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Aging of visual mechanisms

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Abstract

Optical and neural changes in the aging human visual system are reviewed in terms of factors that can influence the study of light-mediated effects on circadian physiology. All aspects of early stage visual mechanisms change continuously from the first days of life, and these changes must be understood when investigating both conscious and unconscious visual responses to light throughout the lifespan.

1. INTRODUCTION

Since Weale's (1963) classic review of *The Aging Eye*, the scientific literature has proliferated and it is now too voluminous to summarize in a single chapter. This chapter will narrow the scope by reviewing what is known about aging of early-stage mechanisms, particularly those that may be important to further investigations of intrinsically photosensitive retinal ganglion cells (ipRGCs). These changes have profound consequences for individuals and society.

At present, the proportion of the world's population that is elderly has never been higher, and it is growing. According to United Nations statistics (1998), each month, the number of individuals entering their sixth decade of life grows by 1 million. Approximately one in ten persons are in this age cohort, and it is expected to increase to one in three by the year 2150. The growth rate for octogenarians is even higher. This is due to many factors, including improved medicine, nutrition, education and safety inside and outside the work place, at least in developed countries. Undeveloped countries will experience these demographic shifts with vastly fewer resources. Yet, more resources are required for elderly individuals in housing,

transportation, and better lighting to compensate for reduced vision, susceptibility to glare and so forth to avoid accidents, falls, and loss of mobility.

In this chapter, we review optical and neural changes in the senescent visual system that are uncomplicated by manifest disease, but it is worth noting that the demographic shifts in the aging population are accompanied by more individuals experiencing visual loss than ever before. Older adults experience higher rates of visual disability and eye disease than younger individuals, in spite of older adults pursuing more visually-dependent activities (e.g., outdoor sports) than in previous generations. Research to Prevent Blindness estimates that number of blind individuals will double from 1999 to 2030. As Weale (1982) put it, “Mathematically speaking, it is permissible to say that those who prolong life promote blindness” (p. 306).

2. OPTICAL CHANGES ASSOCIATED WITH AGING

Before light can reach the retina, it must traverse the optic media which shape its intensity and spectral distribution. This is little affected by normal aging of tear film, corneal, aqueous and vitreous transmittance of the visible spectrum (~400-700 nm), but senescent changes in the iris and crystalline lens have profound changes that influence stimulation of ipRGCs.

i. Senescent Changes in the Eye Pupil

The iris, under control of dilator and sphincter muscles, adjusts the pupillary aperture according to the level of ambient illumination. The dynamic and steady-state mechanisms mediating pupillary responses involve both subcortical and geniculostriate mechanisms (Barbur, 2004) receiving inputs from rods, cones and ipRGCs (Gamlin *et al.*, 2007)

Age-related changes in pupil size begin in the early adult years; subsequently there is a monotonic decrease in pupil diameter throughout life (Kadlecová *et al.*, 1958; Lowenfeld, 1971). Because the lens is thickest in its center, smaller pupils will spectrally filter the incident light more than larger pupils. Changes in the size of the pupil not only affect the retinal illuminance, but also aspects of image formation in a manner that may be beneficial. Smaller pupils decrease the size of the blur circle on the retina which reduces the effects of spherical aberration and increases depth of focus, an important advantage in early presbyopia.

One might expect that smaller pupils in the elderly might compensate for poorer optical quality in older eyes. Indeed, Guirao *et al.* (1999) showed that the smaller pupils of older persons diminish age-related changes in the optical transfer function of the eye at low luminance levels. Although the quality of the retinal image is improved significantly with smaller pupils, sensitivity to contrast is also reduced owing to a reduction in retinal illuminance. Conversely, in younger subjects the large dilation of the pupil in the mesopic range extends the range of good contrast sensitivity to lower ambient light levels (Barbur & Stockman, 2010). In the low mesopic and the scotopic range, high retinal image quality is functionally less important because of the massive loss of retinal sensitivity to contrast, particularly in the high spatial frequency range.

