Flicker Sensitivity in Normal Aging—Monocular Tests of Retinal Function at Photopic and Mesopic Light Levels

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Purpose. Aging can affect many aspects of visual performance. In general, the effects become more significant in those older than 40 to 50 years, with increased intersubject variability and stronger dependence on ambient illumination. This study aimed to establish how healthy aging of the retina affects the detection of 15-Hz flicker under photopic and mesopic lighting.

Methods. We investigated 71 participants aged 20 to 75 years. Thresholds were measured for detection of 15-Hz flicker at the fovea (0°) and at an eccentricity of 4° in each of the four quadrants. The background luminance ranged from 0.6 to 60 cd/m^2 and pupil size was measured continuously. Participants were excluded if they had signs/history of ocular disease, substantial interocular differences in flicker thresholds, or were unable to detect 100% flicker modulation in the high mesopic range.

Results. Mesopic and photopic flicker thresholds were used to calculate an index, the health of the retina index, to determine the limits of flicker sensitivity in healthy aging. Log flicker thresholds changed bilinearly with age; they remained stable until 40 to 50 years, with a linear decline with increasing age. This bilinear pattern of the change in flicker thresholds with age is consistent across photopic and mesopic light levels.

Conclusions. The health of the retina index captures the lowest threshold, usually obtained under photopic conditions, as well as the loss of flicker sensitivity with decreasing light level. The established limits of healthy aging may benefit from future studies in patients with ocular hypertension and/or glaucoma that are known to experience loss of flicker sensitivity.

Keywords: aging, flicker, mesopic, monocular vision, photopic

It is generally recognized that older people have greater difficulty performing visual tasks at low light levels. The effects of low light level and aging have been explored in spatial and color vision studies[1–3]; however, less is known about the effects of aging on temporal aspects of vision at low luminances. The aim of this study is to establish normal limits for the loss of 15-Hz flicker sensitivity with increasing age, taking into account performance at decreasing light levels.

The measurement of flicker sensitivity to assess retinal function is useful clinically in a number of ways. Unlike spatial contrast sensitivity, temporal contrast sensitivity is affected less by scattered light or refractive error. This means that tests using flickering stimuli can provide a sensitive measure that describes the processing of temporal signals in the aging retina, relatively independent of age-related changes to the optics of the eye.[4–12] However, temporal modulation sensitivity declines with decreasing retinal illuminance,[13] which tends to be lower in older people due to pupil miosis,[14,15] and few flicker sensitivity studies control or correct for varying retinal illuminance.

Previous research has consistently found that older people lose sensitivity at high temporal frequencies manifesting as a decline in critical flicker frequency,[4,16] or a decline in modulation sensitivity at mid- to high temporal frequencies.[5–8,17–21] Flicker thresholds measured at a high temporal frequency, but well within the temporal frequency envelope for normal vision, makes the visual assessment very sensitive to age-related changes, with the added advantage of being quicker to assess than other measures that involve the entire temporal contrast sensitivity function (CSF). The latter can be time consuming to perform and clinically impractical.

Reductions in high frequency sensitivity have been observed largely in cases of retinal disease such as AMD,[17,22–26] diabetes,[17] and glaucoma,[27] and loss of rapid flicker sensitivity has also been observed under conditions of mild hypoxia.[28] The loss of flicker sensitivity can be used to separate eyes at risk of AMD from normal eyes[25] and to predict the future progression of the disease.[22,23,29] Tests characterizing the loss of flicker sensitivity could be better indicators of disease progression than the predicted loss based on signs derived from clinical examination of the fundus.[6,22,23]

A number of reasons for the loss of flicker sensitivity in aging and disease have been explored. Both a shift in the peak of the temporal CSF and an overall reduction in sensitivity could produce a decrease in modulation sensitivity at a particular temporal frequency.[5,7] The loss of modulation sensitivity with age is unlikely to be due to age-related changes in the temporal characteristics of neurons, as the timings of peaks in the impulse response function are relatively stable until approximately 80 years[6,30] and the timing of multifocal ERG parameters are stable with age in the central vision (5°), although the amplitude of the response decreases.[31] Other research has established that sensitivity losses in older participants are beyond what one could predict based on reduced retinal illuminance caused by pupil miosis.[16,19] Based on such observations, it has been proposed that the reduction of sensitivity in aging and disease is due to losses of photoreceptors, retinal ganglion cells, or the

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effects of hypoxia caused by overall reduction in blood supply to the retina.[17,24,26,32,33]

The loss of color, acuity, and contrast sensitivity in aging and disease has been investigated as a function of luminance in several studies and found to be more pronounced at lower light levels.[1–3,34,35] Similarly, it may be reasonable to expect that flicker sensitivity would be impaired in older people to a greater extent under low rather than high levels of retinal illuminance. One might therefore expect that measuring flicker sensitivity in the mesopic range may be more effective in separating changes due to healthy aging from age-related disease. In this context, healthy aging of vision describes gradual changes in visual function that do not cause severe loss of any aspect of vision. This kind of label also implies the absence of any clinically recognized disease process that normally leads to severe degradation or complete loss of visual function.

