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## Sleep Medicine Reviews

journal homepage: [www.elsevier.com/locate/smr](http://www.elsevier.com/locate/smr)

## CLINICAL REVIEW

## The role of environmental light in sleep and health: Effects of ocular aging and cataract surgery

Patricia L. Turner<sup>a,\*</sup>, Eus J.W. Van Someren<sup>b,1</sup>, Martin A. Mainster<sup>c,2</sup><sup>a</sup> Department of Ophthalmology, University of Kansas School of Medicine, 7400 State Line Road, Prairie Village, KS 66208-3444, USA<sup>b</sup> Netherlands Institute for Neuroscience, an institute of the Royal Netherlands Academy of Arts and Sciences, Meibergdreef 47, 1105 BA Amsterdam, The Netherlands<sup>c</sup> Department of Ophthalmology, University of Kansas School of Medicine, 7400 State Line Road, Prairie Village, KS 66208-3444, USA

## ARTICLE INFO

## Article history:

Received 2 March 2009

Received in revised form

6 November 2009

Accepted 6 November 2009

## Keywords:

Aging

Circadian

Chronodisruption

Crystalline lens

Hypothalamic–pituitary–adrenal axis

Insomnia

Intraocular lens

Light

Melatonin

Retinal ganglion photoreceptor

## SUMMARY

Environmental illumination profoundly influences human health and well-being. Recently discovered photoreceptive retinal ganglion cells (pRGCs) are primary mediators of numerous circadian, neuroendocrine and neurobehavioral responses. pRGCs provide lighting information to diverse nonvisual (non-image-forming) brain centers including the suprachiasmatic nuclei (SCN) which serve as the body's master biological clock. The SCN exert functional control over circadian aspects of physiology. The timing and strength (amplitude) of SCN rhythmic signals are affected by light exposure. Light deficiency may attenuate SCN function and its control of physiological and hormonal rhythms which in turn can result in a cascade of adverse events. Inadequate pRGC photoreception cannot be perceived consciously, but may aggravate many common age-associated problems including insomnia, depression and impaired cognition. In this review we (1) summarize circadian physiology, emphasizing light's critical role as the most important geophysical timing cue in humans; (2) analyze evidence that typical residential lighting is insufficient for optimal pRGC requirements in youth and even more so with advancing age; (3) show how ocular aging and cataract surgery impact circadian photoreception; and (4) review some of the diverse morbidities associated with chronodisruption in general and those which may be caused by light deficiency in particular.

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## Introduction

Retinal rod and cone photoreceptors send conscious visual information through retinal ganglion cells and the lateral geniculate nuclei to the visual cortex. In 2002, a subset of retinal ganglion cells (<1% in humans) were identified as photoreceptors themselves.<sup>1</sup> These photosensitive retinal ganglion cells (pRGCs) transmit information through the retinal–hypothalamic tract synapsing directly on neurons in the suprachiasmatic nuclei (SCN) and other nonvisual brain centers.<sup>2</sup> pRGCs express the blue light sensitive photopigment melanopsin.<sup>3</sup> Approximately 3000 pRGCs cells per eye form a light sensitive network that spans the retina. Peak absorption of isolated pRGCs and melanopsin is ~480 nm.<sup>1</sup> Human nocturnal melatonin suppression is maximally sensitive at ~460 nm.<sup>4,5</sup> These maxima lie within the blue portion of the visible spectrum. pRGCs mediate a host of nonvisual effects with

a blue-shifted sensitivity quite different from longer (redder) wavelengths optimal for conscious vision, as shown in Fig. 1.<sup>6,7</sup> pRGCs detect ambient illumination allowing optimal physiological and neurobiological responses.<sup>1,6,8,9</sup> Additional unique features of pRGCs include resistance to bleaching,<sup>3</sup> sustained signals with light thresholds significantly higher than those required for conscious vision,<sup>2,3,10</sup> bistability,<sup>10a</sup> seasonal light adaptability and lack of spatiotemporal resolution.<sup>11</sup> Deficient pRGC photoreception cannot be perceived consciously.<sup>12</sup>

## Relevant circadian physiology

In mammals the master circadian clock resides within the paired suprachiasmatic nuclei of the anterior hypothalamus.<sup>2</sup> The SCN originate daily patterns of most physiologic and hormonal processes,<sup>13,14</sup> timing events to allow preparation for anticipated metabolic and physical activities.<sup>15,16</sup> Prior to habitual awakening the SCN initiate actions critical in transitioning from sleep to wakefulness including hepatic and adrenal stimulation which increases serum glucose and produces a morning cortisol surge.<sup>15,16</sup> Morning sunlight increases brain serotonin levels elevating mood,<sup>17</sup>

\* Corresponding author. Tel.: +1 913 345 0596; fax: +1 913 345 0597.

E-mail address: [plturnerm@att.net](mailto:plturnerm@att.net) (P.L. Turner).<sup>1</sup> Tel.: +31 20 5665500; fax: +31 20 6961006. [e.van.someren@nin.knaw.nl](mailto:e.van.someren@nin.knaw.nl).<sup>2</sup> Tel.: +1 913 345 0596; fax: +1 913 345 0597. [mmainste@kumc.edu](mailto:mmainste@kumc.edu).

### Nomenclature

ACTH	adrenocorticotropin hormone
CNS	central nervous system
CRH	corticotropin-releasing hormone
HPA	hypothalamic–pituitary–adrenal
IOL	intraocular lens
LAN	light-at-night
5-HT	serotonin
pRGC	photoreceptive retinal ganglion cell
SAD	seasonal affective disorder
SCN	suprachiasmatic nuclei
SNS	sympathetic nervous system
UV	ultraviolet

vitality and core body temperature. Peak cognition occurs as the day progresses and the SCN begin active inhibition of cortisol release for recovery from its morning peak.<sup>15</sup> By evening the SCN trigger initial secretion of the hormone melatonin which reduces alertness, lowers body temperature and promotes sleepiness. Within the first hours of slumber, cortisol continues to decline to a healthful daily nadir<sup>18</sup> while serum melatonin rises maximally. Two other hormones, prolactin and growth hormone, increase during sleep.<sup>14,15</sup>