Given the interplay between pupil size, aberrations and retinal illuminance, it is of interest to quantify the vision benefit of full correction of higher-order (HO) aberrations in the eye. There is little doubt that when the pupil is dilated, correction of defocus and HO aberrations in normal eyes results in best vision. This is easily demonstrated when the pupil is kept artificially large at photopic light levels, particularly in subjects with large HO aberrations, but less so

when the pupil is allowed to vary in size according to the ambient illumination (Dalimier et al., 2008). Elliott *et al.* (2009) showed that when pupil size is controlled, young and older observers benefited equally from correction of HO aberrations. As the ambient light level is reduced, the largest and most rapid increase in pupil size corresponds to the upper mesopic range (Barbur & Stockman, 2010). Further reductions in ambient illumination in this range are partly cancelled by the corresponding increase in retinal illuminance as a result of rapidly increasing pupil size. A reduced benefit of HO aberration correction can still be observed in this range, but at even lower light levels, the rapid loss of retinal sensitivity to contrast limits spatial vision with no significant benefit from correction of HO aberrations (Dalimier et al., 2008).

The visual benefit of reduced aberrations as a result of small pupils in older individuals, even at lower light levels, provides only a small compensation for the loss of contrast sensitivity. Sloane *et al.* (1988) showed that age-related changes in contrast sensitivity under photopic and mesopic light levels cannot be explained solely by differences in pupil diameter. This observation accounts, at least in part, for the significantly larger levels of ambient illumination needed to achieve adequate visual performance with increasing age.

ii. Senescent Changes in Preretinal Filters

The visible spectrum is normally limited to ~ 400-700 nm; shorter wavelengths are ultraviolet (UV) and longer wavelengths are infrared (IR). At long wavelengths, sensitivity is limited by the absorption spectrum of the rod and cone photopigments, while at short wavelengths it is reduced by the absorption of the ocular media which includes the cornea, aqueous, lens and

vitreous. Boettner and Wolter (1962) measured each of these components and it is clear that most of the absorption by the ocular media is due to the lens.

The lens of the human newborn contains molecules that absorb UV and short-wave visible light, and their numbers increase continuously over the life span. Thus, as the lens increases its thickness, there is a reduction the ability to accommodate (Charman, 2008), and there is a loss of transparency with age; in the extreme, it may form a brunescient cataract that impairs vision. Figure 1 (left) presents the ocular media density spectrum as a dashed curve. This curve represents a young adult, but it can be scaled multiplicatively for other ages. The density increases linearly from infancy to approximately 60 years of age and then accelerates linearly with a steeper slope at higher ages (reviewed by Werner, 2016). Importantly, for any given age, there are large individual differences, on the order of 1 log unit at 400 nm. In addition to substantial individual variation, at 480 nm, the peak of the melanopsin absorption spectrum (Berson, 2014), there is an expected change in optical density from ~ 0.16 to 0.36, or a change in transmission of 70-to-43%, from 20 to 60 years of age based on Pokorny *et al.* (1987).

The central retina contains an inert yellow pigment with peak density in the central fovea and a decline with retinal eccentricity. The solid curve in Figure 1 shows the density of an average observer. While it does not vary with age after early childhood, there are substantial individual differences at each age, with some observers showing little macular pigment and others having a peak density > 1.0 . This variation is related to dietary intake of carotenoids found in vegetables (Murray, 2014). This implies that short-wavelength light reaching the photoreceptors varies significantly among observers, as well as with retinal eccentricity. The combined absorption of short-wavelength light by the macular pigment and the lens can reduce

significantly the signals generated in S-cones, rods and ipRGCs and must be considered in any studies designed to investigate the functions of intrinsically photosensitive ganglion cells