Studies carried out at photopic light levels have found a greater loss of sensitivity for older people outside the fovea and in the superior visual field,[17,20,36] and that people with AMD and diabetes are often outside the normal limits of sensitivity in central vision (4°).[17] It may therefore be useful to additionally quantify the effects of aging on flicker sensitivity at low luminances at the parafovea. In general, the nasal superior field has been reported to have better sensitivity than the temporal inferior field in the healthy eye.[37] However, very few studies have accounted for the size dependence of flicker thresholds with increasing eccentricity. This is important because when stimulus size is scaled to account for the decrease in ganglion cell density with increasing eccentricity, there is virtually no loss of modulation sensitivity,[38] meaning that perhaps temporal sensitivity losses at peripheral locations could in fact be caused by inappropriate spatial scaling that also accounts for loss of spatial contrast sensitivity.

This study aimed to determine whether flicker sensitivity declines with age at the fovea and parafovea by calculating the health of the retina index (HR_{index}) as a measure of integrated loss of sensitivity to flicker as a function of light level at five discrete retinal locations within the central 8°.

METHODS

Participants

Participants were recruited through the City University Eye Clinic. All participants had undergone a detailed ophthalmic assessment to detect severe loss of visual function or the presence of clinically recognized disease. The tests included measurement of visual acuity, refraction, binocular vision assessment, pupil reactions, slit-lamp assessment of the anterior eye and indirect ophthalmoscopy of the macula, optic nerve head, and peripheral retina.

The study was approved by the City University Research and Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained for every participant.

Flicker-*Plus* Test

The modulation sensitivity of each participant was assessed using the Flicker-*Plus* test, which is based largely on observations made in an earlier study of loss of rapid flicker sensitivity in older subjects when small stimuli are involved.[39] Stimuli were presented on a high resolution, 20-in cathode ray tube monitor (Multisync Diamondtron, Model FR2141 SB; NEC Display Solutions; Tokyo, Japan), using a 10-bit graphics card (Elsa Gloria XL; Elsa Electronics, New Delhi, India) with 1600 × 1200 resolution at a frame rate of 120 Hz. The monitor was calibrated automatically with a luminance meter (LMT 1009; LMT Lichtmesstechnik GmbH Berlin, Berlin, Germany) and bespoke software (LUMCAL; City Occupational, Ltd., London, UK).

Participants viewed the display from 1.4 m. A fixation cross and four oblique guides were displayed to maintain central fixation and to aid accommodation. The background was composed of only mid- to long wavelength light (CIE $x = 0.413$, $y = 0.507$) in order to minimize variations in absorption of short wavelength light by the crystalline lens[40] and the macular pigment.

The psychophysical method of measuring flicker thresholds was based on a five-alternative forced-choice (AFC) procedure designed around the five locations of the stimulus. The subject had to indicate the location of stimulus presentation by pressing one of five buttons arranged to simulate the geometry of the screen. A separate button indicated that the subject was totally unaware of any stimulus. When this button was pressed, the program allocated the subject's response randomly to one of the five buttons. Five randomly interleaved staircases with variable step sizes were employed and these corresponded to the five stimulus locations: 0° eccentricity or at one of four parafoveal locations, 4° away from fixation in the inferior nasal, superior nasal, inferior temporal, or superior temporal visual field. The stimulus was a flickering uniform disc subtending 20 min arc at the fovea and 30 min arc at the parafoveal locations. Stimuli were presented for 334 ms at a temporal frequency of 15 Hz (five cycles), as this frequency is well within the normal envelope and has been shown to be sensitive to age-related changes.[6] The temporal waveform of the stimulus was sinusoidal with respect to the luminance of the background. The temporal modulation depth was expressed as Michaelson contrast. The mean luminance of the flickering stimulus remained constant and equal to that of the uniform background. When flicker detection was absent, the participants were unaware of anything being presented anywhere in the visual field. Flicker therefore appears to be the most sensitive visual attribute of the disc stimulus. Each staircase employed 10 reversals using a 2-down, 1-up procedure and the threshold was estimated by averaging the last 6 reversals.[41,42] The staircase algorithm requires two consecutive correct responses at a given stimulus location during the random sequence presentation before a reversal occurs and the stimulus contrast is reduced for the following presentation. In the absence of any signal, the probability of two sequential correct responses is 1/25. This approach is statistically efficient since five locations are measured in the same test and the chance probability of a correct response is small. The step change in the staircase procedure decreased after every reversal according to an exponential function. The starting value for the staircase was also increased from 6% to 60% with decreasing background luminance to minimize the number of steps needed to reach the first reversal. The latest version of the Flicker-*Plus* test supports many more, quadrant-specific locations using the same 5-AFC procedure, but the time needed to complete the test increases with the number of locations and too many locations, although of interest perimetrically, make the test clinically impractical. When five stimulus locations are employed, the subjects take approximately 7 minutes to complete the test. Following a short practice session, the participants were then tested at background luminances of: 0.6, 1.87, 3.75, 7.5, and 60 cd/m^2. A spectrally calibrated neutral density filter was used to produce the lowest background luminance (as seen by the subject) while maintaining an adequate screen luminance, which was needed to ensure accurate reproduction of flicker modulation. For each light level, the participants viewed the screen binocularly, followed by monocular presentations (RE or LE was alternated between participants). This provided comfortable and natural viewing conditions at the start of each light level and reduced initial learning effects on the monocular conditions for this part of the study without introducing significant order effects.[43] The binocular flicker thresholds will be reported in a subsequent paper. The nontested eye was covered with an opaque, infrared transmitting filter allowing for iris illumination and the measurement of pupil size. In order to reduce the cumulative effects of fatigue, participants were tested on the lowest screen luminance first, after verification that they could clearly see the fixation stimulus, followed by the next higher screen luminance, meaning that less time was required for adaptation between luminance levels than using a randomized procedure. Since detection of 15-Hz flicker relies mostly on M and L cone signals, the initial adaption time was limited to 5 minutes before the first test commenced. The following tests used only 3 minutes adaptation time since higher luminances were involved. The test/retest variability varies from subject to subject and with light level, with typical values (i.e., coefficient of variation) in the range 10% and 20%.