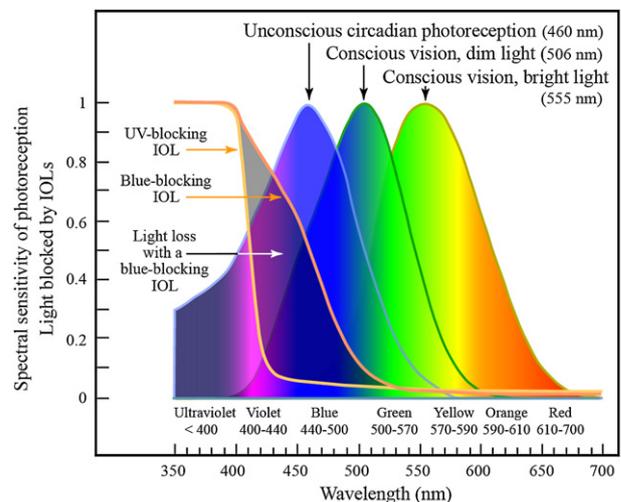
These and other processes occur in an invariant sequence throughout the SCN-controlled cycle which repeats daily, synchronized with the 24 h geophysical day under normally entrained conditions but at a typically non-24 h fixed inherited individual-specific period under experimental conditions without environmental cues.<sup>2</sup> The average human cycle was determined to be 24.2 h in one specific experimental protocol called ‘forced desynchrony’.<sup>19</sup> The molecular systems controlling the self-sustaining SCN clock oscillation have been studied extensively. Similar oscillatory mechanisms are present in most cells of the body.<sup>13,20</sup> These peripheral cell oscillations quickly decay into desynchrony without constant temporal alignment provided exclusively by the SCN via its neural, hormonal and possibly thermal signals.<sup>13,15,20</sup> Proper SCN functioning is critical to good health due to its vital roles including control of sleep–wake cycles, hormonal and metabolic rhythms, and synchronization of internal biological with external geophysical time thereby assuring temporal alignment within and between organs.<sup>13,15,21,22</sup> Without unambiguous SCN signals peripheral organs can become temporally uncoupled resulting in metabolic and biochemical disarray, flattening otherwise robust rhythm amplitudes.<sup>15</sup> This internal chronodisruption has been proposed to increase the risk of various diseases.<sup>16,20,22–29</sup>

Neither human SCN function nor its responses to different light sources can be measured directly so indirect assessments of activity, physiology or hormone levels are required. The hormone most closely associated with SCN function is melatonin, the primary product of the pineal gland.<sup>30</sup> SCN neurons control melatonin amplitudes by suppressing or actively stimulating<sup>31</sup> its pineal synthesis at appropriate times via a circuitous multi-synaptic sympathetic pathway.<sup>30,32</sup> Melatonin is secreted during the dark phase of the light–dark cycle in normally entrained diurnal (day-active) humans so its daytime levels are low.<sup>14</sup> During the dark phase, however, the normal nocturnal melatonin synthesis may be quickly suppressed by the SCN response to ocular light exposure depending on its intensity, spectrum, and duration.<sup>30,33,34</sup> Therefore darkness is required for melatonin

production during the proper phase of the SCN cycle. Nocturnal suppression of melatonin synthesis by light is the accepted surrogate for determining the efficacy of various light sources and exposures at producing the array of nonvisual light-mediated effects.<sup>35</sup> The amplitude (peak–nadir range) of daily melatonin levels is determined by and has been considered to be a proxy for SCN function.<sup>31,32</sup> Higher peak nocturnal melatonin values (greater daily amplitude) would signify robust SCN signal output for the range of physiological processes it controls. Additional proxies for SCN function include the phase relations of hormones, body temperature, activities within the environmental light–dark cycle, and the fluctuation characteristics, fragmentation and day-by-day variations in waveform, phase, and amplitude of activity rhythms.<sup>29,36–39</sup>

Melatonin serves numerous functions.<sup>30</sup> Its small lipophilic nature facilitates blood–brain barrier penetration and a ubiquitous dissemination that provides widespread hormonal timing signals and local effects. Melatonin is one of the most potent antioxidants known. Each melatonin molecule may scavenge up to 10 free radicals in a cascade extending to its secondary, tertiary and quaternary metabolites.<sup>40</sup> Serum melatonin levels contribute significantly to total plasma antioxidant capacity.<sup>41</sup> Melatonin has numerous additional proposed health benefits some of which are neuroprotection, anti-aging, immunomodulation, cardiovascular and oncostatic properties.<sup>30</sup>

Nocturnal plasma melatonin concentrations (amplitudes) are highest at about 3 years of age reaching a mean peak value of about 330 pg/mL.<sup>42</sup> As body weight increases in adolescence, this maximum declines to approximately 65 pg/mL. It remains controversial whether there is further age-related decline in nocturnal melatonin amplitude after puberty. Some studies report this decrease in melatonin and other hormones<sup>43</sup> whereas others show that elderly adults screened for good health may retain relatively youthful hormonal production.<sup>44</sup> Low melatonin levels are found in numerous disease states<sup>30,45–49</sup> while relatively preserved amplitudes occur in healthful advanced age.<sup>50,51</sup>



**Fig. 1.** The spectral sensitivity for unconscious circadian photoreception (melatonin suppression,  $\lambda_{\max} \sim 460$  nm), conscious dim light vision (scotopic luminous efficiency,  $\lambda_{\max} \sim 506$  nm) and conscious bright light vision (photopic luminous efficiency,  $\lambda_{\max} \sim 555$  nm). Also shown is the amount of light eliminated by a 30 diopter ultraviolet (UV)-only blocking or blue-blocking intraocular lens (IOL). The area between the curves is the amount of light lost to circadian and dim light vision when IOL transmission is decreased by visible light absorbers in blue-blocking IOLs.

## The critical role of light in circadian function

### Short wavelengths optimally mediate non-image-forming responses

Skylight was probably the evolutionary stimulus for pRGC photoreception. The dominant wavelength of skylight is 477 nm (blue),<sup>52</sup> close to pRGC's peak sensitivity. Outdoor illumination can exceed 100,000 lux, as shown in Fig. 2. With the advent of electricity and artificial lighting, industrialized society moved indoors isolated from traditional environmental light–dark extremes. Modern lighting provides at best 5% of natural light intensities<sup>11,53</sup> and its longer (redder) wavelength spectra are less efficient for pRGC photoreception.<sup>54</sup> Unconscious pRGC photoreception requires much higher light levels than those needed for conscious vision.<sup>1,2,10</sup> The effectiveness of a specific light exposure at producing pRGC mediated biologic effects depends on its intensity, duration and spectrum.<sup>34</sup> Brighter longer light exposures from sources richest in blue wavelengths most efficiently produce any of a wide range of pRGC mediated effects including melatonin suppression,<sup>4,5</sup> photoentrainment,<sup>55</sup> thermoregulation,<sup>8</sup> improved nocturnal sleep quality,<sup>56</sup> heart rate variability,<sup>8</sup> treatment of nonseasonal<sup>57</sup> or seasonal depression,<sup>58</sup> enhanced mood/well-being,<sup>59</sup> vitality,<sup>60</sup> alertness,<sup>8</sup> cognition,<sup>9</sup> reaction time and vigilance.<sup>6</sup>

