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Orientation Discrimination with Macular Changes Associated with Early AMD

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Abstract

Purpose—Age-related macular degeneration (AMD) is a condition that progressively reduces central vision in elderly individuals, resulting in a reduced capacity to perform many daily activities and a diminished quality of life. Recent studies identified clinical treatments that can slow or reverse the progression of exudative (wet) AMD and ongoing research is evaluating earlier interventions. Because early diagnosis is critical for an optimal outcome, the goal of this study is to assess psychophysical orientation discrimination for randomly positioned short line segments as a potential indicator of subtle macular changes in eyes with early AMD.

Methods—Orientation discrimination was measured in a sample of 74 eyes of patients aged 47 to 82 years old, none of which had intermediate or advanced AMD. Amsler-grid testing was performed as well. A masked examiner graded each eye as level 0, 1, 2, or 3 on a streamlined version of the Age-Related Eye Disease Study (AREDS) scale for AMD, based on the presence and extent of macular drusen or retinal pigment epithelium (RPE) changes. Visual acuity in the 74 eyes ranged from 20/15 to 20/40⁺¹, with no significant differences among the grading levels. Humphrey 10–2 and Nidek MP-1 micro-perimetry were used to assess retinal sensitivity at test locations 1° from the locus of fixation.

Results—Average orientation-discrimination thresholds increased systematically from 7.4° to 11.3° according to the level of macular changes. In contrast, only 3 of 74 eyes exhibited abnormalities on the Amsler grid and central-field perimetric defects occurred with approximately equal probability at all grading levels.

Conclusions—In contrast to Amsler grid and central-visual-field testing, psychophysical orientation discrimination has the capability to distinguish between eyes with and without subtle age-related macular changes.

Keywords

age-related macular degeneration; orientation discrimination; metamorphopsia; Amsler grid; micro-perimetry

Recent estimates indicate that approximately 3 to 4 million Americans have reduced vision as the result of age-related macular degeneration (AMD). The prevalence of intermediate and advanced AMD increases dramatically with age, from approximately 17% of 70 year olds to 35% of people aged 80 or older.¹ Consequently, the number of afflicted individuals in the United States is certain to increase as the population ages. The reported prevalence of AMD

is similar among Whites and Latinos and lower among Blacks.^{1,2} In addition to increasing age, a history of smoking or heavy alcohol use are positive risk factors for AMD.^{3,4} The vision loss that occurs as the result of AMD has severe adverse consequences for many essential day-to-day activities, such as reading, facial recognition, and driving.

The early diagnosis of retinal changes in AMD presents a major clinical challenge.⁵ Because AMD disrupts the foveal photoreceptor layer early in the disease process, perceptual distortions are an expected clinical symptom. Indeed, the Amsler grid has been used for many years as both a clinical screening test and as a home-monitoring device for visual perceptual abnormalities that signal early retinal changes in AMD.⁶ However, studies conducted by several groups demonstrate that the Amsler grid lacks sensitivity.⁷⁻⁹ In particular, a high proportion of patients with documented central or paracentral visual field losses report that their perception of the Amsler grid is complete and undistorted. The explanation offered for this finding is so-called perceptual filling-in, wherein the visual system uses information from intact areas of the retina that surround a region of visual field loss to generate a complete and undistorted perception of continuous edges and regular line or dot patterns that impinge on the scotoma.^{10,11} Filling-in contributes to the perceptual completion reported by normal subjects in the vicinity of physiological scotomas, such as the blind spot, as well as artificial scotomas that are produced by image stabilization.^{10,12} Neurophysiological studies demonstrated that visual stimuli outside the classical receptive field produce responses in the cortical neurons of animals that view artificial scotomas. These responses are qualitatively consistent with the reports made by human subjects of perceptual filling in.¹³

Alternatives to the Amsler grid have been proposed and tested but the stimuli that comprise many of these tests remain spatially regular and, therefore, susceptible to filling-in.¹⁴⁻¹⁸ For example, Preferential Hyperacuity Perimetry was reported to identify perceptual changes associated with the development of choroidal neovascularization in patients with intermediate AMD more accurately than the Amsler grid.¹⁹ Although this instrument is intended primarily for in-office use by eye-care practitioners or their technical staff, a version designed for home use was described recently.²⁰