Pupil Measurements and Retinal Illuminance

Pupil diameter was measured continuously during the Flicker-*Plus* tests using the P_SCAN system.[44] An infrared light source was mounted below the camera to provide illumination of the iris. The pupil of the left eye was imaged using an infrared sensitive charge-coupled device camera and the pupil images were processed using computing language functions (MATLAB; MathWorks, Inc., Natick, MA, USA). Thresholding and edge detection techniques were used to locate the pupil boundary, allowing the pupil diameter to be computed with a resolution better than 0.02 mm. Pupil measurements were taken approximately three times per second. Measurements within 1 SD of the mean were averaged to produce a mean pupil size for each luminance and viewing condition.

Retinal illuminance (E) was calculated in trolands (Td) as $E = L \times PA$, where L is the screen luminance in cd/m^2 and PA is the pupil area in millimeters squared. Estimates of retinal illuminance were obtained separately for binocular and monocular viewing conditions because of expected differences in pupil size.[45]

Modulation Sensitivity as a Function of Retinal Illuminance

Modulation threshold data for each individual across different retinal illuminances were fitted with the following empirical, nonlinear function:

$$FMT = a \times E^{-b} + c, \qquad (1)$$

where FMT is the flicker modulation threshold, a and b are constants, E is retinal illuminance, and c is the subject-specific, asymptote threshold that is normally achieved at high light levels. To improve the stability of the nonlinear fitting algorithm, a pseudopoint was added at 8000 Td which corresponded to 80% of the participant's lowest threshold as shown in earlier studies.[1]

Calculating the HR$_{\text{index}}$ for Flicker Sensitivity

For each participant at each eccentricity, the area (A_p) under the measured FMT versus retinal illuminance curve was calculated between the limits of 900 and 25 Td according to Equation 2. The health of the retina index represents the ratio between the area under the participant's threshold curve (A_p) and the area for the group (A_{group}), as shown in Equation 3; A_{group} represents the mean area under the curve for the 10 participants nearest in age to A_p. For each participant, the HR$_{\text{index}}$ was calculated at the fovea and then separately at the parafovea, using the combined parafoveal measurements. No significant difference was found within this normal group between the areas under the curve at the four peripheral locations. A large, positive HR$_{\text{index}}$ value indicates better performance in relation to the 10 participants of the nearest age, and a negative HR$_{\text{index}}$ value indicates worse performance.

$$A_p = \int_{25}^{900} (a \times E^{-b} + c)dE = \left[\frac{a}{1-b} \times E^{(1-b)} + c \times E\right]_{25}^{900} \qquad (2)$$

$$HR_{index} = 1 - \frac{A_p}{A_{group}} \qquad (3)$$

Identifying Participants With Significantly Elevated Thresholds

The aim was to determine the mean and 95% confidence limits of the HR$_{\text{index}}$ for a normal population. Measures were therefore taken to exclude participants with significantly elevated thresholds that may not reflect normal aging. First, participants with clinical signs of disease such as the presence of drusen or abnormal fundus appearance were excluded.

The second filter excluded participants who could not detect flicker in the high mesopic range. Participants who could not detect flicker of 100% modulation at any retinal illuminance above 1.6 log Td in the high mesopic range were excluded. This was because each of these participants was unable to provide measurable thresholds below 1.6 log Td and therefore their thresholds for the entire mesopic range remained unknown.

Participants were also excluded if they exhibited significant differences in modulation sensitivity between the two eyes at corresponding loci. The justification for the introduction of this filter is based on empirical observations that suggest that in most cases, retinal diseases tend to affect the two eyes differently. The formula described in Equation 4 was used to identify participants with substantial interocular differences (IODs) in modulation sensitivity:

$$\text{IOD} = \frac{|A_{LE} - A_{RE}|}{A_{Bettereye}}, \qquad (4)$$

where A_{LE} is the area under the curve for the particular eccentricity for the left eye and A_{RE} is the area under the curve for the corresponding eccentricity in the right eye. If a participant was excluded based on an IOD outside the 95% limits at a particular eccentricity, all of his/her results were also excluded. The typical upper statistical limits for IODs corresponded to ~30% variation at the fovea and ~23% in the periphery.

Finally, when calculating the HR$_{\text{index}}$ using the moving average method, if the area under the curve of the individual exceeded the 95% limits as computed for the 10 subjects, the participant was excluded from the study.

