Changes in color vision with decreasing light level: separating the effects of normal aging from disease

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The purpose of this study was to obtain additional information about the health of the retina (HR) by measuring the rate of loss of chromatic sensitivity with decreasing light level. The HR_{index} is introduced to separate the effects of normal aging from early stage disease. For normal subjects the HR_{index} is largely independent of age ($r^2 \sim 0.1$), but ~11% of clinically normal, asymptomatic, older subjects exhibit values below the 2σ limit. The HR_{index} provides a single number that captures how light level affects chromatic sensitivity irrespective of age and can be used to screen for preclinical signs of retinal disease.

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1. INTRODUCTION

It is generally accepted that many aspects of visual performance worsen at lower levels of ambient illumination and that the effects can be debilitating in healthy, older subjects [1,2] and more so in patients with ocular pathologies [1,3,4]. Vision at low light levels is also compromised by imposed mild levels of hypoxia in healthy young subjects [5,6]. Other studies have shown that healthy normal observers who are carriers of the CFH, LOC387715, and HRTA1 genotypes and are considered to be of high risk of developing age-related maculopathy later in life perform significantly worse in the mesopic range in some visual tasks, but not at higher light levels [7]. Such observations suggest that measurable changes in visual performance at lower light levels may carry more information about the state of the retina than similar measurements in the photopic range. In addition to lowering the ambient light, a reduction in retinal illuminance can also be caused by the decreased pupil size in older subjects [8–10] and the increased absorption and scattering of light by the lens [11–13]. Although changes in the optics of the eye can affect spatial resolution and contrast sensitivity by reducing retinal image contrast and retinal illuminance, of even greater interest is the worsening of visual performance that can be attributed to changes in the retina and the visual pathways [14–16]. The latter can be indicative of early diseases of the retina and are best detected using visual tasks that do not require high spatial resolution, such as the detection of rapid flicker [17] or color differences with large stimuli [18]. When adapted to photopic light levels, chromatic sensitivity in normal subjects changes only very slowly with changes in retinal illuminance, but this is not the case when low photopic/upper mesopic light levels are involved [19]. When comparing color detection thresholds measured at lower light levels, it is therefore important to minimize the confounding effect of changes in retinal illuminance caused by differences in pupil size and prereceptoral absorption of light. Red–green (RG) and yellow–blue (YB) mechanisms act independently at threshold [20], but it is generally believed that aging affects preferentially the YB mechanism [21,22]. Although several studies have shown that color vision deteriorates with advancing age [23,24], some controversy remains as to whether normal aging affects more the YB mechanism [25]. Diseases of the eye, such as diabetes, tend to affect uniformly both RG and YB mechanisms, although the loss of YB sensitivity precedes RG in early stage age-related macular degeneration [26]. The prevalence of retinal and systemic diseases that affect vision increases with age and almost invariably these cause loss of chromatic sensitivity. Older subjects also exhibit greater variability in both RG and YB chromatic sensitivity and this makes it difficult to detect the very early stages of disease. This study investigates the extent to which the rate of decrease in chromatic sensitivity with decreasing retinal illuminance provides additional information about the health of the retina that can be used to separate changes caused by normal aging and disease. Pupil size and prereceptoral absorption of short wavelength light were measured for each subject in order to obtain a better estimate of effective retinal illuminance. RG and YB color thresholds were assessed separately in order to establish whether the two mechanisms perform differently with changes in retinal illuminance and/or aging.

2. METHODS

A. Subjects

The subjects were recruited by advertising the study locally within City University. The tests were approved by the City University Research and Ethics Committee and the study adhered to the principles of the Declaration of Helsinki. All subjects granted informed consent and underwent a full ophthalmic assessment, including measurement of corrected and/or uncorrected visual acuity, refraction for 2.5 m and 0.7 m, pupil reactions, intraocular pressure measurements, and indirect ophthalmoscopy. All subjects had normal color vision and healthy eyes with no history of ocular disease, surgery, or laser treatment. None of the subjects enrolled in the study suffered from any diseases or took any medication known to affect color vision.

B. Color Assessment

Every subject was assessed for color vision using the Color Assessment and Diagnosis (CAD) test, which employs dynamic luminance contrast noise to isolate the use of color signals without affecting the subject's chromatic sensitivity [18,20]. The test stimuli were generated on a visual display (LaCie Electron Blue, 20 in. CRT monitor) using an ELSA Gloria XL graphics card with 30 bit resolution (ELSA Optical Technology Inc., Aachen, Germany). The monitor was adjusted for stable operation and its spectral and luminance calibration were carried out with a Minolta CS-2000 telespectroradiometer and an LMT-1003 luminance meter, respectively. A hood fitted with a chin/forehead rest was placed 2.5 m away from the display and provided support for the positioning of the subject's head. The subject viewed the display monocularly and the RG and YB color thresholds were measured for screen luminances of 2.6, 7.8, 26, and 65 cd/m^2. The CIE (x, y) chromaticity of the uniform background (0.305, 0.323) was close to that of the D_{65} illuminant and remained unchanged for all background luminances. Before the start of each experiment, the display was allowed to warm up for ~25 min, the subject adapted to the corresponding display background for ~2 min, and the order of selection of the four screen luminances was randomized.