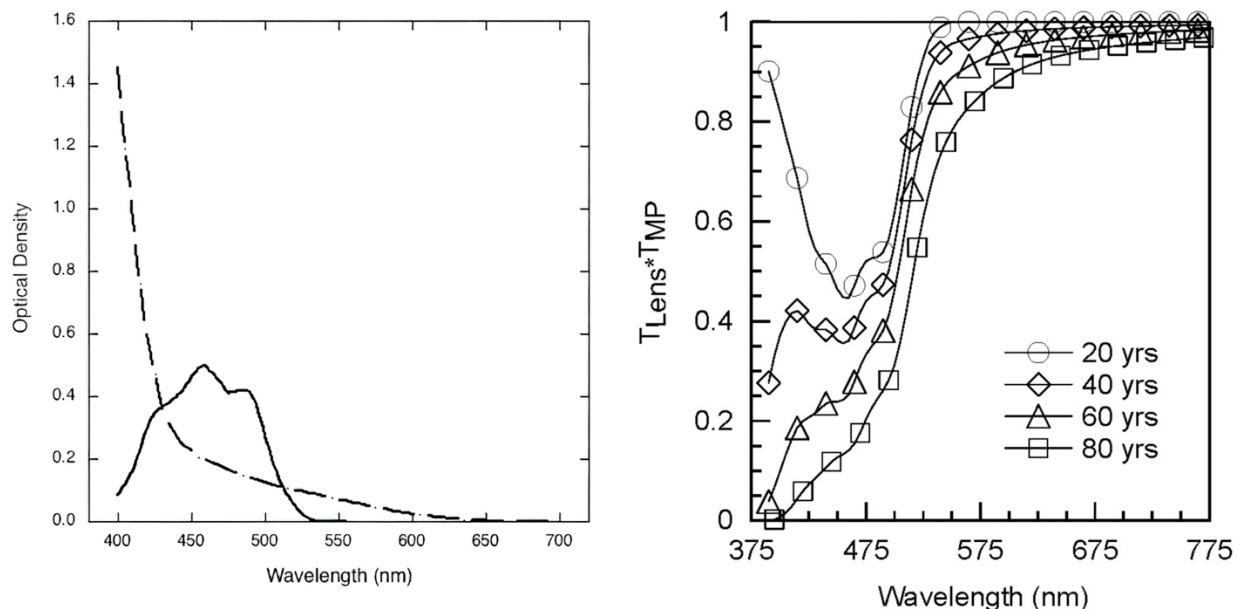


Figure 1. Left: The dashed curve shows the density spectrum of the human ocular media for a young adult (van Norren & Vos, 1974). The solid curve presents the optical density spectrum of the human macular pigment (Wyszecki & Stiles, 1982). *Right:* The top curve shows the transmittance due to the macular pigment; the functions below show the change in transmittance after age 20 from the combined spectral transmission of light by the lens and macular pigment for the discrete ages indicated in the legend (van de Kratts and van Norren, 2007).

iii. Senescent Changes in Retinal Image Quality

In addition to age-related changes in the spectral distribution of light reaching the retina, there are also important age-related changes in the spatial distribution of light on the retina. This is often characterized by the point-spread function (PSF) and light scatter. Using psychophysical methods, Westheimer and Liang (1995) measured the PSF of younger and older observers for a broad-band source and reported that light scatter from $7'$ to 90° is about five times larger in a 69-year-old observer compared to a young adult. Thus, 90% of the light from a point source

falls with a retinal region of 7' for a young adult, but only about 50% falls within that same region for an older adult.

It has been demonstrated that light scatter changes little in adulthood until about 40 years of age. Hennesly *et al.* (1998) showed that over a retinal region of 2.2° to 90°, there is negligible change in light scatter up to 40 years of age, but a rapid increase afterwards (*i.e.*, a factor of 5 increase by 65 years of age). The contrast of the retinal image is reduced by adding a veil of light, produced largely by forward light scatter in the eye, over the retinal image. The inevitable reduction in image contrast caused by stray light usually impairs visual performance, especially in scenes when lighting is highly variable, such as when driving at night. Paradoxically, in the low mesopic range, the increased retinal sensitivity to contrast as a result of scattered light can cancel the loss of retinal image contrast and may even enhance contrast sensitivity under some stimulus conditions (Patterson *et al.*, 2015). In addition to disability glare, scattered light also causes significant visual discomfort. Cataract surgery reduces ocular forward scatter in the eye, but the visual consequences of scattered light cannot be corrected and in visually demanding environments the only solution is to use special design of lamps and working conditions to enhance safety by minimizing glare and visual fatigue.

The optical quality of the eye may be quantified by its modulation transfer function (MTF); the relation between contrast attenuation and spatial frequency. Guirao *et al.* (1999) derived the MTFs from PSFs of 60 observers from 20 to 70 years of age, with pupil size and the refractive state of the eye controlled. Illustrative MTFs are shown in Figure 2 for younger and older observers with modulation scaled logarithmically to highlight differences at middle and high spatial frequencies that are obscured on a linear plot. Overall, optical performance

decreases with both increasing spatial frequency and age. These age-related losses may be attributed to optical aberrations but not ocular scatter which is factored out in the measurement procedure. Inclusion of intraocular scatter would further decrease the contrast of stimuli in the elderly eye.