Statistical Analysis

Customized software was used to fit the nonlinear function describing the variation of modulation thresholds with retinal illuminance, compute the 95% limits of value distributions, and statistical analysis (MathWorks, Inc.).

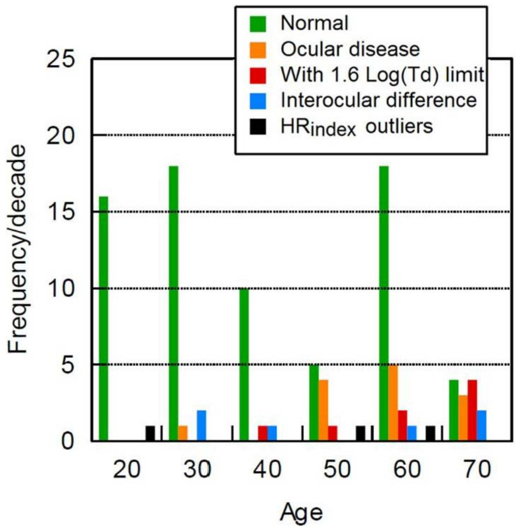

Figure 1. Age distribution and filtering outcomes for the subjects who participated in the study. Normal subjects ($n = 71$); ocular disease ($n = 13$); absence of flicker detection in the high mesopic range ($n = 8$); presence of interocular differences in flicker modulation thresholds outside the 95% limits ($n = 6$); and HR_{index} outliers ($n = 3$).

Results

Included and Excluded Participants

The age distribution of the subjects recruited to the study and the filtering outcomes are summarized in Figure 1, showing 71 included participants (39 females, 32 males, mean age = 44.7, visual acuity = –0.04, sphere = –1.24, cylinder = –0.64) out of 101 who were recruited. None of the subjects was aphakic, but 3 out of the 71 participants had intraocular lenses. In total, 30 (29.7%) participants were excluded from the analysis: 13 (12.9%) presented with abnormal ocular conditions, eight (7.9%) were excluded based on the absence of flicker detection in the high mesopic range, six (5.9%) had interocular threshold differences outside the 95% limits, and three (3.0%) were HR_{index} outliers. The health of the retina index for each subject was calculated with respect to the mean area under the FMT curve estimated for 10 subjects with the nearest age. This "moving average" method accounts for changes in HR_{index} in healthy aging. If the subject's area under the FMT versus retinal illuminance curve was outside the 95% limits, the subject was classified as an outlier and not included in the study ($n = 3$, as noted above).

HR_{index} for Monocular Flicker Thresholds

Flicker modulation thresholds measured at the fovea and the parafovea are shown in Figure 2 for all participants who met the inclusion criteria as a function of retinal illuminance. Individual data points are shown as black symbols together with the best-fit curves (Equation 1) and the 95% confidence limits. The foveal results (Fig. 2A) show data for both eyes since there were no significant differences (t-test) between the areas under the curves measured in the two eyes ($t[140] = 0.026$, $P = 0.979$). Similarly, results for all parafoveal eccentricities (Fig. 2B) for each eye were plotted together because no significant differences were found between eyes or parafoveal eccentricities in the area under the curve, found with a repeated measures ANOVA (right eye versus left eye: $F[1,564] = 2.14$, manifest spherical equivalent (MSE) = 6.62e + 07, $P = 0.14$; nasal versus temporal locations: $F(1,564) = 0.19$, MSE = 5.94e + 06, $P = 0.66$; superior versus inferior locations: $F[1,564] = 2.85$, MSE = 3.09e + 07, $P = 0.09$). It is clear from Figure 1 that mainly participants aged older than 50 years could not detect 100% modulation flicker in the high mesopic range and below. For comparison, Figures 2C and 2D show FMTs for participants aged younger than 50 years.

Figure 3 shows the HR_{index} as a function of age at the fovea and at the peripheral locations. When using the moving average method, there is no change in the mean HR_{index} with age. When the participant's area under the curve fell outside the 95% limits of the window of 10 participants of nearest age, the participant was not included in the study. Three participants failed this criterion and were therefore excluded. Figure 4 shows examples of FMT data for two normal subjects to illustrate how changes in flicker sensitivity with light level determine the corresponding HR_{index} values. The 59-year-old subject shows higher sensitivity at lower retinal illuminance, as reflected by the positive HR_{index} values, in spite of having flicker thresholds that match well the mean group data at the highest retinal illuminance. The 62-year-old subject, on the other hand, shows the lowest thresholds at the fovea at a high retinal illuminance, but a significant loss of sensitivity at lower light levels which results in a negative HR_{index}. His results in the parafovea reveal poorer 15-Hz flicker sensitivity over the whole range of light levels. This decreased parafoveal sensitivity over the whole range of retinal illuminances is captured well by the much larger, parafoveal, negative HR_{index}.

