Circadian photoreception: ageing and the eye's important role in systemic health

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Presented in part at the Annual Meeting of the American Society of Cataract of Refractive Surgery in San Diego, USA (1 May 2007) and the 20th International Congress of German Ophthalmic Surgeons in Nurnberg, Germany (19 May 2007).

Accepted 6 August 2008
Published Online First 29 August 2008

ABSTRACT

Aim: To analyse how age-related losses in crystalline lens transmittance and pupillary area affect circadian photoreception and compare the circadian performance of phakic and pseudophakic individuals of the same age.

Methods: The spectral sensitivity of circadian photoreception peaks in the blue part of the spectrum at approximately 460 nm. Photosensitive retinal ganglion cells send unconscious information about environmental illumination to non-visual brain centres including the human body's master biological clock in the suprachiasmatic nuclei. This information permits human physiology to be optimised and aligned with geophysical day–night cycles using neural and hormonal messengers including melatonin. Age-related transmittance spectra of crystalline lenses and photopic pupil diameter are used with the spectral sensitivity of melatonin suppression and the transmittance spectra of intraocular lenses (IOLs) to analyse how ageing and IOL chromophores affect circadian photoreception.

Results: Ageing increases crystalline lens light absorption and decreases pupil area resulting in progressive loss of circadian photoreception. A 10-year-old child has circadian photoreception 10-fold greater than a 95-year-old phakic adult. A 45-year-old adult retains only half the circadian photoreception of early youth. Pseudophakia improves circadian photoreception at all ages, particularly with UV-only blocking IOLs which transmit blue wavelengths optimal for non-visual photoreception.

Conclusions: Non-visual retinal ganglion photoreceptor responses to bright, properly timed light exposures help assure effective circadian photoentrainment and optimal diurnal physiological processes. Circadian photoreception can persist in visually blind individuals if retinal ganglion cell photoreceptors and their suprachiasmatic connections are intact. Retinal illumination decreases with ageing due to pupillary miosis and reduced crystalline lens light transmission especially of short wavelengths. Inadequate environmental light and/or ganglion photoreception can cause circadian disruption, increasing the risk of insomnia, depression, numerous systemic disorders and possibly early mortality. Artificial lighting is dimmer and less blue-weighted than natural daylight, contributing to age-related losses in unconscious circadian photoreception. Optimal intraocular lens design should consider the spectral requirements of both conscious and unconscious retinal photoreception.

Fewer than 1% of retinal ganglion cells are photoreceptive,[1] but these photoreceptors play a vital role in human physiology and health. Photosensitive retinal ganglion cells (pRGC) were discovered in 2002.[2] They express the blue-light sensitive photopigment melanopsin[3] in their cell bodies and elongated dendrites.[4] Human retinas are spanned by a light sensitive network of roughly 3000 widely dispersed pRGCs.[1 4] Spectral absorption by melanopsin[2] and sensitivity of human nocturnal melatonin suppression[5 6] both peak in the blue portion of the spectrum at 480 and 460 nm, respectively. As shown in fig 1, this short-wavelength sensitivity differs significantly from longer-wavelength peak sensitivities for rod-mediated scotopic (506 nm, green) and cone-mediated photopic (555 nm, green–yellow) vision.[5 7 8]

Suprachiasmatic nuclei (SCN) of the anterior hypothalamus serve as the body's master biological clock.[9] Ganglion photoreceptors send unconscious, non-visual photic information through the retinohypothalamic tract to the SCN permitting alignment of internal biological with external environmental time. They differ in many ways from the rods and cones that subserve conscious image-based vision.[4] Ganglion photoreceptors require much more light to respond than cones and have thresholds well above those for photopic vision.[2 9–11] They lack spatial resolution and can adapt to ambient lighting over days[12] and months.[13] These properties are well suited to non-directional detection of gross environmental illumination essential for integrated circadian, neuroendocrine and neurobehavioural effects.[4] Absent or deficient pRGC photoreception cannot be perceived subjectively,[14] but ensuing circadian disturbances can have significant physiological and psychological consequences.[15 16]