The goal of our study was to evaluate a psychophysical screening test for patients at risk for early AMD that is not susceptible to filling-in. Early detection of AMD would allow clinicians to initiate preventative care, such as counseling about UV protection, lifestyle, and dietary supplements, which have been demonstrated to delay progression from intermediate to advanced stages of the disease.²¹ Currently, recruitment is ongoing for the AREDS-2 clinical trial, to investigate the protection afforded by an increased intake of lutein/zeaxanthin and omega-3 fatty acid.²² These interventions are expected to prolong central vision in persons with AMD, thereby sustaining a better visual quality of life. In addition, early detection may allow pharmacological treatments for AMD that are currently under development to be applied sooner in the disease process and more effectively.

METHODS

Orientation Discrimination

The stimuli used to assess orientation discrimination were $1^\circ \times 1^\circ$ patches of 0.4° vertical bright lines, presented at a distance of 2 m on a 20-inch Clinton DS200 Monoray monitor. Each patch contained four randomly positioned lines, each of which was two pixels (1.4 min arc) wide. Previous studies and our own preliminary observations using young normal observers indicate that lines with a length of 0.4° yield close to asymptotic orientation-discrimination thresholds.²³⁻²⁶ Normal observers' orientation-discrimination thresholds are similar for patches that contain between 2 and 10 lines.²⁶ In the dim ambient lighting of the laboratory room, the luminances of the lines and monitor background were 40 and 0.04 cd/m², respectively. We

used bright lines on a dark background to minimize the effect of light scatter in patients with incipient cataracts. A single presentation consisted of two patches of lines with a center-to-center separation of 1.4° , shown simultaneously on opposite sides of a central bright fixation disk, along the horizontal, vertical or $\pm 45^\circ$ meridians (Fig. 1). No lines were presented within the central 0.4° of the display to avoid overlap with the fixation disk. The duration of each presentation was 200 ms, so that the subjects would not have time to make scanning eye movements. Viewing was monocular through the subject's habitual correction and the non-tested eye was occluded with an opaque patch. In each presentation, all the lines in one randomly selected patch had the same vertical orientation. In the other patch, the orientation of each line varied randomly from vertical according to one of five predetermined angular standard deviations (SDs).

After each presentation, the subject pressed one of four buttons, arrayed on a response box in the configuration of a cross, to identify which patch of lines was less variable in orientation. The observers were instructed to press either of two adjacent buttons to signal when the less variable lines were on one of the oblique meridians. Orientation-discrimination thresholds are the SD of the added orientation variability that can just be discriminated from a patch of physically parallel lines. Thresholds correspond to 75% correct on the cumulative Gaussian function, fit by probit analysis to the responses to 80 trials: two presentations with each of five angular SDs for eight possible meridians of the non-parallel lines. Testing of each eye required between 5 and 10 min to complete.

In addition to determining the orientation-discrimination threshold, we performed a separate analysis to evaluate the geographic distribution of errors for each eye by plotting the number of response errors, accumulated across all orientation SDs, against the retinal meridian with the physically parallel patch of lines. If subtle macular changes distort the perceived orientation of short line segments, then we would expect observers to have difficulty discriminating parallel lines that are imaged near a region with macular changes from patches of lines with added orientation variability. An increase in the number of orientation-discrimination errors therefore was expected to occur when the patch of parallel lines was imaged near a region of observable macular change.

Clinical Measurements and Grading

In addition to orientation-discrimination thresholds, a number of clinical measurements were obtained: (a) best corrected visual acuity in each eye, (b) Humphrey 10–2 visual fields to indicate the depth and extent of any central or paracentral scotomas, (c) digital flat or stereo fundus photography to record the retinal appearance and to allow each subject's macula to be graded subsequently by a masked examiner using standardized clinical criteria (discussed below), and (d) standard black-on-white Amsler grid testing. In 19 subjects, a Nidek MP-1 Microperimeter was used to perform retinally stabilized perimetry within the central 10° and to document the average retinal fixation locus, based on a 1-min sample of fixation. In these 19 subjects, the meridional distribution of orientation-discrimination errors was compared with the results of retinal micro-perimetry, and to the retinal locations of identified macular abnormalities. These comparisons were not made for all eyes because the Nidek Microperimeter became available only after the study started.