Figure 5 shows how modulation thresholds change at the fovea and parafovea for five retinal illuminance levels as a function of age. Points were derived from curves fitted to each individual's data and averaged across eyes at the fovea and eccentricities and eyes at the parafovea. Bilinear fits were required to describe the relative stability of log FMTs in participants aged younger than 40 years and in contrast, the increasing FMTs in participants aged older than 40 years. The results show the expected reduction in flicker sensitivity with decreasing retinal illuminance, but at a constant retinal illuminance and age younger than 40 years, 15-Hz flicker sensitivity shows little or no dependence on age. In individuals older than 40 years, foveal flicker thresholds increase linearly with age and the rate of increase becomes greater at higher retinal illuminance (i.e., 0.16 log units increase per decade at 900 Td, compared to 0.04 log units at 25 Td). To test for differences in the gradient of the fits with light level and eccentricity, two analyses of covariance were carried out to examine the straight lines fitted to the two age groups. For the younger participants (aged younger than 40 years), there was no change in the FMTs with age ($F[1,31] = 0.832$, $P = 0.369$); however, for the older participants (aged 40 years and older), FMTs did increase with age ($F[1,35] = 21.991$, $P < 0.001$). Furthermore, the lack of change in FMTs with age for younger participants was stable across both eccentricities ($F[31,1] = 0.010$, $P = 0.920$) and light level ($F[1,31] = 0.00$, $P = 0.999$). For older people, the change in FMTs was significantly different between the eccentricities ($F[1,35] = 5.987$, $P < 0.05$), as the fovea shows a steeper increase in log FMTs with age (Fig. 5). Furthermore, there is a significant difference in gradient at different light levels, with a steeper increase in log FMT with age at higher light levels ($F[1,35] = 32.497$, $P < 0.001$).

Finally, Figure 5 also shows the 95% limits for both the younger and older participants. The width of these limits is similar for older and younger participants at lower levels of retinal illuminance. However, at higher levels of retinal illuminance, the width of the limits is wider for the older participants, suggesting there is greater individual variability in the log FMTs of older participants at higher retinal illuminances.

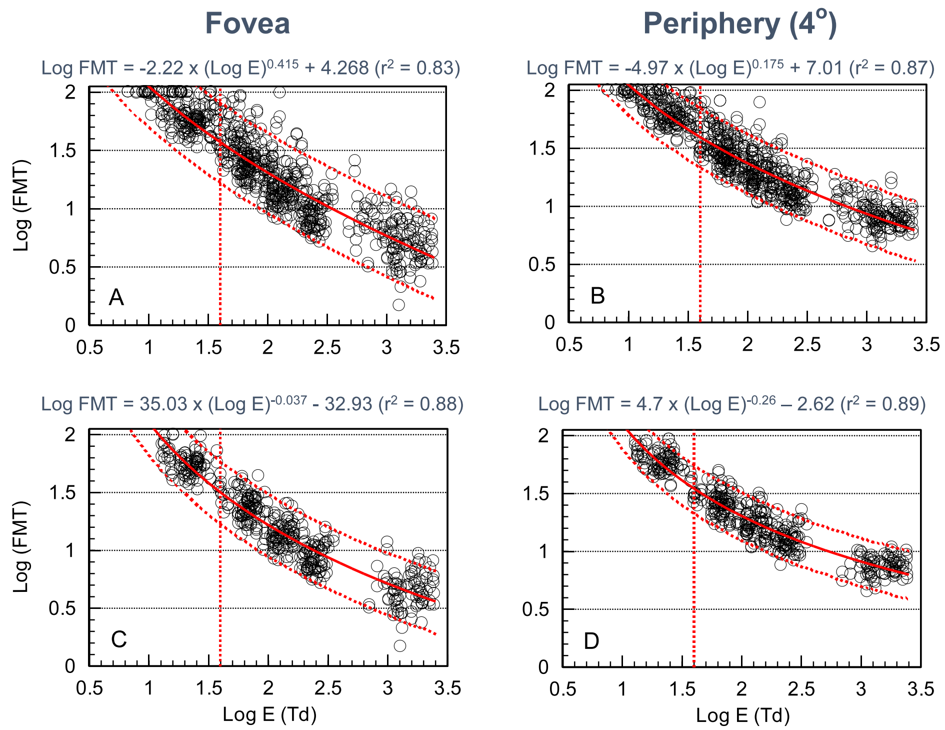

Figure 2. Log FMT plotted as a function of each participant's retinal illuminance measured for each of the five display luminances investigated. Flicker modulation threshold is measured as percentage modulation and the retinal illuminance is measured in trolands. The *solid lines* show the best-fit functions to the data (as indicated above each graph). The 95% confidence intervals (computed using the "predint" MATLAB function) are shown as *dotted lines*. (**A**) Shows thresholds measured at the fovea for the 71 participants included in the study (aged 20–75 years). The foveal data show two points for each participant, one for each eye. (**B**) Flicker modulation thresholds measured in the parafoveal retina for the same participants. The peripheral data also show two points for each participant but each point represents the average of the thresholds measured at the four eccentricities tested in each eye. (**C**, **D**) Show the same data as (**A**) and (**B**), respectively, but only for participants aged younger than 50 years.

