possibility that different results might be obtained at the very earliest stages of the disease process.

Spatial summation varies with eccentricity of stimulus presentation, an observation that is presumed to relate, at least in part, to alterations in retinal ganglion cell coverage. Although summation curves have the same shape with changing eccentricity,\(^\text{23-24}\) the area over which complete summation occurs increases steadily with eccentricity.\(^\text{16,18,20,23,24}\) Consequently, it has been suggested that scaling peripheral stimulus size may significantly improve conventional perimetry.\(^\text{17,18,25,26}\) It has also been suggested that to detect drop-out by small numbers of ganglion cells, perhaps stimuli scaled to the size of Ricco’s area for each retinal pathway, background luminance and retinal eccentricity would be more appropriate than those currently used in conventional perimetry.\(^\text{26}\) Such area scaling would potentially enable more equivalent comparisons across retinal eccentricities. Our study suggests there may be no additional advantage for the detection of glaucoma by the alteration of stimulus size than that which can be predicted from the magnitude of threshold elevation.

In this study, the height and width of each square within the four-square array for foveal testing was varied between 0.125° and 4° (areas of 0.02° to 16° squared). For peripheral conditions, the height and width of each square ranged between 0.216° and 6.92° (areas of 0.05° to 47.89° squared). The discrimination task involved identification of the one different square within the array; therefore, the smallest sizes of the individual squares used in this study for foveal and peripheral testing were smaller than the Goldmann sizes III (0.43° diameter) and V (1.72° diameter) used in conventional perimetry. It is possible that our study would have yielded different results with the use of yet smaller stimuli. However, for our paradigm, using smaller stimuli introduced confounding complications that arose when the individual squares were no longer resolvable. The advantage of adopting the paradigm used in this study was that the M and P pathways could be assessed with identical test stimuli; the only difference was in the adaptation. This minimized the potential for relative performance differences between the two tasks because of factors unrelated to visual function, such as task complexity.

In summary, our results suggest that though spatial summation properties are different for presumed M- and P-mediated pathways, these differences are unchanged between the control and glaucoma participants in this study, foveally and midperipherally, despite the presence of threshold elevations in glaucoma.

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**References**