### Clock resetting by bright light

Daily resetting of the master pacemaker is required to synchronize (entrain) endogenous SCN periods which otherwise usually differ from the 24 h geophysical day–night cycle. Entrainment is defined as the alignment of internal with external time by environmental timing cues (zeitgebers). Environmental light is the strongest and most important human zeitgeber.<sup>33,34</sup> It is perceived only by the eyes in mammals.<sup>1</sup> Sufficient well timed light exposure not only provides optimal timing cues but also enhances underlying SCN function.<sup>23,33,61–63</sup> The effectiveness of a particular light exposure for altering the timing (phase) of the endogenous SCN cycle (photoentrainment) depends on its delivery time relative to the circadian rhythm's phase.<sup>34</sup> Suprathreshold early morning light exposure advances while evening light delays the SCN's phase.

### Light insufficient for photoentrainment leads to free-running

Insufficient or absent<sup>34,64</sup> timing cues allow the SCN's endogenous rhythm to cycle independently of day–night cycles unless or until it receives an external stimulus sufficient to alter its inherent period. Repetitive cycling without daily resetting is termed free-running. Most totally blind individuals display free-running or abnormal circadian rhythms.<sup>34,65</sup> However, some visually blind (no conscious light perception) individuals retain normal unconscious pRGC photoreception and sufficient light exposure allows effective photoentrainment.<sup>66</sup> New definitions of blindness are needed to distinguish between individuals with and those without pRGC photoreception. The latter suffer the added disability of periodic extreme circadian desynchrony resulting in severe daytime drowsiness from increased circadian sleep propensity and surging daytime melatonin<sup>67</sup> with incessant insomnia due to circadian alerting during the geophysical night.<sup>68</sup> This condition is comparable to a lifetime of recurrent profound jetlag, and experienced as almost as disabling as blindness itself.<sup>69</sup>

The importance of light and photoentrainment is highlighted by observations that people free-run after bilateral enucleation (surgical eye removal; no possibility of pRGC photoreception) even when they are exposed to all nonvisual zeitgebers including regular meal, work and social schedules and awareness of time.<sup>34</sup> Blind people with intermittent insomnia and daytime napping<sup>67</sup> who

		Illuminance (lux)			
Photopic	<b>Photopic (cone) vision</b>				pRGC photoreception
		Sunlight, reflective surfaces	150,000		
		Bright sunlight, noon	100,000		
		Hazy sunny day	50,000		
		Cloudy bright day	25,000		
		Overcast day, SAD Rx*	10,000		
		Retail shop windows	1,000–5,000		
		SAD Rx*	2,500		
		Very overcast day	2,000		
		Bright industrial	1,500		
Mesopic	<b>Mesopic (cone &amp; rod) vision</b>				? Lower limits
		Kitchens	200–500		
		Living rooms	50–200		
		Corridors	50–100		
		Sunset	100		
	<b>? Circadian threshold?</b>				
		Nursing home	50		
		Bright street lighting	20		
		Candle at 30 cm	10		
		Full moon	1		
Scotopic	<b>Scotopic (rod) vision</b>				
		Dim street lighting	0.1		
		Quarter moon	0.01		
		Starlight	0.001		
	Moonless night, overcast	0.0001			
	<b>Human visual limit</b>	0.000001			

**Fig. 2.** Typical illuminances encountered in modern society and natural environments from various sources<sup>54,88,89</sup> and verified independently when feasible using two different light meters in a horizontal working plane 750 mm above floor level (Extech Instruments Corporation, Waltham, MA, USA; Model 403125 Light ProbeMeter and Model EA30s). The unit lux (photopic) is used to facilitate illuminance comparisons. A circadian lux would be more accurate for our discussion of pRGC photoreception but this new unit has yet to be standardized and adopted.<sup>189,191</sup> \*Light levels in seasonal affective disorder phototherapy (SAD Rx) are typically 2,500 lux for 2 hours/day or 10,000 lux for 30 minutes/day.<sup>57</sup>

receive sufficient light exposure should be suspected of free-running and typically entrain with daily exogenous melatonin taken evenings at the same time before bedtime, improving their quality of life<sup>70</sup> and possibly reducing risks of early mortality that are associated with visual loss.<sup>71–75</sup> Fortunately, entrainment by exogenous melatonin in totally blind individuals has been shown to improve sleep indices as well as entrain pituitary–adrenal activity, lowering cortisol nadirs and increasing amplitudes.<sup>76</sup> Other approaches for non-photic clock entrainment that have shown some efficacy in rhythm-disturbed Alzheimer patients have not yet been evaluated in the blind.<sup>77,78</sup> Unfortunately, lacking pRGC photoreception permanently excludes totally blind individuals from experiencing the acute direct and immediate benefits of bright light including the enhancement of mood,<sup>17</sup> cognition,<sup>9,59</sup> increased alerting, reduced sleepiness<sup>79</sup> and light-mediated autonomic effects,<sup>8,80</sup> the long-term consequences of which remain unknown.

### Aging and artificial lighting predispose to circadian light deficiency

#### Age progressively limits pRGC photoreception even with normal vision

Regardless of visual acuity, human crystalline lens aging causes a progressive loss of light transmission particularly for shorter (bluer) wavelengths below 500 nm that are most valuable for circadian photoreception.<sup>81</sup> Pupillary area also decreases (miosis)

with senescence, further reducing retinal illumination.<sup>82,83</sup> Both factors produce progressive age-related losses in circadian photoreception<sup>11</sup> as presented in Table 1, which also shows the increase or decrease in illumination needed by one age group to achieve circadian photoreception equivalent to another age group.<sup>11</sup> Our calculations were performed relative to a 10 year old because this age represents a lifetime maximum for retinal illuminance based on crystalline lens transmission and pupillary diameter. Very elderly individuals retain only 10% of a 10 year old's photoreception and therefore require ten times brighter exposures from identical light sources to maintain youthful circadian performance. Fig. 3 displays the uniform decline in circadian photoreception over decades and its improvement following cataract surgery using various intraocular lenses (IOLs). Rod photoreceptor and retinal ganglion cell populations decline with aging, but cone photoreceptor populations remain relatively stable.<sup>84,85</sup> The effect of aging on retinal ganglion photoreceptor populations is not currently known. Glaucoma is associated with ganglion cell losses, but pRGCs were resistant to ocular hypertension in one experimental rodent study.<sup>86</sup> Photoreceptive losses shown in Table 1 will be underestimated if (1) pRGC populations decline with aging or, are lost due to ocular disease,<sup>11</sup> or (2) ocular media clarity is reduced or visible light blocking filters are used.<sup>7</sup>