Discussion

These findings show that 15-Hz flicker sensitivity declines with decreasing retinal illuminance (Fig. 2) and age (Fig. 5), in agreement with results from other similar studies.[5–8,19–21] Flicker studies in patients with diseases of the retina, such as glaucoma and hypertension, also reveal loss of flicker sensitivity.[27,46–49] There is little doubt that visual tests based on the measurement of flicker thresholds offer great promise as early screening tools for retinal and optic nerve disease. It remains, however, difficult to compare results from such studies since flicker sensitivity is strongly affected by stimulus size, temporal frequency, and retinal illuminance and many earlier studies employed a range of stimulus parameters and eccentricities. In order to make the use of flicker measurements more useful in clinical applications, it is important to establish response templates that describe the loss of flicker sensitivity in healthy aging under a comprehensive but simplified set of stimulus conditions. The new approach developed here is based on the use of relatively small stimuli over a range of light levels and a temporal frequency of 15 Hz, which has been shown to be most effective in patients with glaucoma or hypertension.[47,48] The five stimulus locations tested yield flicker thresholds at the fovea and in each of the four quadrants. The choice of these parameters reveals significant loss of flicker sensitivity in the mesopic range in a

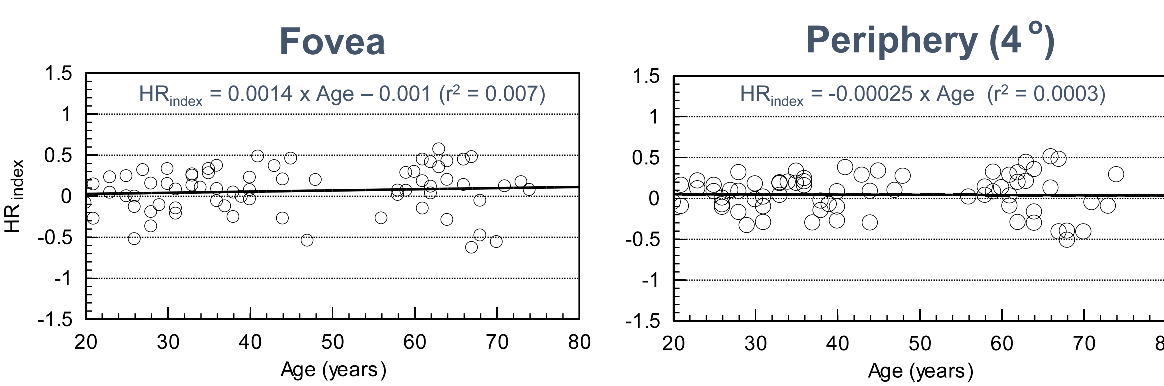

Figure 3. Values of HR_{index} calculated for the foveal and parafoveal data using a "moving average" method that allows for the effects of normal aging. The area under the FMT curve for each participant is compared with the mean for the 10 participants of nearest age and forms the basis for the calculation of the HR_{index} (Equation 3).

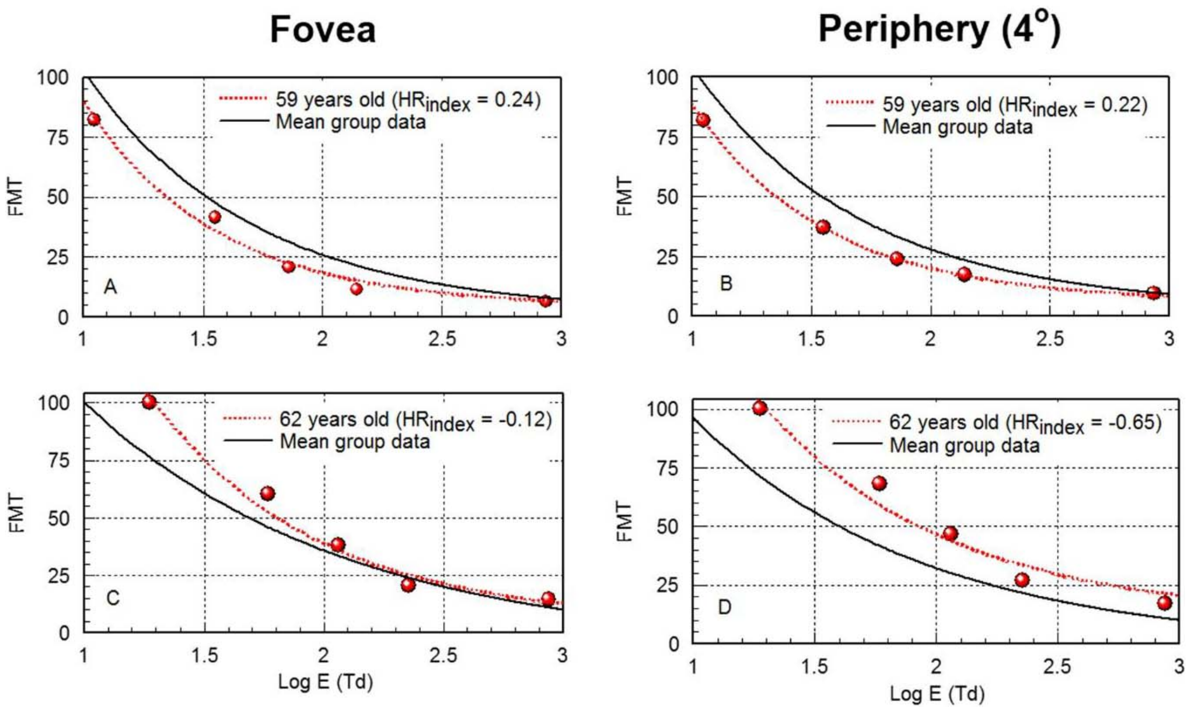

FIGURE 4. Examples of foveal and parafoveal changes in FMTs with log retinal illuminance and the corresponding HR_{index} values for two normal participants, aged 59 and 62 years. The mean curve for the 10 subjects nearest in age is shown as *solid black lines*.