Experimental Subjects

Measurements were obtained for 85 eyes of 43 subjects, aged 47 to 82 years old. Subjects were recruited primarily from the University of Houston, University Eye Institute Family Practice clinic. The experimental protocol was reviewed by the University of Houston Committee for the Protection of Human Subjects and all subjects granted voluntary informed written consent. Twenty-four of the subjects were women and 19 were men. Subjects were selected to have

20/40 or better corrected visual acuity and either a normal appearing retina or a retinal appearance consistent with early AMD (levels 1 to 3 on the AREDS scale for AMD²⁷). Subjects were not recruited if they had ocular conditions that affect the macula other than early AMD, although one female subject was included who had a diagnosis of normal tension glaucoma. The data for one male subject were discarded because he did not perform the orientation-discrimination task reliably. The data for another male subject were eliminated because he exhibited marked and repeatable central field losses that were unrelated to any observable retinal abnormality. Finally, data were obtained from only one eye of a third male patient, who had reduced visual acuity (20/60) and previously diagnosed atrophic macular degeneration in the untested eye.

A single masked examiner evaluated a digital flat fundus photograph for each eye using a streamlined version of the Age-Related Eye Disease Study system for the classification of AMD.²⁷ A set of standard photographs was obtained from the Fundus Photograph Reading Center, Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison for training and reference. Because the psychophysical orientation-discrimination stimuli were presented only within the central 2° of the visual field, the examiner considered just the central subfield of the fundus photographs, with a radius of 1/3 disk diameter (approximately 500 μ m), rather than the entire grid system described by the AREDS group. The two features considered in grading each eye were drusen and retinal pigment epithelial abnormalities. Digital magnification was employed to help identify smaller features, while maintaining appropriate scaling factors for both the central subfield and the graduated measurement circles. In seven eyes of five subjects, the quality of the fundus photographs was not adequate to allow accurate grading. These seven eyes were eliminated from further analysis. The final sample comprised 74 eyes of 39 patients.

If drusen were present within the central 500 μ m zone, both the maximum size and their total area were estimated. Similarly, the examiner noted the presence and size of any RPE abnormalities, such as increased pigmentation or de-pigmentation that are associated typically with AMD. Following the criteria provided in the AREDS study, each eye was assigned an AMD level between 0 (no abnormalities noted) and 3. Although the AREDS grading system extends to level 4, none of the eyes that were included in this study had a macular appearance consistent with intermediate or advanced AMD.

RESULTS

Characteristics of Normal and At-Risk Eyes

The numbers of eyes categorized into the different levels of the AREDS scale for AMD are presented in Table 1. Neither the average age of the subjects ($F_{[3,68]} = 0.81$, $p = 0.49$) nor the visual acuity ($F_{[3,68]} = 1.93$, $p = 0.13$)^a differed significantly among the four groups of eyes. In addition, the frequency of defects found using the Humphrey 10–2 program at one or more of the four test points located 1° from the fixation locus was similar in the eyes with grades 0 through 3 (for $p[\text{defect}] < 0.05$, $\chi^2_{[3]} = 0.27$, $p = 0.97$; for $p[\text{defect}] < 0.01$, $\chi^2_{[3]} = 1.26$, $p = 0.74$). Amsler-grid defects were reported in only 3 eyes, 1 graded as AREDS level 2 and 2 graded as AREDS level 3.

Orientation Discrimination

Average orientation-discrimination thresholds increase systematically from $7.35^\circ \pm 0.66^\circ$ (SE) in the 15 normal (level 0) eyes to $11.32^\circ \pm 1.23^\circ$ in the 18 eyes categorized as level 3 early AMD (Fig. 2). The observed change in orientation discrimination with AREDS grade is

^aThe denominator of the F ratio has only 68 dF because visual acuities were not recorded for one subject.

statistically significant ($t_{[72 \text{ df}]} = 3.45$, $p = 9.4 \times 10^{-4}$). Repeatability of the orientation-discrimination thresholds was evaluated in 16 eyes of 8 subjects, graded as normal to AREDS level 3, after an average interval of 11 months. For these eyes, the correlation between the repeated threshold measurements was 0.78 ($t_{[14]} = 5.02$; $p = 0.0002$).