*Human circadian thresholds exceed average residential lighting levels*

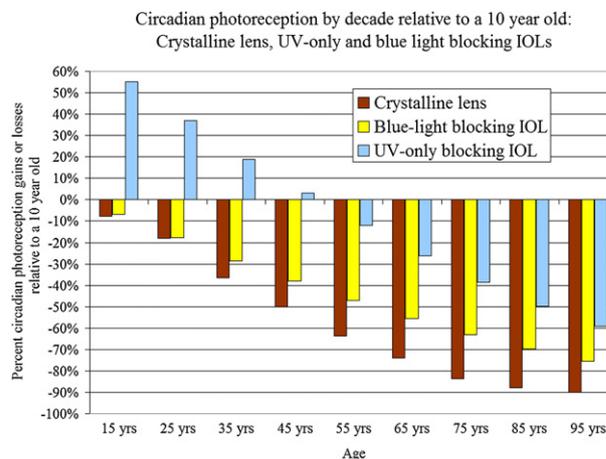
Home illumination averages 100 lux or less.<sup>32,53,87</sup> Typical environmental illuminances are shown in Fig 2.<sup>54,88,89</sup> Residential lighting is dim compared to natural lighting.<sup>90</sup> Additionally, corneal irradiance is typically only 10–20% of values reported for horizontal surface measurements.<sup>53,90,91</sup> Minimum daily light exposure necessary for nonvisual photoreception varies with numerous intrinsic and extrinsic factors.<sup>11</sup> For example, poorly timed, dimmer, blue wavelength-deficient light exposures require longer durations to produce any specific nonvisual pRGC mediated effect in older individuals assuming the pRGC threshold is exceeded.

Most human studies of photic neurobiological effects employ one or more physiologically artificial techniques including head stabilizing chin rests, pharmacologic pupillary dilation,<sup>92</sup> monochromatic light sources and monitored fixation directed at or adjacent to light sources for many hours. Circadian photoreceptive

**Table 1**  
Comparative circadian photoreception at different ages in phakic eyes.<sup>a</sup>

	10 yrs	15 yrs	25 yrs	35 yrs	45 yrs	55 yrs	65 yrs	75 yrs	85 yrs	95 yrs
10 yrs	1	0.92	0.82	0.64	0.50	0.36	0.26	0.16	0.12	0.10
15 yrs	1.08	1	0.89	0.69	0.54	0.39	0.28	0.18	0.13	0.11
25 yrs	1.22	1.12	1	0.77	0.61	0.44	0.32	0.20	0.15	0.12
35 yrs	1.57	1.45	1.29	1	0.79	0.57	0.41	0.26	0.19	0.16
45 yrs	2.00	1.85	1.64	1.27	1	0.73	0.52	0.33	0.24	0.20
55 yrs	2.75	2.54	2.26	1.75	1.38	1	0.72	0.45	0.34	0.28
65 yrs	3.84	3.55	3.15	2.44	1.92	1.40	1	0.63	0.47	0.38
75 yrs	6.08	5.61	4.99	3.87	3.04	2.21	1.58	1	0.74	0.61
85 yrs	8.21	7.58	6.74	5.22	4.10	2.98	2.14	1.35	1	0.82
95 yrs	9.99	9.22	8.20	6.35	4.99	3.63	2.60	1.64	1.22	1

<sup>a</sup> Age-related decreases in pupil area<sup>82</sup> and crystalline lens transmission<sup>81</sup> cause an age-related decrease in circadian photoreception in phakic individuals. Circadian performance for an age in the top row is shown relative to that of an age in the left column. To determine the relative circadian photoreception for undilated persons of different ages, select a reference age from the top row and compare it to ages in the left column. For example, a 45 year old has roughly half the circadian photoreception of a 10 year old and 3 times that of a 75 year old. To determine the relative illumination needed by individuals of different ages to achieve equivalent circadian photoreception, select an age from the left column and compare it to an age in the top row. For example, a 45 year old needs roughly twice the illumination of a 10 year old and a third of that of a 75 year old.<sup>11</sup>



**Fig. 3.** Circadian photoreception relative to a 10 year old phakic eye for individuals at different ages with a crystalline lens or with either a 30 diopter ultraviolet (UV)-only blocking (Tecnis, Abbott Medical Optics, Santa Ana, CA, USA) or blue-blocking (Alcon, Fort Worth, TX, USA) IOL. Age-related decreases in pupillary area and crystalline lens transmittance reduce circadian performance in individuals who have not had cataract surgery. Age-related decreases in pupillary area reduce circadian performance in individuals who have had cataract surgery. Circadian performance improves after cataract surgery regardless of age, but improvements are highest in individuals with colorless UV-only blocking IOLs that do not reduce blue light transmission to the retina.

thresholds for white light exceed typical residential light levels (cf., Fig. 2) in unrestrained, undilated humans.<sup>10</sup> Young adult subjects (~25 years old) free-run when lighting is less than 80 lux<sup>93</sup> or 200 lux.<sup>94</sup> Astronauts (ages 37–46) free-run at typical space shuttle illuminances below 80 lux, producing circadian disruption, sleep impairment and reduced neurobehavioral performance.<sup>64</sup> Adults under 35 years old do not suppress melatonin when exposed to 200 lux for 3 h.<sup>95</sup> How much additional illuminance would have been required to exceed threshold and produce the photoentrainment or melatonin suppression studied in these experiments is unknown. Under these experimental conditions 80–200 lux were insufficient for pRGC photoreception in healthy sighted 25–35 year old subjects. Significantly higher illuminances would also be inadequate for older adults with their decreased crystalline lens transmittance and pupil area. For example, 128–320, 184–460, 256–640, 400–1000, 536–1340, and 656–1640 lux would be insufficient in 45, 55, 65, 75, 85 and 95 year old adults, respectively (cf., Table 1).<sup>11</sup> These illuminances are much higher than average residential light levels as shown in Fig. 2.<sup>10,53</sup>