The SCN initiate events timed to allow preparation for impending metabolic, biochemical and physical activities.[15] Prior to awakening, they activate a morning cortisol surge and trigger changes vital to transitioning from sleep to wakefulness.[14] Morning exposure to sunlight increases core body temperature,[17] alerting,[18] cognition[19] and brain serotonin levels[20] which enhance mood and vitality. As the day progresses, peak cognition occurs commensurate with maximal core body temperature. By evening, SCN actively inhibit cortisol secretion for recovery from the morning surge[15] and initiate pineal secretion of the hormone melatonin which reduces alertness and decreases core body temperature.[14] As sleep ensues, its slow wave stages and SCN suppression reduce cortisol to a healthy daily nadir as SCN orchestrate a nightly surge of melatonin and other sleep-related hormones.[15 16 21]

Molecular mechanisms controlling self-sustaining SCN clock oscillations have been studied extensively.[22] Similar mechanisms generating daily rhythms are present in most cells.[23] Peripheral cell oscillations quickly desynchronise with each other,

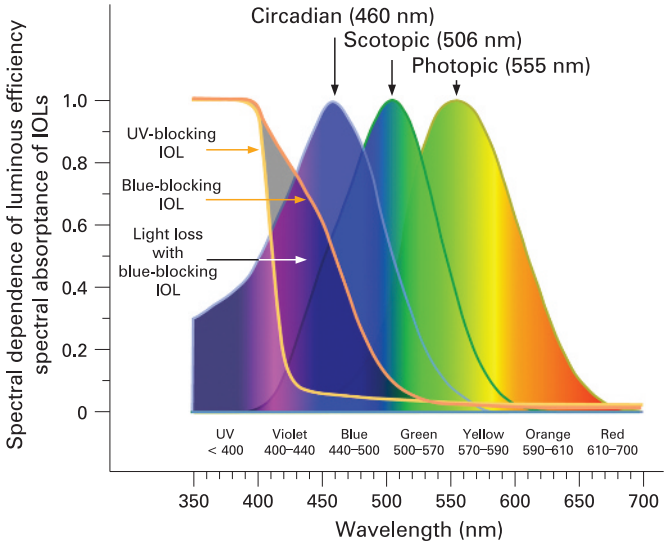

Figure 1 Spectral sensitivity of photopic, scotopic and circadian (melatonin suppression) photoreception.[5 7] Peak sensitivities of circadian, scotopic and photopic photoreception are 460 nm (blue), 506 nm (green) and 555 nm (green-yellow), respectively. Spectral absorptance is shown for 30D blue blocking (AcrySof SN60AT, Alcon Laboratories, Fort Worth, TX) and UV-only blocking (ClariFlex, Advanced Medical Optics, Santa Ana, CA) intraocular lenses (IOLs).[8] The area between the two IOL curves is the violet, blue and green light blocked in comparison with a UV-only blocking IOL.

however, unless constant temporal alignment is provided by the SCN's neural and hormonal timing signals.[22 23] Proper SCN functioning is critical for good health due to the numerous functions it coordinates.[15 16 18 21 23 24] Without robust SCN signals, circadian rhythms of peripheral organs and cells can decouple, producing biochemical disarray and flattened rhythm amplitudes, and increasing risk of disease.[15 25–27]

Melatonin produced by the pineal gland is the hormone most closely associated with SCN function.[28 29] SCN neurons suppress or stimulate melatonin synthesis at appropriate times using a multisynaptic sympathetic pathway.[28 30] Upregulation of the rate-limiting enzyme in melatonin synthesis (N-acetyltransferase) is directly and immediately suppressed by the SCN in response to light.[10 28 31] Darkness therefore permits pineal melatonin production during the proper phase of the SCN cycle. Melatonin signals time of day and simultaneously provides potent antioxidant and numerous other beneficial effects.[28] Experimental nocturnal suppression of melatonin synthesis by light is the widely used surrogate for photic effects on SCN function.[32]