Additional comparisons indicate that the measured orientation-discrimination thresholds also correlate significantly with age ($t_{[72 \text{ df}]} = 3.96$, $p = 1.8 \times 10^{-4}$) and with logMAR visual acuity ($t_{[72 \text{ df}]} = 4.18$, $p = 8.1 \times 10^{-5}$). However, these correlations can not account for the relationship observed between orientation-discrimination and the AREDS grade, as the AREDS grade was not significantly correlated with either age or visual acuity (discussed above).

The Nidek MP-1 was used to assess the mean retinal fixation locus and to perform retinally stabilized micro-perimetry in 37 eyes of 19 patients. An AREDS grade could not be determined for one of the tested eyes. In the remaining 36 eyes, the AREDS grade had no significant relationship with the presence of central micro-perimetry defects ($\chi^2_{[3]} = 0.53$, $p = 0.91$), which we defined as a sensitivity poorer than 20 dB (the maximum attenuation that can be achieved using the MP-1) at one or more of the test points at 1° retinal eccentricity along the 45° , 135° , 225° , and 315° retinal meridians. Comparison of visual sensitivities obtained using the Nidek MP-1 micro-perimeter and the Humphrey 10-2 for test locations at a retinal eccentricity of 1° indicated a moderate and significant correlation ($r = 0.35$, $p = 2.6 \times 10^{-5}$).

Geographic Comparison between Macular Changes and Orientation Errors

We also used the Nidek MP-1 to assess the mean retinal fixation locus in 36 eyes. For the 29 eyes that were categorized as AREDS level 1 to 3, composite fundus photographs were constructed using Adobe Photoshop to superimpose the digital Nidek image, with a cross to indicate the average fixation locus, onto a flat digital fundus photograph of the same eye. Accurate superimposition was achieved by appropriately scaling and rotating the Nidek image to match the locations of major vessel features in the flat fundus image. The Nidek image was then removed, except for the cross that specified the average fixation locus. The clinical examiner used these composite fundus images to identify the location(s) of the previously noted macular changes in each eye within one or more retinal quadrants, centered on the 45° , 135° , 225° , and 315° meridians with respect to the average fixation locus.

The locations of the observed retinal change(s) in each eye were compared to the distribution of orientation-discrimination errors, expressed in terms of the retinal meridian that contained the patch of parallel lines. Subsequently, these plots of orientation errors were downsampled from 8 to 4 meridians (45° , 135° , 225° , and 315° , Fig. 3), to permit direct comparison with the geographic location of the macular changes in the composite fundus photographs of the 29 eyes with AREDS grades of 1 to 3. The down-sampled number of errors was obtained by averaging the number of orientation-discrimination errors on each oblique meridian (E_{Ob}) with half the numbers of errors on the adjacent horizontal (E_H), and vertical (E_V) meridians:

$$\text{Weighted average errors} = (E_{Ob} + 0.5 \times E_H + 0.5 \times E_V) / 2$$

Agreement between the downsampled psychophysical error plot and the location of macular changes was defined as three or more orientation-discrimination errors (out of 10 trials) in one or more retinal quadrants with observable macular changes. This criterion is based on the binomial distribution, which indicates that three or more orientation-discrimination errors correspond to a deviation of 2.9 SDs from error-free performance. The filled symbols in Fig. 4 show that agreement between the quadrants with three or more orientation-discrimination errors and observable macular defects improves with the AREDS grade level. Based on our definition of agreement, it is possible that this improvement occurs because the number of

quadrants with macular abnormalities increases with the AREDS grade level. However, this explanation is inadequate because the average number of quadrants with observable defects changes only from 2.71 ± 0.35 (SE) for eyes graded as AREDS level 1 to 3.14 ± 0.40 for eyes graded as AREDS level 3. The unfilled symbol in Fig. 4 shows the percentage of eyes (64%) without observable macular changes, in which two or fewer orientation-discrimination errors occurred in all four quadrants.