*Optimal neurobiologic function depends on exposures to sunlight*

Midwinter insomnia is common at high latitudes, affecting 80% of some populations.<sup>96,97</sup> Extended bed rest studies (subjects 25–51 years old) in windowless rooms result in progressive sleep deterioration, free-running rhythms, and dampening of circadian amplitudes, even with brighter-than-average daytime illuminance of 200–500 lux.<sup>27</sup> Sighted individuals with minimal sunlight exposure may experience insomnia, free-running rhythms, flattened hormonal profiles, cognitive difficulties and undetectable nocturnal melatonin levels which subsequently normalize with restoration of normal sunlight exposure.<sup>98,99</sup>

Daily illumination and depressed mood are inversely correlated.<sup>100</sup> Over 90% of people experience mood reductions during periods of overcast weather or seasonal reductions in length or intensity of daylight.<sup>101–103</sup> Seasonal affective disorder (SAD) is one debilitating extreme in a continuum of sunlight-deficiency-induced neuropsychological disorders. SAD causes distress in up to 10% of

general populations with higher incidences in women. The sub-syndromal yet clinically significant milder form of SAD causes difficulty in an additional 20% of people.<sup>104</sup> Interior residential and industrial lighting does not change in brightness daily or seasonally, suggesting that artificial lighting is often inadequate for neurobiological needs and that most people require intermittent sunlight exposures at illuminances typically much higher than 1000–3000 lux for optimal well-being (cf., Fig. 2). Nonseasonal depression is also inversely correlated with average illuminance.<sup>105,106</sup> The elderly have higher incidences of nonseasonal-type depression positively correlated with age.<sup>100,107,108</sup>

*Exposure to sunlight is usually minimal and declines with aging*

Young adults in industrialized countries typically receive only 20–120 min of daily light exceeding 1000 lux.<sup>56,105,109,110</sup> Elderly adults receive only 1/3–2/3 as much daily bright light exposures.<sup>56,111</sup> Additionally, older women average 1/2 to 1/4 of the light exposures as age-matched men.<sup>111,112</sup> These lifestyle preferences for reduced light exposure in older adults occur when they instead should progressively increase ambient lighting by at least: 2, 3, 4, 6, 8 and 10-fold by ages 45, 55, 65, 75, 85 and 95, respectively, to maintain the circadian photoreception of their youth (cf., Table 1).<sup>11</sup> Alzheimer's patients receive less light than age-matched controls.<sup>111</sup> Once institutionalized they may receive fewer than 10 min of daily light exceeding 1000 lux, with median ambient light levels as low as 54 lux.<sup>113,114</sup>

### Morbidity associated with chronic circadian disruption

*Shift work: circadian disruption, depressed melatonin and increased morbidity*

People with normally entrained diurnal rhythms receive a nightly surge of melatonin. The duration of nocturnal melatonin secretion parallels the length of the daily dark period which varies seasonally at higher latitudes. Melatonin's anti-gonadal properties reduce fertility during certain months mediating optimal birth timing for seasonal breeding animals.<sup>30</sup> Prior to the 1930s, before electric lighting became routine, human conception was seasonal and correlated with photoperiod at higher latitudes.<sup>115</sup> Melatonin has also been reported to possess oncostatic properties.<sup>48,116,117</sup> Oncostatic and anti-gonadal effects may help explain the protection offered by optimal nocturnal melatonin levels against the incidence and mortality of various cancers, particularly hormonal-dependent malignancies such as breast or prostate cancer.<sup>30,53</sup>

Up to 20% of industrialized employees work at night exposing themselves to light that could potentially suppress normal nocturnal melatonin secretion if exposures are sufficient to do so.<sup>53</sup> The "melatonin hypothesis" postulates that "light-at-night" (LAN) is an important factor in explaining the higher cancer risks found in industrialized countries.<sup>53,118</sup> Light suppression of nocturnal melatonin probably does contribute to this higher cancer incidence especially in younger night workers exposed to bright lighting such as that found in operating rooms, intensive care units and industrial applications (cf., Fig. 2). The prevalence and degree of nocturnal melatonin suppression during a nightshift depends critically on the spectrum, intensity, duration, and timing of light exposures.<sup>53</sup> Also important is retinal illumination which varies among individuals, with age and lens status (cf., Table 1).<sup>11,119</sup>

Nightshift workers have been shown to receive less daily bright light (>1000 lux) at less optimal times than dayshift workers.<sup>53,120</sup> SCN function is enhanced with bright properly timed light exposures, deficiency of which may lead to pacemaker dysfunction.<sup>23,33</sup> Perhaps most importantly, the majority of nightshift workers appear to maintain entrainments typical of day-active people

thereby being awake and working 4–5 nights per week during their biologic night.<sup>120</sup> Chronodisruption itself is known to significantly flatten melatonin amplitudes<sup>27</sup> reflecting the dampened rhythms of the underlying SCN which controls its pineal secretion. The flattened melatonin amplitudes generally associated with rotating shift work are therefore potentially largely attributable to their chronic desynchrony and bright light deficiency rather than just nocturnal suppression of melatonin. Supporting underlying SCN dysfunction as a source of the morbidity of shift workers is their higher incidences of numerous diverse signs and symptoms typical of circadian dysfunction<sup>53,121–123</sup> including insomnia, depression,<sup>124</sup> elevated cortisol levels, cognitive impairment with hippocampal atrophy,<sup>23,122,123</sup> metabolic disorders, increased cardiovascular disease<sup>121</sup> and premature mortality.<sup>125</sup>

*Visual loss: circadian disruption, reduced cancer risk but early mortality*

Blind women have half the incidence of breast cancer as sighted cohorts suggesting their deficient photoreception protects their daily melatonin secretion from light suppression.<sup>53,126</sup> Indeed, the incidence of most types of cancers in blindness is half that of sighted people of either gender,<sup>127</sup> a relationship that also holds for visual loss.<sup>128</sup> In a cohort of over 17,000 persons followed for 20 years, the incidence of breast and prostate cancer was directly correlated with visual acuity.<sup>128</sup> Remarkably, however, numerous investigators report that overall life expectancy of totally blind persons or those with varying degrees of visual loss is significantly reduced compared to sighted controls even after controlling for other risk factors.<sup>71–75,129</sup> This reduced life expectancy is surprising because relative immunity from cancer presumably should extend survival. There has been no compelling explanation to date for the association of vision loss with premature mortality, which has been described as not explained "by potential confounders"<sup>74</sup> or "by traditional risk factors for mortality".<sup>71</sup>