small number of older subjects that may or may not reflect changes that can be attributed to normal aging. In the absence of additional information, we have taken the view that severe loss of flicker sensitivity at low light levels cannot be attributed entirely to healthy aging. The reasons for this severe loss remain unknown and may require further studies. Those unable to detect flicker at 100% modulation (~8% of participants) at lower light levels with complete absence of flicker detection below 1.6 log Td, were not therefore included in the study. These participants were unable to provide measurable thresholds in the mesopic range, although they all passed the screening tests and were classed as clinically normal. Since the flicker modulation technique employed generates only time-averaged equiluminant stimuli, the method does not allow estimation of flicker sensitivity that would require more than 100% modulation. For reasons that are not clear from this study, the 8% of the older subjects that cannot detect 15-Hz flicker at 100% modulation have extremely low sensitivity to rapid flicker that cannot be considered the norm in healthy aging. Indeed, the inclusion of these subjects within the data set would have made the estimation of norms incalculable. A future, longitudinal study would be needed to determine whether those with elevated thresholds or complete absence of flicker sensitivity in the mesopic range go on to develop recognizable, preclinical retinal changes that at a later stage can be detected by standard ophthalmologic tests.

In addition to the choice of stimulus size and temporal frequency which increase the sensitivity of the test at low light levels, the choice of test parameters also minimized the effects of interparticipant variation in the absorption of short wavelength light by the lens and the macular pigment. It also produced individual measures of retinal illuminance to account for differences in pupil size. When flicker measurements can be carried out over a range of light levels, the participants' sensitivity to 15-Hz flicker can be captured by a single number: the HR_{index} (Figs. 3, 4). Age reduces flicker sensitivity under both mesopic and photopic conditions (Fig. 5) and this makes the HR_{index} an appropriate parameter to capture 15-Hz flicker performance across these light levels (Fig. 3). Although the use of several light levels provides additional information, much is to be gained from flicker thresholds measured only at one light level. Figure 5 shows how flicker thresholds change as a function of age and retinal illuminance. The provision of bilinear fits to flicker thresholds with limits of normal performance at a number of retinal illuminances facilitates direct clinical application of these findings. For clinical use, when time is important, one may wish to restrict the test to only one light level. It remains to be established experimentally what the optimum light level is for use in patients with diseases of the retina. Flicker thresholds show only a small increase with age until the fifth decade, after which there is an accelerated linear increase when the thresholds are plotted on a log scale. This study supports the previously reported finding that the rate of the decline in flicker sensitivity with age is nonlinear (Fig. 5).[6] Furthermore, statistical analysis shows that in ages older than 40 to 50 years, the increase in log flicker thresholds with age is steeper at the fovea and at higher light levels (Fig. 5). Thresholds measured in the parafoveal locations show similar dependence on retinal illuminance and age, but the rate of increase in thresholds with increasing retinal illuminance in ages older than 40 to 50 years is somewhat reduced (i.e., 0.11 log units increase per decade at 900 Td, compared with 0.04 log units at 25 Td).

In contrast, other studies have found a greater decline in modulation sensitivity outside the fovea[17,20] when using a fixed stimulus size. The results of Figure 5 suggest that when the stimulus size is scaled to partly compensate for loss of spatial sensitivity with eccentricity, the decline with age is steeper at the fovea. Since flicker thresholds depend strongly on stimulus size, it remains of great interest to establish how stimulus size affects the measured rate of decline with age and also the effects of stimulus size at reduced retinal illuminances.

The bilinear fit to flicker thresholds, with apparent stability until age 40 to 50 years, are a somewhat different trend to the