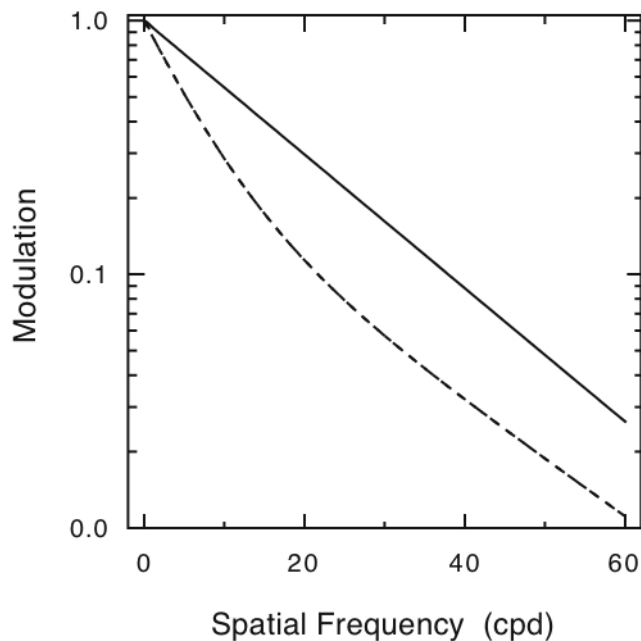


Figure 2. Modulation transfer functions for average younger (23 years, solid curve) and older (63 years, dashed curve) observers calculated from equation and parameters of Guirao *et al.* (1999) for a 3 mm pupil and a 543 nm stimulus.

In summary, a number of factors influence the spatial and spectral composition of the retinal image of the aging eye. The primary effects are due to a reduction in pupil size, changes in the lens that reduce light transmission and impair the ability to focus near objects, and light scatter.

3. SENESCENT CHANGES IN SENSITIVITY OF ROD AND CONE PATHWAYS

The sensitivity of the visual system under scotopic and photopic conditions changes throughout the life span as a result of both optical and neural factors. Changes that cannot be accounted for by optical factors are assumed to be due to changes in neural mechanisms. A greater challenge is separating receptor and postreceptor factors contributing to sensitivity losses.

i. Dark Adaptation and Rod Sensitivity

The dark adaptation function quantifies absolute threshold over time in the dark, typically following exposure to an adapting (bleaching) light. The resultant function contains two scalloped-shaped branches with the first mediated by cones and the second by rods.

Numerous studies have demonstrated that the rate of dark adaptation and the asymptotes of these branches are elevated with increasing age (*e.g.*, Domey *et al.*, 1960). More recent studies have confirmed these results (*e.g.*, Jackson *et al.*, 1999), but focus on separating ocular and neural contributions to these changes, as preretinal factors alone (*i.e.*, smaller pupils, reduced lens transmission) would be expected to reduce sensitivity. Studies that have taken pupil size and ocular media density into account show that scotopic threshold elevation is partially due to neural changes that take place at or beyond the level of photoreceptors (Scheffrin *et al.*, 1998).

Changes at the level of the rod photoreceptors are partially responsible for age-related decreases in scotopic sensitivity and slower dark adaptation. Coile and Baker (1992) demonstrated an age-related slowing of photopigment regeneration. Loss in the efficiency of quantal capture may also occur in older rods as a result of changes in the outer segments. While there is significant loss in rod numbers with age (Curcio *et al.*, 1993), the amount of extractable rhodopsin photopigment changes little with age (Plantner *et al.*, 1988). Surviving rods expand to fill the spaces left by necrotic photoreceptors and there is a suggestion that there is functional reorganization postreceptorally that may reduce the losses in scotopic sensitivity (Scheffrin *et al.*, 1998).

ii. Age-Related Changes in Cone Sensitivity

Owing to the overlap in the short- (S-), middle- (M-) and long-wave (L-) cone photopigment absorption spectra, it is challenging to measure the isolated sensitivities of individual cone pathways in the living eye. The most common approach is to measure two-color increment thresholds in which adapting backgrounds are chosen to suppress the sensitivity of two cone classes so that thresholds are mediated by the less adapted cone type. Changes in S-cone sensitivity have been well documented (Werner, 2016), but Werner and Steele (1988) showed that all three cone types decrease in sensitivity from adolescence through old age. Figure 3 shows that the rate of sensitivity loss is similar for all three cone types, $\sim 26\%$ per decade of life. Further analyses using somewhat different methods demonstrate losses in both receptor and postreceptor mechanisms (Scheffrin *et al.*, 1992).