Most totally blind individuals experience abnormal circadian rhythms.<sup>34,65</sup> Visual impairment may also reduce light exposure and restrict outdoor activities resulting in pRGC light deficiency despite viable photoreceptors that might otherwise provide effective photoreception and SCN function.<sup>100</sup> The insomnia of blindness<sup>69</sup> and visual loss<sup>130</sup> produces a nearly 3-fold increased prevalence of short sleep syndrome (sleeping 5 or less hours nightly) in comparison to sighted controls.<sup>131</sup> Sleep loss is a risk factor for metabolic and cardiovascular disease.<sup>15</sup> Blind subjects are predisposed to metabolic, cardiovascular and memory deficits which have been attributed to their overall elevations of adrenocorticotropin hormone (ACTH) and cortisol, flattened rhythms with loss of the important early night nadir of these hormones, and sleep fragmentation with deficient slow wave sleep activity.<sup>76</sup> All of these are signs of SCN dampening which may initiate a chain of adverse sequelae.<sup>15,16,18,132–142</sup>

Chronic circadian disruption may lead to suboptimal internal synchronization of physiological processes that could interfere with each other if not properly timed<sup>29</sup> and consequently induce biological stress. The stress response may or may not activate the two functionally interrelated and reciprocally innervated pathways of the stress cascade, the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system (SNS).<sup>143</sup> HPA axis glucocorticoids and SNS catecholamines mediate morbidity associated with chronic activation of the stress cascade. SCN set the daily rhythm and amplitude of cortisol by maintaining simultaneous excitatory and inhibitory connections within the HPA axis responsible for glucocorticoid production.<sup>15,18</sup> SCN normally restrain the HPA axis and check excessive stress responses, but this inhibition may be lost if its efferent signals are dampened.<sup>15,18</sup>

We hypothesize that the increased risks of morbidity and early mortality associated with visual loss and blindness may be due to the many consequences of chronic chronodisruption with reduction of SCN output amplitudes, metabolic imbalances and an unchecked activation of the stress cascade. This may lead to chronic hypercortisolemia, as well as dampening of hormonal and physiological rhythms and peripheral cell asynchrony. Sighted non-shift working individuals have the same potential risks if bright light exposures are insufficient or ocular aging predisposes them to light deficiency.<sup>11,27,64,83,98,99,142</sup>

### Light deficiency may contribute to common age-related morbidities

By 45 years of age circadian photoreception has already decreased by 50% (cf., Table 1) which combined with typical patterns of reduced bright light exposure<sup>105,109</sup> may explain why significantly reduced melatonin amplitudes have been found by the fourth decade in some individuals.<sup>144</sup> Bright light exposure has been shown to increase nocturnal melatonin amplitudes in both young and elderly adults, restoring them to youthful levels in the older patients.<sup>56</sup> Higher melatonin levels are associated with fitness<sup>51</sup> and levels are found to be relatively preserved in healthy medically screened elderly.<sup>44</sup> Conversely, low melatonin amplitudes are correlated with diverse diseases.<sup>45–49</sup> Prospective studies nested within the Harvard Nurses Study have shown that higher nocturnal melatonin amplitudes were associated with a lower incidence of breast cancer over four year follow-up periods for both pre and postmenopausal women.<sup>48,145</sup>

Herljevic et al.<sup>119</sup> compared nocturnal melatonin suppression by monochromatic blue (456 nm) light in two groups of women with mean ages of 24 and 57 years. Older women were insensitive to blue light sufficiently intense to significantly suppress melatonin in youthful women. This study demonstrates that age-related crystalline lens yellowing reduced ocular transmission of the blue wavelengths optimal for circadian photoreception to levels ineffective for nonvisual photoreception, even under the best of circumstances (dilated pupils, light source-directed gaze fixation and optimal monochromatic wavelength). The younger women moreover produced twice the total daily melatonin as the older women. A similar experimental protocol in younger (mean age, 23 years) and older (mean age, 66 years) men also demonstrated blue light suppression by the crystalline lenses of the older group reducing otherwise significantly enhanced short-wavelength-light-induced responses to subjective alertness, sleepiness and mood.<sup>79</sup> Unfortunately environmental light exposures appear to decline with advancing age<sup>56,111</sup> just as pupillary miosis and crystalline lens yellowing block more of the blue light optimal for circadian photoreception.<sup>11</sup> This decreasing bright light occurs at ages when older people should instead be increasing their ambient illumination by factors ranging from 2 to 10 fold to simply maintain the equivalent circadian photoreception of their youth (Table 1).<sup>11</sup>

Melatonin is considered the most accurate marker of human SCN function because the timing of its plasma rhythm<sup>30</sup> and amplitude<sup>31</sup> is directly orchestrated by the circadian pacemaker.<sup>32</sup> Human melatonin levels decline with light deficiency, flattening progressively as bright light deficiency persists over days,<sup>27</sup> and falling by as much as 33% after only four days of near darkness.<sup>146</sup> Melatonin levels may become undetectable with protracted light insufficiency.<sup>98</sup> These and other studies suggest that light deficiency is detrimental to SCN function even in young people and, as will be discussed below, that bright environmental light may restore effective underlying pacemaker function even in elderly subjects.

Light intensities of at least several thousand lux can compensate for age-related reductions in retinal illumination,<sup>11</sup> so elderly adults

with intact pRGCs who spend ample time outdoors should receive sufficient illumination for circadian demands (cf., Fig. 2). Environmental light exposures have not been monitored in studies examining whether melatonin levels decline with aging. Varying light histories may explain conflicting reports of possible declines in nocturnal melatonin production. Lifestyles of healthy elderly retaining youthful melatonin levels likely include regular exposures to bright environmental light.<sup>44,51</sup>

### Light deficiency as a possible cause of chronodisruption

Light is the primary zeitgeber in humans.<sup>33,34</sup> Illuminance and photoperiod are key environmental factors influencing human SCN function.<sup>24</sup> The strength (amplitude) of SCN rhythmic signals are influenced by bright light exposure, deficiency of which may initiate an interlocking cascade of events potentially causing loss of physical and psychological well-being.<sup>15,16,18,132–142</sup> With insufficient light exposure, hormonal and physiological amplitudes may be reduced.<sup>23,27,98</sup> One dampened rhythm is associated with others, reflecting their common origins in weakened SCN control<sup>22,27,76,98,147</sup> that may increase the risk of all-cause morbidity.<sup>25</sup> We therefore suggest that pRGC light deficiency may contribute to chronodisruption in some individuals, even if light exposures are otherwise properly timed, and that this risk increases substantially with age in phakic (native crystalline lens in place within the eye) subjects due to ocular senescence which reduces retinal illuminance for pRGC photoreception.<sup>11,83</sup> Restoring bright properly timed light exposures sufficient to compensate for possible age-related crystalline lens yellowing and pupillary miosis improves SCN function as measured by restored hormonal levels and core body temperature amplitudes.<sup>56,98,99</sup>

### Bright light's effects on human disease, physiology and function

This section examines some of the proven nonvisual effects of bright light, describing how morbidity from light deficiency may be reversible with restoration of effective environmental illuminance.