The effectiveness of light exposure for pRGC-mediated biological effects depends on its intensity,[33] duration,[34] spectrum[5 6] and timing relative to the phase of the circadian rhythm.[35] Internal biological clocks are entrained to external environmental time by timing cues known as zeitgebers.[28] Daily environmental light is by far the most important zeitgeber in humans,[4 9 10 36] photoentraining the SCN to light–dark cycles. Suprathreshold early morning light advances, while evening light delays rhythms.[35]

Sunlight has been the primary stimulus for pRGC photoreception throughout human history. Skylight has a dominant wavelength of 477 nm,[37] similar to peak pRGC sensitivity. Daylight illuminance can exceed 100 000 lux, as shown in fig 2. Contemporary artificial sources rarely provide more than 1% of the brightness of outdoor natural light,[38] with spectra shifted to longer (redder) wavelengths that are less effective for pRGC photoreception.[39]

Brighter, longer, bluer light exposures are most efficient for retinal ganglion mediated effects including melatonin suppression,[5 6] photoentrainment,[40] thermoregulation,[17] improved nocturnal sleep quality,[41–43] heart-rate variability,[17] treatment of non-seasonal[44] or seasonal depression,[45] enhanced mood/well-being,[46 47] alertness,[17 18 46 48] cognition,[19 46 49] reaction time, performance and vigilance.[18 48] The crystalline lens transmits progressively less visible light and particularly less blue light as it ages.[50 51] Senescent miosis also progressively reduces retinal illumination.[52 53] Deficient circadian photoreception results in significant neurobiological morbidity. We therefore examined how ageing and cataract surgery potentially affect the light available for circadian photoreception.

METHODS

Figure 2 is a compilation of published environmental and therapeutic light levels.[39 44 54–57] Typical indoor and outdoor illuminances were confirmed with standard light meters

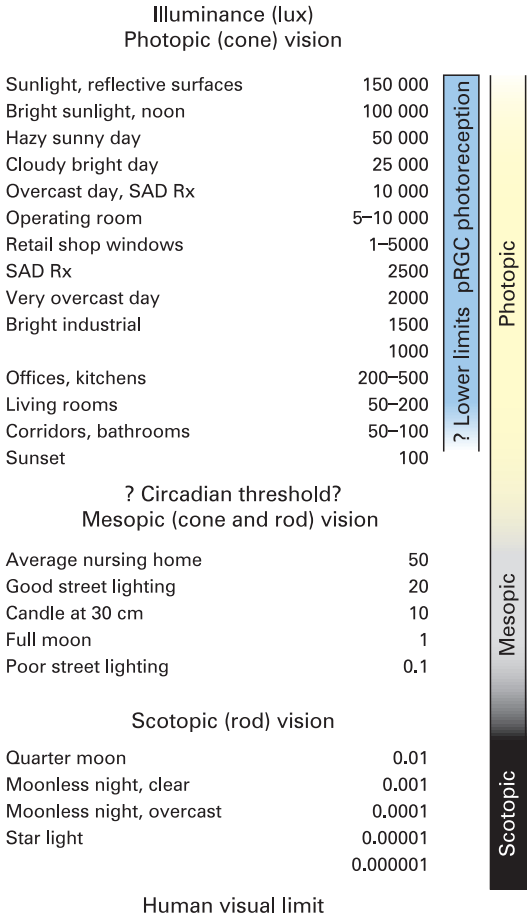

Figure 2 Light levels in contemporary and natural environments[39 54–57] and also in phototherapy for seasonal affective disorder, which is typically 2500 lux for 2 h/day or 10 000 lux for 30 min/day.[44] Illuminances are given in units of photopic lux. Photopic lux accurately describe the effectiveness of a particular light exposure for overall cone photoreception, which has a peak sensitivity at 555 nm in the green–yellow part of the spectrum (cf, fig 1). A standard circadian lux unit is needed[10 40] but has not been adopted yet for comparing the effectiveness of different light exposures for circadian photoreception, which has peak sensitivity at 460 nm in the blue part of the spectrum (cf, fig 1).