The measurement procedure was described fully in earlier publications [20,27]. The CAD test has been employed in a number of previous studies that involved mostly young subjects, usually less than 50 years old, to examine how various parameters, such as the screen luminance, stimulus size, level of light adaptation of the eye, and stimulus eccentricity, affect chromatic sensitivity [19,20]. For convenience, the measurements are expressed in standard normal (SN) CAD units, which reflect the mean RG and YB thresholds measured in 330 normal trichromats [18]. A subject with unit threshold performs as well as the median normal trichromat. In terms of cone-specific signal changes, the RG median standard CAD observer thresholds correspond to ~0.75% and ~0.4% M- and L-cone contrast, respectively. The YB median threshold, on the other hand, corresponds to ~8% S-cone contrast [20]. The lower normal sensitivity for detection of yellow–blue changes may be due to the much reduced S-cone density in the retina [28], but when expressed in SN CAD units, the median thresholds correspond to one unit for both RG and YB discrimination.

C. Pupil Measurements

Pupil diameter was measured using the P_SCAN 100 system [29]. The instrument employs infrared video imaging techniques to measure the center coordinates of the pupil and compute its size [30] A pulsed, infrared illumination system is used to illuminate the iris for ~4 ms within each image frame in order to eliminate pupil image smear caused by eye movements. The system is focused as the patient fixates the center of the screen. Several pupil measurements were averaged, with the subject viewing monocularly a uniform background of 2.6, 7.8, 26, and 65 cd/m^2, under conditions identical to those employed for the CAD test.

D. Estimates of Lens and Macular Pigment Optical Density

The Macular Pigment Optical Density (MPOD) profile and the short wavelength absorption of the crystalline lens were measured with the Macular Assessment Profile (MAP) test [31]. The instrument employs an optical notch filter to separate the outputs of the three phosphors into two components, the test beam and the reference beam. The short wavelength (SW) test beam is absorbed maximally by the macular pigment (MP) and the crystalline lens, whereas the reference beam consists of long wavelength (LW) light that is not absorbed significantly by prereceptoral filters or by the MP. The two beams are modulated sinusoidally in counterphase at 17 Hz. The stimuli are generated on a high-luminance, 17 in., CRT display (using an ELSA Gloria XL graphics card) at a frame rate of 140 Hz. The MAP test was designed to measure the spatial profile of the MP optical density at a number of stimulus eccentricities (i.e., 0°, 0.8°, 1.8°, 2.8°, 3.8°, 6.8°, and 7.8°) [27]. The test stimulus changes from a 0.36° diameter disk, when presented at the fovea, to a sector annulus at all other eccentricities, while the width of the annulus increases with eccentricity to facilitate flicker detection. The subject's task is to cancel the perception of flicker by adjusting the luminance of the test beam using a modified staircase with variable step sizes until the perception of flicker is canceled. At the flicker-null point, the threshold is recorded. Both the lower and the higher flicker-null thresholds were measured at each eccentricity and the average of the two thresholds was then recorded. Four, randomly interleaved, repeat measurements were made at each spatial location investigated.

The MP is assumed to have negligible effects on the absorption of blue light beyond 5° to 7° from the fovea [32]. In the MAP test, all measurements are referenced to the mean value measured at 6.8° and 7.8° eccentricity. The crystalline lens continues to absorb the SW blue test beam in the same way, irrespective of stimulus eccentricity. The luminance of the SW test beam needed to cancel the perception of flicker at the largest eccentricity reflects only the absorption of SW light by the lens and not the MP. The average lens transmittance (T_{AVG}) for the short wavelength light that makes up the test beam is given by

$$T_{\mathrm{AVG}} = \frac{\int_{380}^{780} T_L(\lambda) L_B(\lambda) \mathrm{d}\lambda}{\int_{380}^{780} L_B(\lambda) \mathrm{d}\lambda}, \tag{1}$$

where $T_L(\lambda)$ is the spectral transmittance of the lens and $L_B(\lambda)$ is the wavelength radiance distribution of the SW (blue) test beam employed in the MAP test. The latter peaks at ~450 nm and has a half-maximum spectral width of ±28 nm [27]. The integration is carried out over the wavelength range of 380 to 780 nm. Although the absolute T_{AVG} value cannot be measured, the technique makes it possible to estimate the subject's lens optical density for SW light with respect to the mean density measured in young observers. Previous experiments involving 35 young subjects yielded a measure of the mean luminance of the SW test beam. The optical density of the lens for any subject can be measured with respect to the young subject group (i.e., the mean value for 24 subjects, less than 24 years old):

$$\mathrm{OD} = \log_{10} \frac{L_p}{L_o}, \tag{2}$$

where L_p represents the subject's mean test beam flicker-null threshold at 6.8° and 7.8° eccentricity and L_o represents the

median threshold value for the young subject group at the same eccentricity [27]. A negative value for optical density means that the subject's lens absorption of blue light is less than the mean value for the young subject group. The test was performed monocularly at a viewing distance of 0.7 m. A full description of the MAP test, including the spatial configuration of the stimuli, has been given elsewhere [31].