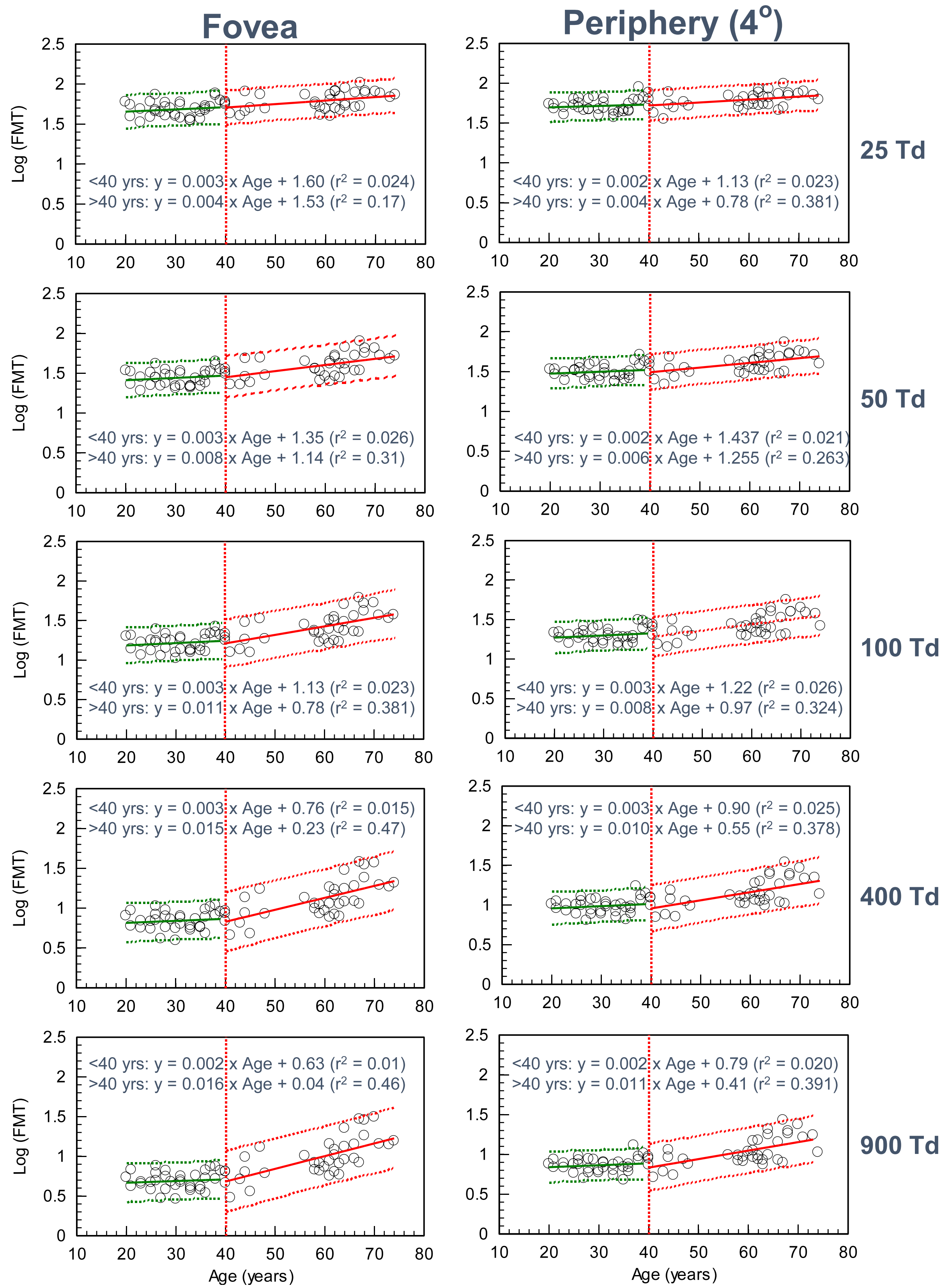

FIGURE 5. Effects of age on log FMTs derived at discrete retinal illuminance levels. Data are presented for the fovea and the parafoveal retina. The results show that when plotted on a log scale, 15-Hz flicker thresholds can be fitted well with two linear functions. The bilinear fit algorithm employed produced age break points around 40 to 50 years of age. One function was needed to describe flicker thresholds for participants below the fifth decade (when thresholds are largely independent of age) and the other to account for the more rapid increase observed in ages older than 40 to 50 years.

more linear declines observed for the aging of red-green and yellow-blue chromatic sensitivity and contrast sensitivity from young adulthood,[1,2,50] suggesting that different retinal mechanisms mediate these attributes of vision and that each is affected differently in aging. Rod photoreceptors reduce in number with age at the parafovea,[51,52] but are not likely to contribute significantly to the detection of 15-Hz flicker. Furthermore, given that our findings also reveal a greater decline in flicker thresholds at the fovea rather than parafovea, the loss of 15-Hz flicker sensitivity with age may not be related in any way to the known decline with age in rod photoreceptor density. Instead, the loss of flicker sensitivity may be due to the well-documented changes in retinal ganglion cells with increasing age,[38,52–54] and in particular to the loss of axons in the optic nerve.[55–57] Variability between observers also increased with age, as can be seen from the wider normal limits measured at the fovea in older versus younger participants (Fig. 5). This finding is not unexpected in older eyes, which are likely to exhibit greater variability in the numbers of photoreceptors and retinal ganglion cells.[52] Interestingly, when log FMTs are large, such as at lower light levels, this is no longer the case and variability in flicker sensitivity becomes relatively independent of age.

Conclusions

For the stimulus conditions employed in the Flicker-*Plus* test, normal aging reveals relatively stable thresholds for 15-Hz flicker in central vision until approximately age 40 to 50 years. The results confirm that retinal illuminance affects sensitivity to 15-Hz flicker at any age. In addition, the HR_{index} captures changes in flicker sensitivity over the whole range of light levels, which may be clinically important as visual function at low light levels is impaired in people with retinal disease[34] such as AMD,[58] glaucoma, and ocular hypertension.[59] Nevertheless, older participants will in general have decreased retinal illuminance, often caused by pupil miosis and absorption of light by the increasing optical density of the lens. The health of the retina index captures such losses and may therefore be appropriate to detect and quantify early stage loss of flicker sensitivity in patients with diseases of the retina. Although this expectation remains to be validated through further studies, the availability of age-related, normal threshold limits is a prerequisite for such studies both in terms of the HR_{index} and healthy aging.

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