Related results were reported by Knoblauch *et al.* (2001) using a cone-isolating stimulus with an early version of the Colour Assessment and Diagnosis test. Behavioral methods were used that allowed the full age-range to be tested. The results show that the lowest threshold occurs in adolescence and then increases with increasing age. Importantly, all three cone types change with age in parallel. One can think of these results as equivalent for younger and older individuals, but with the latter operating at a reduced light level.

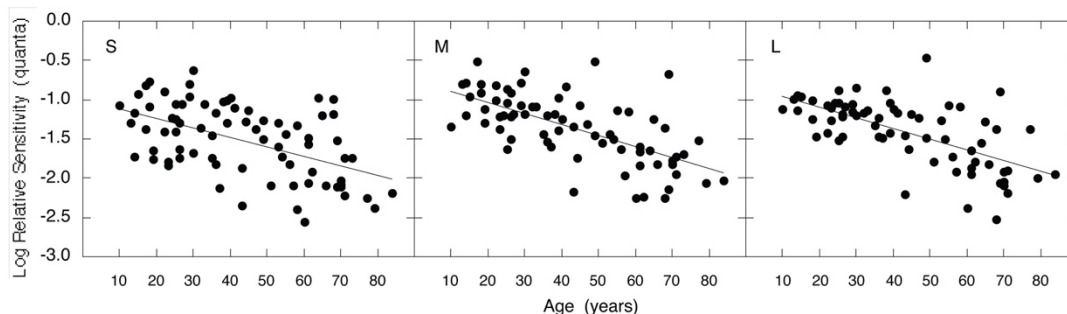


Figure 3. Cone sensitivities measured by increment thresholds for each cone type shown in separate panels plotted as a function of age (Werner & Steele, 1988).

iii. Color Discrimination

Hue discrimination assessed with standardized tests declines from early adulthood on color matching (Lakowski, 1962) and arrangement tests (Verriest, 1963). These losses in color discrimination may be due, largely, to smaller pupils and more dense ocular media that reduce retinal illuminance. For example, results from the FM-100 hue test show that the largest changes in discrimination occur along a tritan axis, and earlier in life, than changes along other M- and/or L-cone axes. This has been interpreted as a loss in S-cone signals, but this is partly related to the construction of the test (Birch, 1993). Knoblauch *et al.* (1987) showed losses on a tritan axis simply when tests are repeated at lower luminance levels. When pupil diameter is controlled with a Maxwellian-view optical system and stimuli are equated individually for retinal illuminance, losses in color discrimination occur not only for S-cone discriminations (Scheffrin *et al.*, 1995), but throughout color space for both spectral (Shinomori & Werner, 2001) and nonspectral (Kraft & Werner, 1999) stimuli. Thus, poorer color discrimination in the elderly are due not only to smaller pupils and reduced ocular media transmission, but also by neural factors.

iv. Spatial Vision

The most common measure of spatial vision in most clinical settings is limited to visual acuity or the minimum angle of resolution. A variety of test patterns may be used, but the most common are high contrast Snellen letters or Landolt C's. Documenting age-related changes requires screening for retinal disease and refraction for the test distance. When this is carried out (*e.g.*, Frisen & Frisen, 1981; Elliott *et al.*, 1995), the average visual acuity begins to decline at

about 25 years of age, much like the changes in visual sensitivity. With habitual refractive correction and no screening for disease, visual acuity is much worse, as is to be expected.

The contrast sensitivity function (CSF) represents the minimum contrast to detect sinusoidal gratings as a function of spatial frequency in cycles per degree (cpd). It provides a general characterization of spatial vision much as the MTF provides a more general characterization of the eye's optics. The CSF varies with stimulus parameters and retinal location; Figure 4 shows results for nonflickering stimuli under photopic conditions for hypothetical observers ages 20- (filled symbols) and 75 (open symbols) years of age. The photopic contrast sensitivity function shows relatively little change with age at low spatial frequencies, while sensitivity losses at middle and high spatial frequencies are substantial.

Functional contrast sensitivity measured with Landolt C optotypes is also highly dependent on retinal illuminance below 100 td (Gillespie-Gallery *et al.*, 2013), with significant variability between observers. The area under the curve obtained by measuring the subject's contrast thresholds as a function of retinal illuminance may be compared to normal group averages using the formula, $HR_{index} = 1 - \text{Area}_{\text{participant}} / \text{Area}_{\text{group}}$. This index captures the combined effects of aging and / or disease on the contrast thresholds measured in the photopic range and the rate of increase in these thresholds with decreasing retinal illuminance into the mesopic range. The HR_{index} is a more informative parameter designed to capture the loss of visual performance over a range of retinal illuminances (Gillespie-Gallery *et al.*, 2013).