E. Estimating Retinal Illuminance

Retinal illuminance (E) was computed after accounting for pupil size and the combined SW transmittance of the lens and the MP. RG thresholds depend on signal changes in L and M cones, which are affected much less by absorption of SW light. The measure of retinal illuminance for RG color vision assessment was therefore based only on screen luminance (L) and the pupil area (P):

$$E = L \cdot P. \tag{3}$$

Since YB color thresholds as measured in the CAD test rely only on S-cone signal changes [20], an appropriate estimate of retinal illuminance for SW light should take into account the optical density of the lens and the average absorption of blue light by the MP. The total displacement of the moving colored stimulus in the CAD test covers a visual angle of ~2.9°. It was, therefore, deemed appropriate to use the average MPOD value provided by the MAP test over the central ±2.8°. The calculation of retinal illuminance for SW light included the combined transmittance of the lens and the macular pigment:

$$E = L \cdot P \cdot T_C. \tag{4}$$

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F. HR_{index}

The HR_{index} captures the subject's color detection sensitivity as a function of light level in the low photopic, high mesopic range. The group data provides an average measure of the rate of change of threshold sensitivity with light level. The HR_{index} reflects the fractional difference between the area under the subject's threshold curve and the corresponding median curve for the group (see Appendix A).

G. Statistical Analysis

The JMP statistical software program was used to fit the nonlinear function that describes the variation in the subject's threshold with retinal illuminance (SAS Institute Inc., Cary, North Carolina). The MATLAB (The MathsWorks, Inc.) stats module was used to estimate the density functions for the measured HR_{index} values and to compute the equivalent $\pm 2\sigma$ limits.

3. RESULTS

The three principal variables that affect retinal illuminance when viewing a stimulus display of known luminance, L, are shown in Fig. 1. Figure 1(a) shows the optical density of the crystalline lens for absorption of SW light for each of the subjects investigated in this study. Figure 1(b) shows the mean pupil diameter for each subject measured when viewing the uniform screen of luminance 26 cd/m^2. Similar data were obtained for the remaining three screen luminances employed. Figure 1(c) shows an example of the spatial profile of the MP optical density measured using the MAP test [31]. These data were used to calculate the average transmittance of the MP over the central ±2.8°. A measure of retinal illuminance was then computed for each subject and each light level separately.

The effect of pupil size changes on effective retinal illuminance can also be confounded with the associated changes in directional sensitivity of cones [34,35]. The Stiles–Crawford effect is difficult to account for accurately when the area of the retina stimulated is not restricted to the fovea [36] and when the entry pupil location for peak maximum sensitivity is not known [37].

In order to appreciate the magnitude of the changes in effective retinal illuminance that can be caused by the Stiles–Crawford effect, we assumed the center of the pupil as the entry point of peak sensitivity and computed the change in effective retinal illuminance for the pupil data shown in

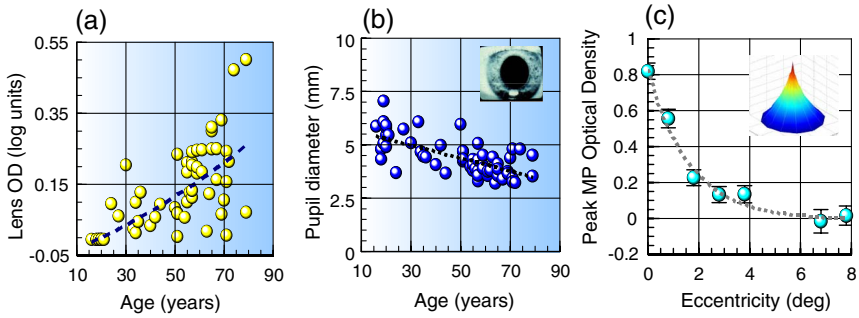

Fig. 1. (Color online) (a) Measurements of lens absorption of short wavelength light as a function of age for the group of subjects investigated in this study (age range: 16 to 79 years). The age distribution of the subjects is shown as an inset in Fig. 3(a). The optical density in Fig. 1(a) describes the average absorption of short wavelength light by the lens [as given by Eq. (1)] when referenced to young subjects (i.e., <24 years) for light of spectral radiance equivalent to that employed in the MAP test. The latter peaks at ~450 nm and has a half-maximum spectral width of ±28 nm [27]. The integration is carried out over the wavelength range of 380 to 780 nm. The dotted curve in (a) represents a second-order polynomial fit that accounts for ~40% of the measured variability. Panel (b) shows the average pupil size as a function of age when viewing monocularly the visual display for a screen luminance of 26 cd/m^2, under conditions identical to those employed in the CAD test. The dotted curve shows the best linear fit and is given by: $y = 5.96 - 0.0315 * x$, $r^2 = 0.47$. Unless otherwise stated, a least-squares, straight line was fitted to the data and the goodness of the fit is described by the square of the product moment correlation coefficient. Panel (c) shows a typical spatial profile for the macular pigment optical density measured with the MAP test [31]. The dotted curve represents the best exponential fit of the form, $OD = 0.832 * \exp^{-0.609 * \theta}$, where θ represents the stimulus eccentricity in degrees [33].