(Models 403125 and EA30s, Extech Instruments Corporation, Waltham, MA). The age-related decline in retinal illumination in fig 3 was calculated by multiplying human crystalline lens transmittance at different ages[51] with photopic pupil area for those ages.[53] Results are presented relative to a 10-year-old eye. Pupil-weighted spectral retinal illumination was multiplied wavelength by wavelength with melatonin suppression sensitivity[5 58] between 350 and 700 nm to determine how ageing affects circadian photoreception for an isoquantal light source. Resultant areas under the curve for 10 years of age and 15 through 95 years of age represent relative circadian illumination and are presented in table 1. Similar calculations are shown in fig 4 but with the spectral transmittance of 20 and 30-dioptre blue-blocking (AcrySof SN60AT, Alcon Laboratories, Fort Worth, TX) or UV-only blocking (ClariFlex, Advanced Medical Optics, Santa Ana) intraocular lenses[8] (IOLs) used in addition to that of crystalline lenses (cf, fig 1).

RESULTS

Figure 3 shows how losses in crystalline lens transmittance and pupil area due to ageing produce progressive decreases in pupil-weighted spectral retinal illumination. Percentage losses are reasonably uniform with each passing decade. They are most prominent at shorter violet (400–440 nm) and blue (440–500 nm) wavelengths.

Table 1 presents relative effectiveness of circadian photoreception at different ages. By 45 years of age, crystalline lens yellowing and pupillary miosis reduces circadian photoreception to roughly half that of a 10-year-old. People in their eighth and ninth decades retain only 10% of a 10-year-old's circadian photoreception, so they need 10 times more light for equivalent circadian photoreception under similar illumination, in agreement with Charman's findings.[58] Deficits will be underestimates if pRGC populations decline with ageing as do those of non-photoreceptive retinal ganglion cells.[59] Additional reductions in pRGC photoreception may occur if ocular light transmission is decreased further by factors such as ethnicity, iris pigmentation,[60] reduced corneal clarity, cataract or sunglass usage.

Figure 4 illustrates age-related losses or gains in circadian photoreception relative to a 10-year-old eye. Cataract extraction with implantation of a UV-only blocking IOL results in

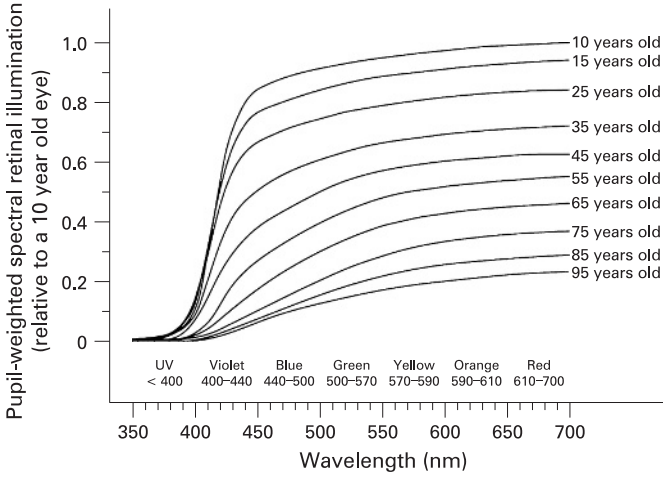

Figure 3 Age-related losses in retinal illumination due to decreasing crystalline lens light transmission and pupil area. Percentage losses per decade are reasonably uniform and most prominent at shorter violet (400–440 nm) and blue (440–500 nm) wavelengths.

significant gains, with performances in older adults comparable with phakic individuals up to four decades younger. People under 50 years of age with UV-only blocking IOLs attain better circadian photoreception than in their youth. UV-only blocking IOLs provide circadian photoreception at any given age roughly 15–20 years younger than blue-blocking IOLs, depending on the latter's dioptric power.