#### Insomnia

Insomnia in elderly people may be aggravated by low ambient illumination levels.<sup>56,114</sup> Bright daytime light consolidates fragmented into continuous sleep patterns fortifying circadian rhythms.<sup>148</sup> Threshold intensities of at least 2500–3000 lux have been shown to reduce or alleviate insomnia<sup>56,149,150</sup>; increase sleep efficiency, total sleep time, and restorative slow wave sleep<sup>151</sup>; and improve daytime vigilance and sleepiness.<sup>149</sup> Light therapy for insomnia is also effective for the institutionalized elderly.<sup>152,153</sup> Cataract surgery alone with colorless ultraviolet (UV)-only blocking IOLs has been shown to reduce the incidence of insomnia by 50%,<sup>130,154</sup> without altering habitual light exposures. Reduced circadian photoreception due to crystalline lens yellowing and pupillary miosis becomes significant by early middle age. Cataract surgery can restore the youthfulness of circadian photoreception by up to 4 decades when colorless UV-only blocking IOLs are utilized.<sup>11,79,119</sup>

The mechanisms by which bright daytime light improves nighttime sleep quality have yet to be determined, but light is the paramount zeitgeber<sup>33</sup> and enhanced SCN sleep/wake signal generation may be involved.<sup>21,150</sup> Light may modulate sympathoexcitation.<sup>62</sup> Bright evening light alters sympathovagal balance, decreasing sympathetic activation which might otherwise prevent deeper and slow wave sleep.<sup>155,155a</sup> Light-induced increases in central nervous system (CNS) serotonin<sup>17</sup> may facilitate sleep by stimulating serotonergic brain centers such as the raphe nuclei implicated in the promotion of slow wave sleep.<sup>156</sup> Sleep and particularly slow wave sleep have been proposed to inhibit the HPA axis and cortisol secretion.<sup>76,157</sup>

### Subjective mood and well-being

Bright light significantly improves subjective mood,<sup>100</sup> well-being, optimism, quality of life and social function in general<sup>60</sup> and elderly<sup>158</sup> populations free of depression. Employees experience improved vitality and reduced depressive mood with increased workplace illumination.<sup>59,60</sup>

Lambert et al.<sup>17</sup> sampled internal jugular vein blood to determine CNS neurotransmitter concentrations under different light exposures. Brain serotonin (5-HT) production rate varied immediately and directly with prevailing brightness and duration of sunlight.<sup>17</sup> Serotonin levels also increase with light therapy for nonseasonal depression,<sup>159</sup> suggesting that serotonin contributes to the strongly positive effect of bright light on mood. Serotonin stimulates neurogenesis and activates the 5-HT<sub>1A</sub> receptors<sup>160</sup> responsible for reducing anxiety, depression and increasing feelings of well-being.<sup>161</sup>

### Depression

Morning light therapy for seasonal (SAD and sub-syndromal variants) depression with 2 h of 2500 lux or 30 min of 10,000 lux light-box illumination provides 70% response rates compared to no light intervention.<sup>104</sup> Meta-analyses confirm that bright light therapy is effective for treating both seasonal and nonseasonal depression and that shorter (bluer) wavelengths are more effective than longer (redder) ones.<sup>57,58,162</sup> Beyond improving depression, light treatment increases circadian amplitude of core body temperature, enhances energy and improves sleep in nonseasonal major depression,<sup>163</sup> corroborating suggestions that SCN dysfunction contributes to depression and its circadian control is enhanced by bright light.<sup>23,33</sup>

### Melatonin amplitudes

Bright daytime light ( $\geq 2500$  lux) increases nocturnal melatonin amplitudes in young<sup>164–166</sup> and restores youthful levels in older adults.<sup>56,167</sup> Elderly insomniacs produce less nocturnal melatonin and receive less environmental light than controls without insomnia.<sup>56</sup> Light therapy with 2500 lux for 2 h twice daily restores melatonin amplitudes and reduces insomnia in elderly patients.<sup>56</sup> Sighted individuals restricted to prolonged indoor lighting such as extended convalescences or choosing minimal bright light exposure lifestyles may experience circadian disruption including dampening of normal hormonal amplitudes and sleep disturbance.<sup>27,98</sup> Undetectable melatonin levels may normalize with restoration of adequate light and sleep disturbances resolve.<sup>98</sup>

### Cognition

Bright light immediately enhances cognitive performance depending on its intensity and spectrum. Cognition for complex tasks significantly improves with blue ( $\sim 470$  nm) as compared to monochromatic green ( $\sim 550$  nm) light.<sup>9</sup> Sunlight is much brighter than typical indoor lighting and has an optimal spectrum rich in blue wavelengths. Student performance in sunlit classrooms is 5–14% better than test scores under artificial lighting.<sup>168</sup> Daylit workplaces significantly increase office productivity<sup>169</sup> whereas windowless settings reduce jobsite productivity and increase absenteeism.<sup>170</sup> Workplace lighting rich in blue wavelengths reduces fatigue and daytime sleepiness while increasing alertness, performance and accuracy.<sup>59</sup> Cognition of Alzheimer patients improves with bright light exposures.<sup>152,171</sup> This effect may in part be mediated by light-induced improvements of sleep – hippocampal function in elderly people which have been shown to be very sensitive even to mildly disrupted sleep.<sup>172</sup> These studies suggest that blue light blocking by the aged crystalline lens<sup>79,119</sup> may contribute to age-related cognitive declines and that cataract surgery with IOLs transmitting blue light may be helpful in improving cognition. Cataract surgery with colorless UV-only blocking intraocular lenses reduces daytime sleepiness.<sup>154</sup>