Additional investigations indicate that preretinal factors such as reduced retinal illuminance due to smaller pupils and increased ocular media density and scattered light in the elderly can contribute to loss of spatial vision, particularly in the high spatial frequency range. The extent to

which pre-retinal factors can be used to account for loss of spatial vision with increasing age has been examined by Elliott *et al.* (1990). Findings from this study suggest that pre-retinal factors cannot account fully for the measured losses in spatial vision observed experimentally and that neural factors must also be involved with increasing age.

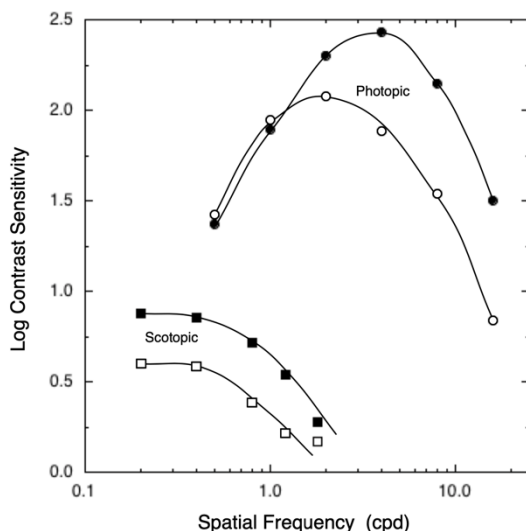


Figure 4. Log contrast sensitivity as a function of spatial frequency (cpd) for static gratings presented to the fovea (photopic; Owsley *et al.*, 1983) or at 8° nasal (scotopic; Scheffrin *et al.*, 1999). Curves for average younger (20 years, filled symbols) and older (75 years, open symbols) observers were based on regression equations fitted to data from large groups of observers.

The scotopic CSF undergoes a different pattern of age-related loss from that observed under photopic conditions, as shown in Figure 4. These data were obtained following 30 mins of dark adaptation, using an artificial pupil and wavelengths that minimize retinal illuminance changes with age. The observed changes at low spatial frequencies requires an explanation in terms of age-related changes in neural factors.

The CSF has also been measured with chromatic modulation of sinusoidally-varying gratings (Fiorentini *et al.*, 1996). To isolate purely chromatic systems, it is critical to control for individual differences in chromatic aberration and luminosity. Hardy *et al.* (2005) obtained

measurements separately for S-cone and L-M-cone modulation. Older observers demonstrated lower chromatic contrast sensitivity for all spatial frequencies and both axes of chromatic modulation. With controls for ocular media density differences between the two groups remained, implying that both optical and neural factors contribute to the age-related loss of chromatic contrast sensitivity.

v. Estimating Sensitivity Changes of ipRGCs

Retinal illuminance as a function of age can be estimated from models of pupil size (Winn *et al.*, 1994) and lens density (Pokorny *et al.*, 1987) as shown in Figure 5. Age-related losses of luminance (L+M) sensitivity obtained by L-cone and M-cone sensitivities measured by increment thresholds (Werner & Steele, 1988) and contrast sensitivity at 16 cpd (Owsley *et al.*, 1983) are poorer than predictions based on reduction of retinal illuminance, suggesting that in addition to the reduction of receptor (cone) sensitivity, loss of ganglion cells and other neural changes also affect spatial vision with increasing age.

Currently, there is no direct evidence about the age-related changes in ipRGC signals and it is hard to estimate directly the normal functioning of ipRGCs, although some predictions can be made based on the loss of cone and rod photoreceptor sensitivities with increasing age, simply because at lower light levels ipRGCs are largely driven by signals from rods with increasingly greater contribution of cone signals with increasing retinal illuminance (Berson, 2014). Taking account of these changes and the spectral sensitivity of melanopsin (Lucas *et al.*, 2001; DeLawyer *et al.*, 2020), it is reasonable to assume that visual signals that contribute to a number of functions in the absence of normal perceptual experience, including the control of circadian rhythms will be affected by normal aging.