DISCUSSION

There is little current information on the susceptibility of retinal ganglion photoreceptors to ocular disease. Retinitis pigmentosa may affect ganglion as well as rod and cone photoreceptors because by 50 years of age, 95% of people with retinitis pigmentosa experience intermittent insomnia, daytime sleepiness and reduced alertness.[61 62] Glaucoma is associated with ganglion cell losses, but pRGCs were resistant to ocular hypertension in one experimental rodent study.[63] Cortical blindness would not affect light-mediated pRGC functions so patients should retain normal sleep patterns with appropriate light exposure and potentially benefit from light therapy for coincident depression even though visually blind. Conversely, whiplash injury,[64] tetraplegia,[30] autonomic neuropathy or other conditions affecting the retinohypothalamic tract, SCN-pineal connections or intermediate nuclei can impair or abolish specific circadian rhythms.

SCN cycle at fixed, inherited, individually specific periods that typically differ from 24 h and average 24.2 h in humans.[9] If environmental timing cues are inadequate or absent,[36 65] SCN cycle daily at their own intrinsic period independent of geophysical day–night cycles. Repetitive cycling without daily resetting is termed free-running.[9] In free-running, the phase of physiological cycles progressively deviates from and then returns to that of environmental day–night cycles over days or months.

Most totally blind individuals have abnormal or free-running circadian rhythms,[36 66] but some visually blind individuals retain pRGC photoreception.[67] Visually blind people without pRGC photoentrainment suffer the additional burden of periodic extreme circadian desynchrony with daytime drowsiness from elevated daytime melatonin levels and night-time insomnia due to circadian alerting.[68] Their condition is equivalent to a lifetime of recurrent profound jetlag which in itself is disabling.[69] Blind individuals with intermittent insomnia and daytime napping despite adequate light exposure[36] should be suspected of free-running. They typically entrain with daily exogenous melatonin, which can improve their quality of life[70] and possibly reduce otherwise increased early mortality risks.[71–76]

Inadequate environmental light exposure can also cause free-running circadian rhythms. People with normal vision in their mid-twenties free-run at room illuminances under 200 lux[77] or even 80 lux.[78] Astronauts (37–43 years of age) become free-running at typical space shuttle illuminances below 80 lux, producing circadian disruption, poor sleep quality and neurobehavioural performance decrements.[65] If 80–200 lux does not prevent free-running with its adverse consequences in 25-year-olds, much higher illuminances would be inadequate for older people with their declining crystalline lens transmittance and pupil area (cf, table 1). For example, 184–460, 256–640, 400–1000 and 536–1340 lux would be inadequate to prevent free-running in 55, 65, 75 and 85-year-old adults, respectively. Residential illuminances are much lower than those needed to prevent free-running in older adults, typically averaging only 100 lux (cf, fig 2).[29 38 57] This light level is very dim compared with natural outdoor lighting.[39]