Fig. 1(b). When integrated over the pupil, the change in luminous efficiency at either extreme (i.e., 2.75 and 7.1 mm) with respect to the efficiency computed for the mean pupil size (i.e., 4.36 mm) is less than 0.14 log units. Corrections have not, therefore, been made to account for changes in effective retinal illuminance caused by the Stiles–Crawford effect.

The RG and YB thresholds measured in 237 normal trichromats as part of an earlier study [38] for a screen luminance of 24 cd/m^2 are shown in Fig. 2 as a function of age. The inset in Fig. 2(a) shows the age distribution within this group, with a mean and standard deviation of 29.5 and 9.7 years, respectively. The measurements were carried out binocularly, under optimum conditions, and show little or no effects of aging, but the sample includes only a small number of subjects above 45 years of age.

Figure 3 shows similar thresholds measured monocularly for a screen luminance of 26 cd/m^2 in a smaller group of 60 subjects examined in this study. These subjects were selected to spread more uniformly the age range of 16 to 79 years. The inset in Fig. 3(a) shows the age distribution of the subjects with a mean and standard deviation of 47.6 and 19 years, respectively. Figure 4 shows the thresholds measured for all four screen luminances (2.6, 7.8, 26, and 65 cd/m^2) as a function of the corresponding retinal illuminance, with appropriate correction for pupil size [Eq. (3)] and, in the case of YB thresholds, with additional correction for the mean absorption of SW light by the lens and the macular pigment [Eq. (4)].

The HR_{index} was then computed separately for each subject, as described in Appendix A. When expressed as standard deviations from the mean, five of the subjects had indices well outside the normal range and were removed from the sample. The frequency distributions and the equivalent $\pm 2\sigma$ limits of the recomputed RG and YB HR_{index} values for the 55 normal subjects included in the analysis are shown in Fig. 6. The revised analysis identifies only two subjects as lying just marginally outside the -2σ limit. The computed HR_{index} values are shown as a function of subject's age in Fig. 7 for RG and

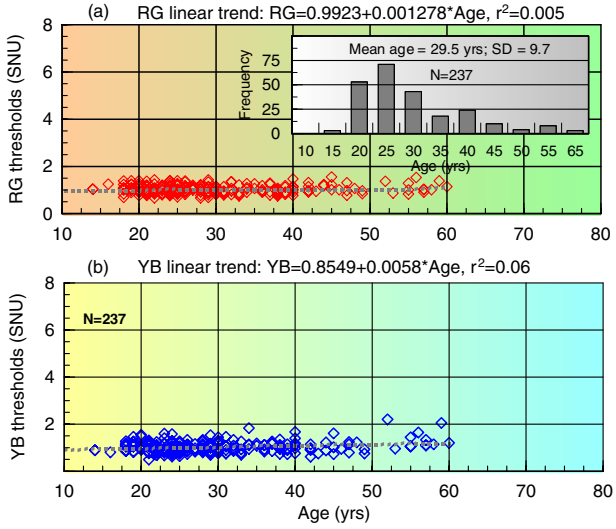

Fig. 2. (Color online) Measurements of color detection thresholds, expressed in standard normal units (SNU), in a group of 237 subjects when adapted to a uniform screen of luminance of 24 cd/m^2. The standard normal CAD units are based on the mean RG and YB thresholds measured in 330 normal trichromats [18]. According to this definition, the median normal trichromat has a threshold of 1 SNU. A threshold of 2 SNU means that the subject requires twice the color signal strength of the median normal trichromat. In cone contrast space, this corresponds approximately to doubling the cone photoreceptor contrasts [39].The inset histogram shows the age distribution within the group with a mean age of 29.5 years. The display was viewed with both eyes under optimum conditions and the measurements were carried out using the CAD test. The effects of age on the measured thresholds are very small ($r^2 < 0.06$) [38].