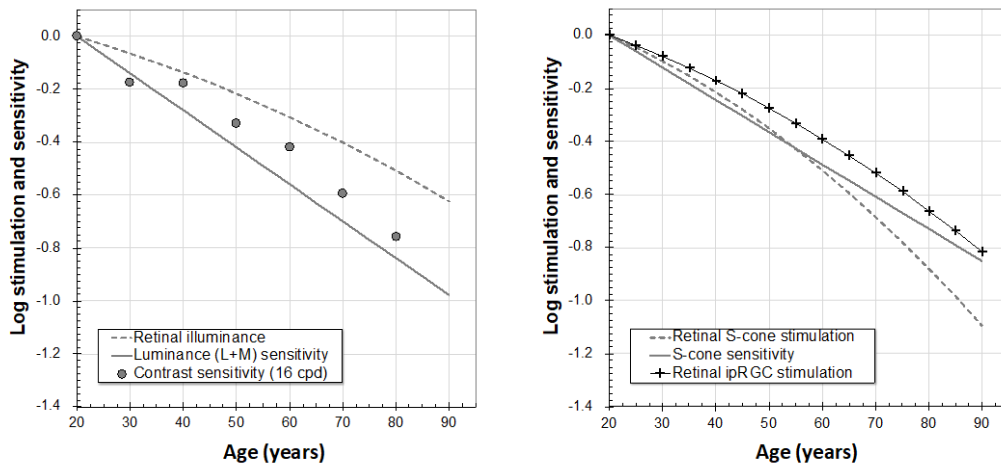


Figure 5. Left panel shows logarithmic retinal illuminance calculated from pupil diameter (at 44 cd/m^2 ; Winn *et al.*, 1994) and lens density (Pokorny *et al.*, 1987) for D65 daylight illumination, luminance (L+M) sensitivity (measured by increment threshold; Werner & Steele, 1988), and contrast sensitivity (at 16 cpd; Owsley *et al.*, 1983). Right panel shows logarithmic retinal S-cone stimulation for D65, S-cone sensitivity (Werner & Steele, 1988), and ipRGC stimulation at the retina calculated from a peak spectral sensitivity function for melanopsin stimulation of 489 nm (DeLawyer *et al.*, 2020) using a pigment template nomogram (Lucas *et al.*, 2001) and a peak axial optical density of 0.4.

vi. Temporal Vision

Temporal resolution has been defined by critical fusion frequency (CFF), the lowest frequency of flicker that can be discriminated from a steady light. CFF declines with age, in part because of reduced retinal illuminance in older individuals. The temporal contrast sensitivity function (tCSF) attempts to quantify temporal processing by determining the contrast required for detection over a range of temporal frequencies. Tyler (1989) and Kim and Mayer (1994) showed losses with age that were greater for higher temporal frequencies. These losses were interpreted as due to age-related losses in both optical and neural factors.

Temporal sensitivity has also been quantified by the impulse response function (IRF), the theoretical response to a pulse of short duration. The IRF allows predictions of response to any time-varying stimulus and its Fourier transform allows the tCSF to be calculated. Shinomori and

Werner (2003) measured the IRF for 62 observers ranging in age from 16 to 85 years. All were screened for abnormal optics and posterior segment. The IRF has an excitatory phase followed by an inhibitory phase for most observers. For 9 of 25 observers above age 55 years, however, the inhibitory phase is reduced. When transformed to the tCSF, observers with reduced inhibition had a tCSF that was low-pass while for others it is bandpass as shown in Figure 6. The difference of IRFs and tCSFs among older observers implies that those with reduced inhibitory phase will have difficulty detecting visual stimuli of short duration. The age-related decline of visual performance (for example, visual acuity tests) can partly be attributed to this disappearance of the inhibitory phase. For other elderly observers, there was a reduction in amplitude of the tCSF indicating that when ocular factors are controlled, the visual system maintains a stable speed of response over the life span.