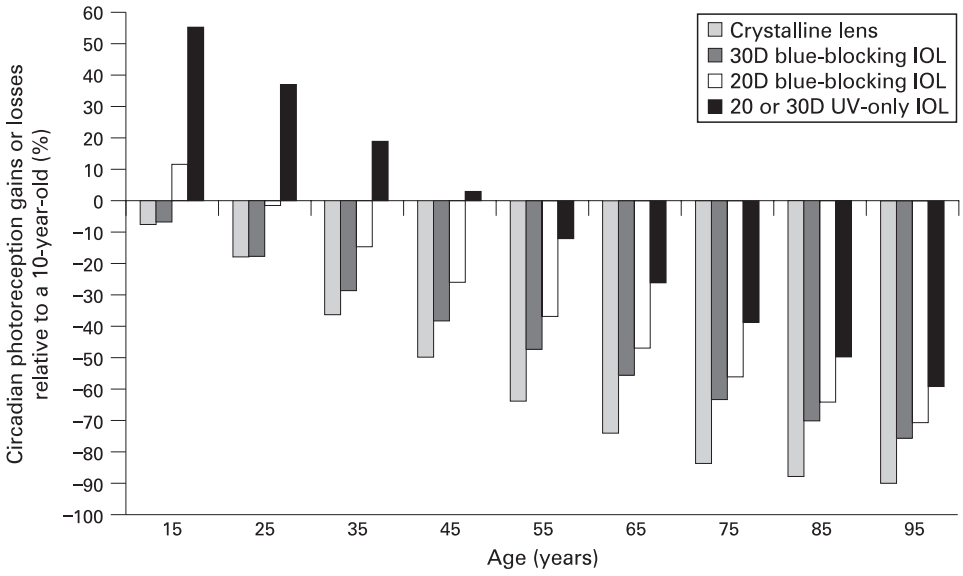

Figure 4 Age-related losses or gains in circadian photoreception relative to a 10-year-old eye for phakic eyes, for 20 and 30D blue-blocking (AcrySof SN60AT, Alcon Laboratories, Fort Worth, TX) and for UV-only blocking intraocular lenses (IOLs) regardless of dioptric power (ClariFlex, Advanced Medical Optics, Santa Ana, CA). Cataract extraction with IOL implantation produces significant gains over phakic eyes, particularly with UV-only blocking IOLs that do not filter out shorter wavelengths vital for non-visual photoreception.

Daily light exposures necessary for non-visual photoreception depend on numerous intrinsic[13 60 79 80] and extrinsic factors.[5 33–35] For example, older women even with dilated pupils are insensitive to blue light exposures sufficient to suppress melatonin significantly in younger women, demonstrating that age-related crystalline lens yellowing reduces circadian photoreception.[81] As shown in fig 4, cataract surgery provides older adults with more youthful circadian photoreception.

Sunlight's importance is underscored by seasonal and weather-related neuropsychological disorders that would not occur if indoor lighting were sufficient for all neurobiological needs. Midwinter insomnia affects up to 80% of certain populations at higher latitudes.[82] Over 90% of people have some mood reduction during sporadically overcast weather or seasonal decreases in daylight length or intensity.[83–85] Seasonal affective disorder (SAD) causes disabling depression, hypersomnolence and weight gain during the fall and winter in approximately 10% of the population.[86] Non-seasonal depression is also closely associated with reduced light exposure.[87 88] Reduced sunlight exposure in sighted individuals can cause insomnia, free-running rhythms, extreme flattening of hormonal profiles and cognitive difficulties that are reversible with restoration of adequate sunshine.[89 90]

Environmental illumination is inversely correlated with insomnia[42 91] and depression,[87 88] both of which increase with ageing.[92] Chronic sleep disturbances affect 40–70% of elderly populations.[92] Indeed, only 12% of 9000 subjects aged 65 or older denied sleep complaints.[93] Chronic insomnia and depression are closely associated.[93 94] Up to 30% of older populations have depression,[95 96] which, like insomnia, frequently goes undiagnosed.[97 98] Insomnia and depression are significant risk factors for cancer,[99] diabetes,[100] cognitive deficiencies,[93 101] dementia,[102] cardiovascular disease[95] and premature mortality.[96 103] Flattened nocturnal melatonin amplitudes occur with ageing in some[104] but not all[105] people probably because of differences in environmental light exposure.[42] Reduced circadian amplitudes are also associated with higher risks of cancer[106] and other diseases.[107] Bright light (≥2500 lux) particularly from bluer sources such as outdoor daylight can reduce or eliminate insomnia[42] and depression;[44] immediately increase brain serotonin,[20] mood,[47] alertness, and cognitive function;[17 19 49] and normalise otherwise decreased circadian hormonal amplitudes including nocturnal melatonin levels that may have been undetectable previously.[42 89 90]