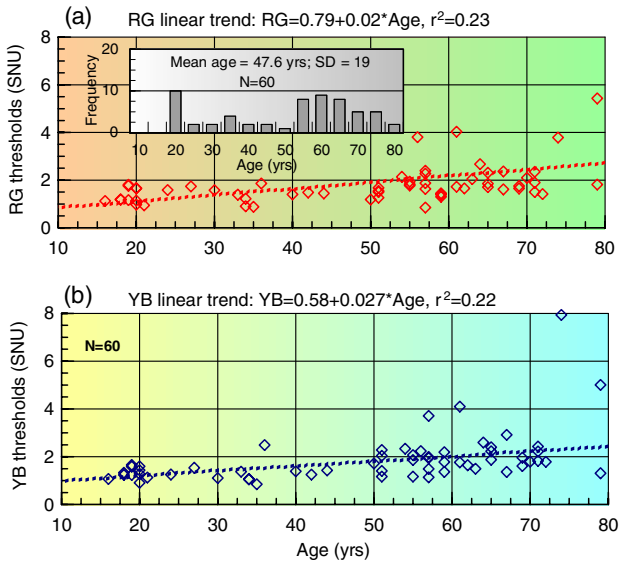

Fig. 3. (Color online) Monocular measurements of color detection thresholds in a group of 60 subjects when adapted to a uniform background field of 26 cd/m^2. The subjects were more uniformly distributed as a function of age (ranging from 16 to 79 years). The inset histogram shows the age distribution within the group with a mean of 47.6 years). The effects of age are significant for RG and YB detection thresholds, as indicated by the dotted curves ($r^2 = 0.23$ and $r^2 = 0.22$, respectively, and $p < 0.001$).

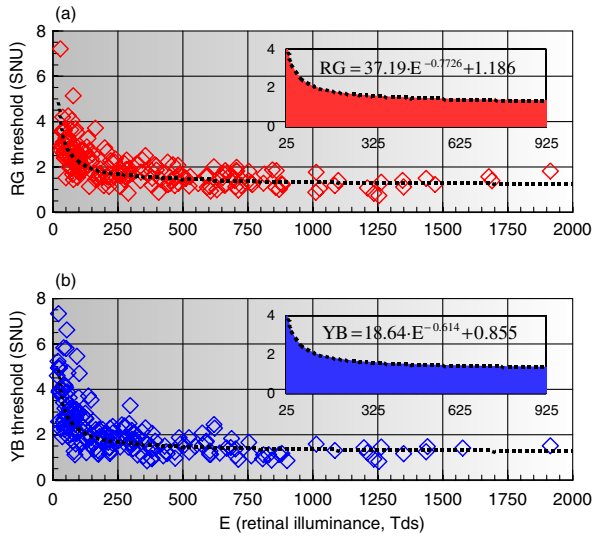

Fig. 4. (Color online) Color thresholds measured as a function of retinal illuminance (E) after appropriate correction for pupil size (RG). In the case of YB thresholds, the retinal illuminance was also corrected for the absorption of SW light by the lens and the MP. The screen luminances employed were 2.6, 7.8, 26, and 65 cd/m^2. The dotted curves show the optimized power law functions that predict the increase in color detection thresholds with decreasing retinal illuminance for the group of subjects examined in the study.

YB thresholds. Black symbols are used to identify the seven subjects (i.e., 11.7% of the group) with HR_{index} values well outside the normal limits.

4. DISCUSSION

Aging causes structural changes in the retina as well as increased absorption and scatter of light by the optics of the eye. The latter reduces the amount of light that reaches the retina and alters selectively its spectral composition. Such changes affect many aspects of visual performance and, in particular, contrast sensitivity and our ability to detect rapid flicker and small color differences at lower light level. As one grows older, color vision is arguably affected most because of changes in the retina and the more extensive spatial processing associated with the extraction of color signals. Diseases of the retina are also more common in old age and almost invariably lead to rapid worsening of color vision. Deciding what is normal aging and what is indicative of retinal disease remains a challenge, particularly when the aim is to detect the earliest stages of disease.

Retinal illuminance can have a large effect on the processing of retinal signals and, hence, on various measures of visual performance, such as reading, contrast acuity and driving [1,40,41]. Color vision thresholds are also affected at lower light levels in normal subjects and particularly the detection of YB color differences [19,42]. Knoblauch and his colleagues also showed that performance on the FM100 test worsens with increasing age, but the differences reduced at higher light levels [43]. Reduction in retinal illuminance caused by pupil miosis and selective absorption of SW light by the lens in older subjects can cause significant, additional loss of YB chromatic sensitivity, particularly when the ambient illumination is already low. Intersubject differences in retinal illuminance cause increased variability in color thresholds and this makes it even more difficult to detect the presence of early stages of retinal pathology. The age distribution of the subjects, the light level employed, and whether color thresholds are measured monocularly, so as to reveal eye-specific changes in chromatic sensitivity, or binocularly, to indicate overall functional performance, can affect significantly the magnitude and the variability of the thresholds measured, as well as the observed correlation with age. Monocular thresholds tend to