A similar analysis indicated poorer agreement between the meridians with retinal sensitivity defects, defined as a value <20 dB as measured with the Nidek MP-1 micro-perimeter, and the observed geographic location of macular changes in the same eyes ($t_{[3]} = 6.92$; $p = 0.006$). Specifically, agreement on one or more meridians occurred in 5 of 15 eyes graded as AREDS level 1, four of eight eyes as AREDS level 2, and five of seven eyes as AREDS level 3. Two of the five eyes with no observable macular defects exhibited retinal sensitivities of 20 dB in all four quadrants using the Nidek micro-perimeter.

DISCUSSION

Evaluation of Results

Average orientation-discrimination thresholds are systematically higher in eyes categorized as levels 2 and 3 AMD than in eyes with no or minimal signs of early AMD (levels 0 and 1). We conclude that the orientation-discrimination test described here is sensitive to subtle disruptions of the macula that occur in conjunction with the drusen and pigment epithelial defects that define the early stages of AMD. Elevation of the orientation-discrimination threshold is associated with the presence of subtle macular changes more reliably than visual-field deficits measured using the Humphrey 10–2 protocol or stabilized retinal micro-perimetry.

The smallest orientation-discrimination thresholds that we measured in our subjects are similar to those reported recently by Morgan et al.,²⁸ who asked normal observers to discriminate between displays of parallel and non-parallel Gabor patches. Nevertheless, the range of orientation thresholds measured in the eyes graded as clinically normal (AREDS level 0), from 4.4° to 11.9° , is of some concern. One possible explanation for the broad range of orientation thresholds that we found is that orientation thresholds increase systematically with age, regardless of any observable macular changes. However, among the 35 eyes in the current study that were graded as AREDS level 0 and 1, no significant correlation exists between the orientation-discrimination threshold and age (age range = 52 to 82 years; $r = -0.27$, $p = 0.11$). This observation agrees with the results of previous studies that found little evidence for a worsening of orientation-discrimination thresholds with age, when these thresholds were measured using high-contrast targets.^{29,30}

Comparison with the Amsler Grid

The rationale for the test of orientation discrimination described here is similar to that offered originally for the Amsler grid.⁶ Disruption of the photoreceptor topography, initially by drusen and later by pockets of subretinal fluid, would be expected to produce visual distortions such as perturbations in the spacing of regular patterns and bending of physically straight lines. Although some patients report perceptual distortions in the Amsler grid,^{6,16} a large percentage of patients with documented macular abnormalities perceive the grid to be regular and complete. The relative insensitivity of the Amsler grid to perceptual distortions is attributed to the normal perceptual process of “filling in.” In regions where retinal information is compromised or missing (for example, in normal eyes because of overlying retinal vessels or the absence of photoreceptors in the physiological blind spot), the brain interpolates using visual information from neighboring areas. This filling-in process helps persons with both

normal and abnormal vision to maintain the perception of a complete and relatively undistorted visual scene.

In our orientation-discrimination test, we attempted to minimize the likelihood of perceptual filling in by using short (0.4°), randomly positioned line segments. Because optimal orientation thresholds require a somewhat longer line length,^{23-26,31} even a slight disruption of the normal photoreceptor layer would be expected to impair discrimination. However, small amounts of optical blur, which could result from inaccurate refraction, mild cataract, or pupillary dilation, produce only a minimal effect on normal observers' thresholds for orientation discrimination using 0.4° lines.^{26,32}

Wang et al.³³ reported that patients with early and intermediate AMD had higher thresholds than age-matched control subjects on a global shape-discrimination task, i.e., to distinguish between spatially modulated and unmodulated radial frequency (fourth derivative of a Gaussian) patterns. Although optimal performance on this task involves the global pooling of contour information, Wang et al. concluded that the elevated thresholds in patients with AMD are most likely attributable to distortions of contour encoding at the level of the retinal photoreceptors. For clinical application, an advantage of the bright lines that we used compared to Gaussian and related spatially modulated targets is that the lines require less precise calibration and control of the stimulus luminance values.