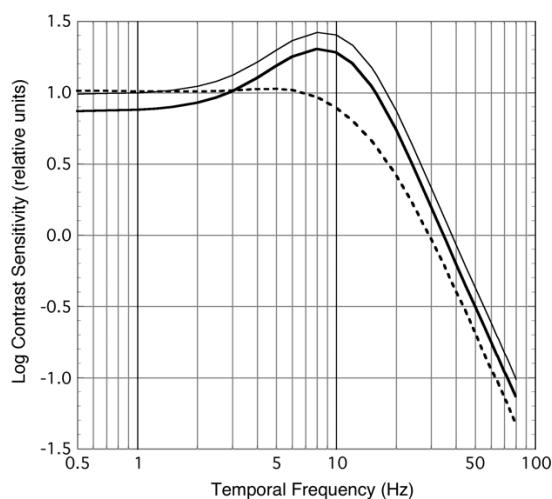


Figure 6. Temporal contrast sensitivity function for theoretical 20-year-old (gray) and 80 year-old observers (solid black). The dashed curve is calculated for elderly observers with reduced IRF inhibition. (After Shinomori & Werner, 2003).

The influence of retinal illuminance on flicker modulation thresholds around 40 and 75 years of age is shown in Figure 7 (replotted from Bi et al. 2016). The threshold difference between young and old observers at this retinal illuminance level were 0.28 log units at the fovea and 0.21 log units at 4 deg in the periphery; these are close to the 0.36 log unit difference in the temporal contrast sensitivity (Figure 6) at 15 Hz when comparing the weighted averages for the young and the older observer groups. The corresponding observed differences are larger when higher retinal illuminances are employed. The experiments reported by Bi *et al* (2016) were carried out at constant retinal illuminance using a closed-loop system that linked the continuous measurements of pupil size to the luminance of the display. Changes in light absorption of the optics of the eye with increasing age have not, however, been accounted for in this study. It is therefore likely that the higher sensitivity (lower threshold) measured in young observers at higher retinal illuminances may not be as evident in older subjects as a result of lower than expected retinal illuminances.

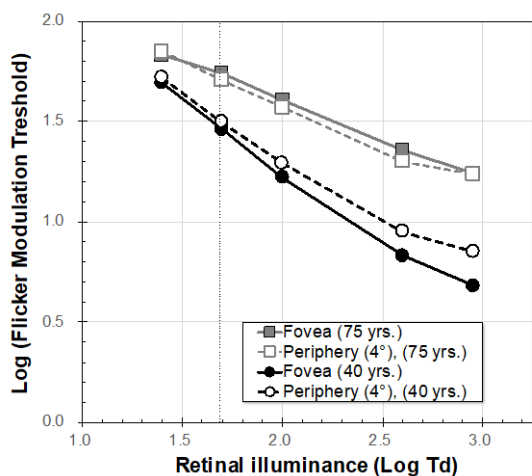


Figure 7. Logarithmic flicker modulation threshold (FMT) as a function of the retinal illuminance at age 40- and 75-years old (replotted from regression lines of Figure 5 in Bi *et al.* 2016). The vertical line denotes the illuminance (50 Td) used in the IRF measurement in Figure 6.

4. A NOTE ABOUT UNCONSCIOUS VISUAL PROCESSES

This short review has emphasized age-related changes in conscious visual functions that may be important for understanding and studying unconscious visual functions controlling circadian rhythms. There are significant changes in most visual functions across the life span. Studying age-related changes in the absence of conscious visual perception is challenging because one has to rely on involuntary responses such as the pupil light reflex, involuntary saccades in 'blindsight' or visually-evoked electrical potentials in cortically blind patients. Other behavioral changes caused by altered circadian rhythms are equally difficult to assess in older subjects.

A starting point for studying unconscious vision is to consider what is known about shared mechanisms from experiments that involve conscious vision tests. The loss of photoreceptors and reduction in photoreceptor sensitivity can be expected to affect ipRGCs over most of the operating range as reflected in pupil dynamics. The spatiotemporal properties of the visual stimuli required to elicit certain responses such as eye-movements, light/dark differentiation, spatial localization and motion detection in the absence of conscious perceptual awareness are similar. The probability of a correct response in many of these tasks can be affected strongly by the shape of a temporal envelope employed for stimulus presentation (Barbur et al., 1988). Best responses require either fast moving or briefly presented visual stimuli with sharp temporal edges and high luminance contrast (Barbur et al, 1980; 1994). If the temporal changes demonstrated in normal vision also affect the temporal characteristics of ipRGCs inputs, the ability to process visual information in the absence of conscious vision may also be affected in the same way by normal aging. Considering the age-related deterioration in circadian rhythms, it could be expected that the age-related changes in signals from melanopsin in the ipRGCs

occur and have to cause mostly declines in circadian rhythms. We expect further investigation about the direct measurement of the ipRGC response.

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