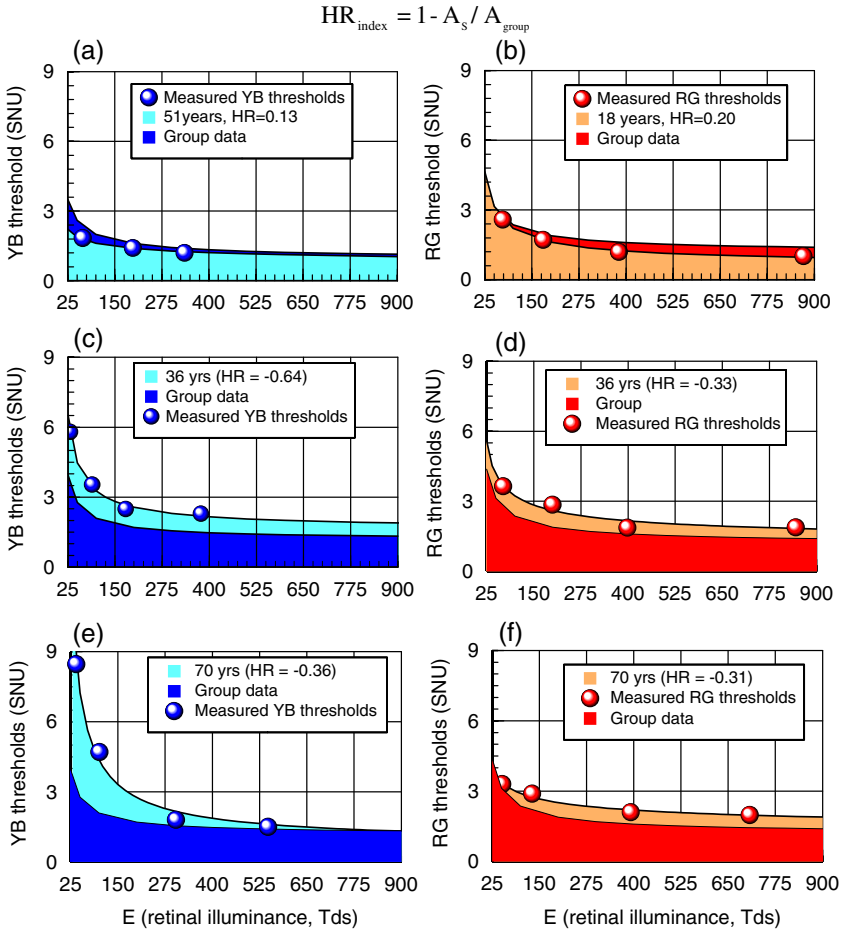

Fig. 5. (Color online) Examples of YB and RG color thresholds and the corresponding HR_{index} values for young and old subjects. The HR_{index} is defined as the difference in area under the subject's threshold curve (A_S) and the normal group (A_{group}) expressed as a fraction of the area for the group, as illustrated in each diagram. The mean pupil size and the absorption of the lens and the MP (in the case of YB thresholds) affect the subject's retinal illuminance. The optimum threshold measured at the highest illuminance together with the rate of increase in thresholds with decreasing retinal illuminance determine the subject's HR_{index}. Panel (a) shows data in an 18-year-old subject with a positive HR_{index} indicative of performance better than average. Panel (b) also shows better than average performance for YB thresholds in a 51-year-old subject. The 36-year-old subject shown in (c) and (d) falls outside the normal range for YB thresholds, while the 70-year-old subject shown in (e) and (f) is within the 2σ limits established for the group (see Fig. 6).

show increased variability and also to be significantly larger, even in young normal subjects, as can be seen by examining and comparing the data shown in Figs. 2 and 3. Preliminary findings show that the ratio of monocular to binocular thresholds shows large intersubject variability with extreme values of 1 and 1.86. A subject's improvement can, therefore, differ significantly from statistical predictions based on independent, stimulus correlated signals and uncorrelated noise (i.e., $\sqrt{2} \sim 1.41$) [44]. To reveal eye-specific loss of retinal sensitivity, one needs to measure monocular thresholds and to account for large changes in retinal illuminance caused by the principal factors shown in Fig. 1. When these factors are accounted for, the variation in color thresholds with retinal illuminance is more likely to reflect the properties of the retina. Figure 4 shows the fitted functions, which describe well the dependence of RG and YB thresholds on retinal illuminance. Above some 300 trolands (Tds) the data show relatively small intersubject variability, but both thresholds increase rapidly at lower retinal illuminances, with very large variability below some 125 Tds. The HR_{index} captures both the subject's best color threshold, as represented by the parameter T_o (see Appendix A), as well as the rate of increase in color threshold with decreasing retinal illuminance. The choice of the low integration limit was constrained by the need to have an accurate prediction of the subject's threshold at the lowest effective retinal illuminances measured, with several values in the range of 20 and 30 Tds (Fig. 4). 25 Tds was therefore selected as the lower integration limit. The upper integration limit was selected as 900 Tds simply because the rate of decrease in thresholds above this limit is very small. Any higher value would overrepresent the contribution the parameter T_o makes to the area under the subject's curve and this, in turn, would reduce the relative contribution the higher thresholds, measured at lower retinal illuminances, make to the area under the subject's curve. Figure 5 shows both RG as well as YB thresholds and the corresponding