In addition to the filling-in phenomenon, perceived distortions in the Amsler grid may be "averaged out" over time if patients do not maintain accurate fixation at the center. In the orientation-discrimination test described here, the possibility of scanning eye movements is reduced by flashing the line segments for 200 ms, a duration approximately equal to the latency for saccades.^{34,35} Predictive eye movements were discouraged further by presenting the patches of lines on each trial on random pairs of meridians that were arrayed symmetrically on opposite sides of the fixation stimulus.

A potential advantage of the Amsler grid is that it evaluates a wider region of the visual field than the orientation-discrimination test described here. Clearly, the current test could be modified to evaluate more than the central 2.4° of the visual field. However, the cost would be an increase in the testing time. The Amsler grid already has the advantage that it is faster and simpler to use than a computer-based test of orientation discrimination. Currently, we are evaluating a modified version of the orientation-discrimination test that uses an adaptive psychophysical technique³⁶ to reduce the time to test each eye to approximately 1 min. To increase the ease of use outside the clinical environment, we envision that the orientation-discrimination test will be implemented eventually on the screen of a readily available personal electronic device, such as a personal digital assistant or cell phone. Implementation using these devices would allow patients to perform the test quickly and conveniently on a regular basis at home, similar to the way that the Amsler grid is employed now.

Finally, with suitable modifications of the stimulus parameters, the orientation-discrimination test described here might be applied also to monitor eyes for the progression from the dry to the wet form of AMD or, in eyes that have progressed to wet AMD, to monitor the response to anti-VEGF treatments. If deleterious macular changes can be identified accurately in a timely fashion in eyes with advanced AMD, then medical treatments can be provided when needed to minimize disease progression and preserve each patient's maximum vision. In addition to eliminating the cost and risk of potentially unnecessary treatments, a test that allows patients to monitor at home for the occurrence of macular changes, such as retinal thickening and fluid accumulation, would decrease cost and inconvenience by reducing the number and frequency of office visits.

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Drs. Bedell, Tong, and Woo submitted a patent application on the orientation-discrimination test described in this paper.

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FIGURE 1.

To assess orientation discrimination, $1^\circ \times 1^\circ$ patches of random-line stimuli were presented on opposite sides (here, on the 45° and 215° visual-field meridians) of a central fixation target. To avoid overlap with the fixation disk, each patch of lines was centered 0.9° away from the middle of the disk.

FIGURE 2.

Orientation-discrimination thresholds (± 1 SE) are shown as box-and-whisker plots for eyes categorized with different levels of early macular changes, using a modified version of the AREDS grading scale as described in the text. The top and bottom of each box demarcate the 75th and 25th percentiles, respectively, and the line inside the box indicates the median threshold for each AREDS grade level. The whiskers specify the range of orientation-discrimination thresholds. The unfilled circle above the plot for AREDS level 3 indicates a statistical “outlier,” defined as more than 1.5 times the interquartile range above the 75th percentile. Filled squares represent the mean orientation-discrimination threshold for each AREDS level.

FIGURE 3.

The number of orientation errors per 10 trials is plotted against the retinal meridian that received the image of a patch of physically parallel lines. Data are for a right eye with 20/20 visual acuity, graded as AREDS level 1 because of small drusen scattered in all four quadrants around the macula. Unfilled symbols and dotted lines show the number of errors for eight retinal meridians. Filled symbols and solid lines show the number of orientation errors downsampled from 8 to 4 meridians.

FIGURE 4.

Filled symbols indicate the percentage of eyes, categorized as AREDS levels 1 to 3, in which agreement exists between retinal quadrants with observable macular defects and quadrants with three or more orientation-discrimination errors. The unfilled symbol shows the percentage of eyes with no observable macular defects and no more than two orientation-discrimination errors in any quadrant. Errors bars are ± 1 SE, based on the binomial distribution.

TABLE 1

Characteristics of eyes classified at different AREDS levels

AREDS level	Number of eyes (males/females)	Age in years Mean (range)	LogMAR visual acuity Mean (range)
0	15 (3/12)	69 (52–81)	0.057 (–0.025 to 0.176)
1	20 (10/10)	65 (55–82)	0.010 (–0.125 to 0.113)
2	21 (7/14)	66 (57–75)	0.042 (–0.125 to 0.301)
3	18 (10/8)	68 (47–82)	0.076 (–0.025 to 0.276)