Young adults in industrialised countries typically receive only 20–120 min of daily light exposure exceeding 1000 lux.[42 87 108 109] Elderly adults' bright light exposures average only 1/3 to 2/3 that duration.[42 110] Institutionalised elderly receive less than 10 min per day of light exposure exceeding 1000 lux,[55 111] with median illuminances as low as 54 lux.[55] The declining bright

Table 1 Relative circadian photoreception vs age*

	10 years	15 years	25 years	35 years	45 years	55 years	65 years	75 years	85 years	95 years
10 years	1.0	0.9	0.8	0.6	0.5	0.4	0.3	0.2	0.1	0.1
15 years	1.1	1.0	0.9	0.7	0.5	0.4	0.3	0.2	0.1	0.1
25 years	1.2	1.1	1.0	0.8	0.6	0.4	0.3	0.2	0.1	0.1
35 years	1.6	1.5	1.3	1.0	0.8	0.6	0.4	0.3	0.2	0.2
45 years	2.0	1.8	1.6	1.3	1.0	0.7	0.5	0.3	0.2	0.2
55 years	2.8	2.5	2.3	1.8	1.4	1.0	0.7	0.5	0.3	0.3
65 years	3.8	3.5	3.2	2.4	1.9	1.4	1.0	0.6	0.5	0.4
75 years	6.1	5.6	5.0	3.9	3.0	2.2	1.6	1.0	0.7	0.6
85 years	8.2	7.6	6.7	5.2	4.1	3.0	2.1	1.4	1.0	0.8
95 years	10.0	9.2	8.2	6.4	5.0	3.6	2.6	1.6	1.2	1.0

*Circadian photoreception declines with ageing due to pupillary miosis and decreased crystalline lens transmission. This table presents circadian performance for an age in the top row relative to that of an age in the left column. For example, a person aged 45 has photoreception roughly half that of a 15-year-old and twice that of a 65-year-old. The table can also be used to estimate the light requirements for an age in the left column relative to that of an age in top row. For example, a person aged 65 needs roughly three times the illuminance of a 25-year-old and half that of a 85-year-old for equivalent circadian photoreception performance.

light exposure of many older adults combined with their reduced retinal illuminance due to pupillary miosis and crystalline lens yellowing places them at risk for retinal ganglion photoreception deficiency, possibly contributing to age-related insomnia, depression and cognitive decline. Cataract surgery with a UV-only blocking IOL has been shown to decrease the incidence of insomnia and daytime sleepiness.[112 113]

CONCLUSION

The eye's critical role in good health has become increasingly evident. Unconscious retinal ganglion photoreceptor responses to bright, properly timed light exposures ensure optimal circadian rhythms, photoentrainment and other neurobiological responses. Inadequate environmental light and/or ganglion photoreception can cause circadian disruption, increasing the risk of insomnia, depression and numerous systemic disorders. Complete blindness involving both conscious vision and unconscious, non-visual photoreception should be differentiated from visual blindness affecting only the conscious perception of light. Visually blind patients should be encouraged to get sufficient light, while completely blind individuals typically benefit from melatonin therapy.

Circadian photoreception decreases with ageing caused by age-related pupillary miosis and reduced crystalline lens transmission, particularly of blue light. Circadian studies should control for subjects' pupil size and crystalline lens or IOL transmittance. Patient lifestyle education and architectural designs addressing the increased photic needs of older adults are potentially beneficial, as are retinal photocoagulation procedures localised to the outer retina that potentially spare ganglion photoreceptors.[114 115] Light deficiency, whether due to improper timing, suboptimal spectrum or insufficient intensity, may contribute to medical conditions commonly assumed to be age-related inevitabilities. Unconscious and conscious photoreception should both be considered in IOL design and selection in order to maximise the non-visual as well as visual benefits of cataract surgery.[8 43]

Competing interests: PLT has received travel grants from Advanced Medical Optics, Incorporated. MAM serves as a consultant for Advanced Medical Optics, Iridex and Ocular Instruments Corporations.

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