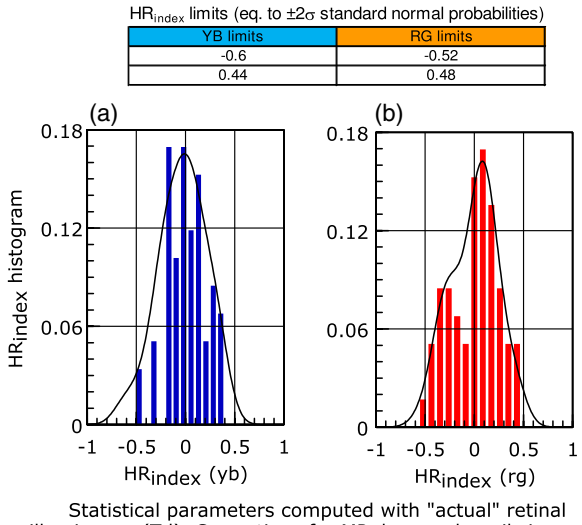

Fig. 6. (Color online) Frequency distribution of HR_{index} values within the normal group ($N = 55$) were computed for both YB and RG thresholds and are shown together with the corresponding, best-fit probability density functions. The 95% limits were estimated from the fitted functions shown by computing the cumulative probability values that correspond to $\pm 2\sigma$ limits on the normal distribution.

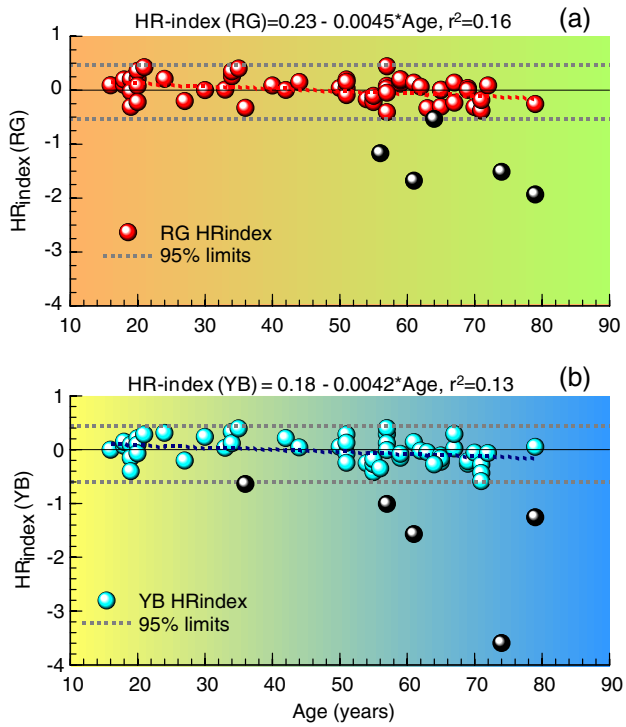

Fig. 7. (Color online) HR_{index} values plotted as a function of age for the 60 subjects investigated in this study. The $\pm 2\sigma$ limits are shown as dotted curves. Age appears to have only a small effect on the HR_{index} for both RG and YB color vision, for subjects falling within the $\pm 2\sigma$ limits ($r^2 = 0.16$ and $r^2 = 0.13$, respectively, and $p < 0.001$). The linear regression lines indicated above each graph are based only on the subjects who had $HR_{indices}$ within the specified limits. Seven subjects (~11%) produced HR_{index} values that fall below the -2σ limit; two subjects failed only RG and two others only YB. The remaining three subjects failed both RG and YB tests.

HR_{index} values. Positive values indicate better than average performance. Figure 5(b) shows data for an 18-year-old subject with an HR_{index} of 0.2, caused largely by lower than average thresholds at higher retinal illuminances. Figure 5(a) shows a 51-year-old subject with slightly larger than average thresholds at high retinal illuminances and an index of 0.13. The positive HR_{index} for YB thresholds reflects the subject's smaller than average thresholds at low retinal illuminances, in spite of his age. The remaining graphs show negative HR_{index} values caused either by higher overall thresholds [Figs. 5(c), (d) and (f)], or a rapid increase in YB thresholds at lower retinal illuminances [Fig. 5(e)] with normal thresholds at high retinal illuminances. The ratio of the area under of the curve fitted to the group data and that of a single subject provides a measure of overall chromatic sensitivity:

$$\frac{A_{group}}{A_S} = \frac{1}{1 + HR_{index}}. \quad (5)$$

The $\pm 2\sigma$ limits shown in Fig. 6 convert to a threefold variation in RG and a 3.6-fold variation in YB chromatic sensitivity. As an overall measure of chromatic sensitivity over a range of light levels in the high mesopic and the photopic range, the computed variation in chromatic sensitivity for the normal group is relatively small. The HR_{index} shows only a small correlation with age within the normal group up to 79 years of age. The inevitable conclusion of these findings is that

normal aging has only a small effect on overall chromatic sensitivity when examined in the photopic and high mesopic range. A 75-year-old subject can, therefore, match the color vision performance of a 20-year-old subject, provided retinal illuminance is adjusted for pupil size and additionally for prereceptoral absorption of light by the lens and the MP, in the case of YB color discrimination.

Although the great majority of subjects stay well above the computed -2σ limit, approximately 11% fall below this limit (Fig. 7). It is of interest to discuss the significance of this finding in relation to the earliest detection of retinal disease. The subjects identified as abnormal do not present any clinically recognizable signs of disease and are asymptomatic. According to routine optometric/ophthalmological examination, these subjects would be designated as "clinically normal." As pointed out recently [45], it is important to have sensitive and objective criteria that experts can use to decide whether small changes in vision in older subjects can be attributed entirely to normal aging or reflect early signs of retinal pathology. Since visual performance at lower light levels is more compromised in patients with early signs of ocular pathology [4] and the effects of mild acute hypoxia in normal subjects are also more detectable at lower light levels [5,6,46,47], it may be desirable to assess changes in visual performance over a range of light levels and not just photopic vision under optimum conditions. Indeed, if the HR_{index} does reflect retinal susceptibility to disease, and hence hypoxia, imposed mild systemic hypoxia may exacerbate the loss of chromatic sensitivity as reflected in the HR_{index}, more so in older subjects and/or those with more severe damage to the retina. If subjects who are clinically normal, but have HR_{index} values well below -2σ, are more likely to develop retinal disease, then they might also exhibit more severe hypoxic impairment of color vision than age controls, with HR_{index} values within the normal range. Further studies are needed to test these hypotheses. Assessments carried out at even lower light levels may not be clinically as valuable since variability in results is also increased [40]. The light levels employed in the HR test may, therefore, represent a good compromise by assessing photopic and high mesopic color vision and, hence, avoiding increased variability and variation in rod–cone interaction effects that are to be expected at even lower light levels.

5. CONCLUSIONS

The HR_{index} captures the loss of chromatic sensitivity in the photopic and upper mesopic range. After correction for changes in retinal illuminance, the HR_{index} shows only a small correlation with age ($r^2 \sim 0.1$) for both RG and YB color vision. The normal range of HR_{index} values is tightly distributed around zero, with positive values indicating better than average performance. The preliminary findings in the small group of asymptomatic and clinically normal subjects examined in this study show that ~11% of the population exhibit HR_{index} values outside the normal range. There is also a high probability that subjects that fall outside the normal range exhibit both RG and YB loss.

All subjects tested and identified clinically with some form of retinal disease, such as age-related macular degeneration and diabetic retinopathy, exhibited grossly abnormal indices for both RG and YB color vision.

The HR_{index} index captures in a single parameter the subject's chromatic sensitivity and how this changes with light level, irrespective of age. A longitudinal study is needed to establish whether the subjects identified as outside the normal range according to their HR_{index} values go on to develop clinically recognizable retinal or systemic disease.

The preliminary findings reported here suggest that the new HR_{index} yields information about the overall health of the retina and may be useful to detect early, preclinical signs of retinal or systemic diseases that affect vision.

The approach developed here can also be applied to study how sensitivity to rapid flicker detection or contrast sensitivity for letter recognition worsen with decreasing light level in older subjects. Capturing the signals of the dark may provide the methodology needed to separate the effects of normal aging from disease. It remains to be established which of these aspects of visual performance is most informative and appropriate to describe the effects of normal aging and to detect the earliest signs of disease.

APPENDIX A: COMPUTATION OF HR_{INDEX}

The change in color detection thresholds as a function of retinal illuminance (Fig. 4) can be fitted well by an equation of the form

$$T = k \times E^{-a} + T_o, \tag{A1}$$

where T is the measured color threshold, E is the retinal illuminance, T_o is the asymptotic threshold (i.e., the subject's expected, best threshold at a high retinal illuminance) [19], and k and α are constants. The best-fit parameters k, α, and T_o were computed for the group of subjects and the fitted curves for RG and YB for the group thresholds are shown in Figs. 4(a) and 4(b), respectively.

Equation (A1) was then integrated to compute the area under the curve for RG and YB thresholds [Figs. 4(a) and 4(b), insets]:

$$A = \int_{25}^{900} (k \times E^{-a} + T_o)\mathrm{d}E = \left[\frac{k}{(1-a)} \times E^{(1-a)} + T_o E\right]_{25}^{900}. \tag{A2}$$

The fitted curve for the group was used as a reference against which every subject was then compared. Equations (A1) and (A2) were then used separately to compute the subject-specific threshold dependence on retinal illuminance and the corresponding HR_{index}. To improve the stability of the nonlinear fitting algorithm, a fifth point was added to the dataset to correspond to twice the subject's largest retinal illuminance. The threshold for the fifth point was fixed as 85% of the threshold measured at the highest retinal illuminance. This chosen reduction in threshold is justified since the doubling of the screen luminance from 26 to 65 cd/m^2 causes a similar reduction in mean threshold for the group data.

The HR_{index} was defined as the difference between the area under the subject's threshold curve (A_S) and the corresponding area computed for the normal group (A_{group}):

$$HR_{index} = 1 - A_s/A_{group}. \tag{A3}$$

A positive HR_{index} indicates performance better than the average normal subject. Correspondingly, a negative value indicates color detection performance that falls below that expected for the average normal subject. Examples of RG and YB thresholds, measured in subjects of varying age, together with the corresponding best-fit curves, are shown in Fig. 5. The limits listed in Fig. 6 represent HR_{index} values for which the cumulative probability computed from the fitted functions (shown in Fig. 6) corresponds to the $\pm 2\sigma$ limits on the normal probability distribution curve.

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