### Alzheimer's disease

Alzheimer's disease disrupts sleep-wake and other biological rhythms. Melatonin amplitudes are typically low and correlated with disease severity.<sup>46</sup> Sleep-wake rhythms become increasingly disturbed with disease progression.<sup>46,113</sup> Nursing home lighting is typically poor<sup>114</sup> and circadian rhythm abnormalities including free-running<sup>46,173</sup> may occur in up to 97% of residents.<sup>174</sup> Nineteen nursing home residents were each objectively monitored for one day and found to display both sleep and wakefulness during each of the 24 h.<sup>175</sup> Dampened SCN rhythms may prevent consolidated alterations of active alerting for wakefulness and active sleep promotion during their respective circadian phases.<sup>21,174,176</sup> If vision is intact,<sup>23</sup> restoring bright daytime light ( $\geq 2500$  lux) can improve cognition and nocturnal sleep, and reduce daytime napping and agitation<sup>171,177</sup> except in the most advanced stages of Alzheimer's disease. Artificial dawn-studies indicate that not only the level of daytime light exposure, but also the presence of a clear daily dark-light transition signal may be important to support SCN function.<sup>178</sup>

A diagnosis of Alzheimer's disease is sometimes considered a contraindication for cataract surgery thus placing this largely indoor-dwelling population<sup>174</sup> in greater jeopardy of pRGC light deficiency. Modern cataract surgery using topical or local anesthesia requires patient cooperation which could be problematic in demented patients. General anesthesia for cataract extraction is now uncommon but used occasionally when necessary. Patients in the earliest stages of dementia and Alzheimer's disease may benefit from an ophthalmic evaluation while their cooperation is still possible. Cataract surgery, in at least one eye if indicated, can improve circadian photoreception and possibly reduce the adverse effect of chronodisruption in these patients.<sup>11</sup>

### Therapeutic intervention

#### Cataract surgery

Cataract surgery removes a barrier to short wavelength light optimal for circadian photoreception. The yellowed crystalline lens is surgically replaced with an intraocular lens (IOL). UV-only blocking IOLs are the current standard of care in ophthalmology. They absorb most UV radiation and possibly some additional violet light, but they maximally transmit blue light.<sup>7,179</sup> Asplund and Lindblad demonstrated that cataract surgery with UV-blocking IOLs significantly improves nocturnal sleep and reduces daytime sleepiness.<sup>130,154</sup> These benefits increase with second eye surgery and over a 9 month follow-up. Anticipated prevalence of poor sleep was reduced by 50% without altering habitual light exposure patterns.<sup>130,154</sup>

In the early 1990's yellowish blue-blocking IOLs were designed with the expectation that they might improve photopic vision and later promoted to reduce the hypothetical risk of age-related macular degeneration (AMD). These conjectured benefits have never been proven clinically.<sup>180</sup> Blue-blocking IOLs occlude most UV radiation which is potentially harmful and not useful for vision. They also eliminate substantial amounts of violet light and the blue light which is optimal for pRGC photoreception. Blue blocking IOLs are still in use today.<sup>180</sup>

Evidence documenting the vital role of blue light for optimal systemic and mental health has grown rapidly. Cataract populations potentially have the most to benefit from optimal pRGC photoreception because they typically have less daily light exposure than younger adults, smaller pupils, and higher prevalences of insomnia, depression and cognitive difficulty.<sup>11</sup> IOLs that maximally transmit blue light may potentially help compensate for suboptimal environmental light exposures and potential pRGC population losses due to aging or disease.<sup>7,11,79,119</sup>

### Phototoxicity

The retinal phototoxicity-AMD hypothesis posits that AMD results in part from cumulative retinal damage due to repetitive acute retinal phototoxicity (photic retinopathy) caused by environmental light exposure.<sup>7,180</sup> This hypothesis remains unproven after decades of careful study. The vast majority (10/12) of the large major epidemiological investigations found no correlation between AMD and environmental light exposure.<sup>180</sup> They should have provided convincing evidence if a significant correlation did exist. Their failure to do so may be due to an otherwise weak correlation being confounded by variability in lifestyle choices, genetic susceptibility or diet.<sup>7</sup> Cataract surgery markedly increases retinal illuminance from environmental light, as shown in Fig. 3, identifying another critical weakness of the AMD-phototoxicity hypothesis: large prospective trials demonstrate conclusively that cataract surgery does not increase the progression of AMD.<sup>181</sup> Long-term follow-up of SAD patients treated with 10,000 lux light box therapy reveal no ocular abnormalities.<sup>182</sup> Taken together the weight of clinical evidence indicates that normal environmental light exposure does not pose a retinal hazard for phakic or pseudophakic (cataract surgery with an artificial lens implanted) adults. Phakic individuals are at risk of cataractogenesis from solar UV-B radiation, so brimmed hats and UV-protective sunglasses are advisable when they are outdoors near midday in bright sunny environments.<sup>179,183–185</sup> Habitual or fashion use of sunglasses may be counterproductive for nonvisual photoreception and good health in most people when used outside the brightest midday period (11:00 to 15:00 h), unless the landscape is highly reflective.<sup>183</sup>

### Architectural lighting and public education

Modern illumination engineering has produced a growing range of energy efficient light sources with luminance spectra closer to natural outdoor lighting than conventional incandescent sources. This work continues with emphasis on higher luminances and environmentally friendlier components. There is still a need to update existing work place and residential lighting to provide the higher illuminances that older adults need to achieve more youthful circadian photoreception. Residential lighting could be optimized by time-structured illuminance designed for circadian demands during daytime hours and limited to lower thresholds required for conscious vision during the geophysical night. Architectural trends already support this concept with the use of skylights, large windows, passive light pipe illuminators, and temperature-controlled solariums that are especially valuable for retirement living and extended care facilities. Medical and public education programs disseminating information regarding the inadequacies of exclusive reliance on residential levels of artificial lighting, importance of avoiding light-at-night and potential benefits of properly timed bright, ideally natural, light exposures may also reduce morbidity.

### Conclusions

Environmental illumination plays an important role in human health. The eye mediates this effect because retinal ganglion photoreceptors provide vital information about ambient illumination and light–dark cycles to nonvisual (non-image-forming) brain centers including the SCN. These data are necessary to coordinate metabolic homeostasis thus avoiding physiological stress and assure optimal levels and proper timing of the synthesis of essential CNS hormones and neurotransmitters including cortisol, melatonin and serotonin. SCN control timing and coordination of numerous central and peripheral physiological processes, but require bright, properly timed environmental light exposures for robust circadian amplitudes, optimal

neuropsychological functioning and photoentrainment of their typically non-24 h periodicity to match geophysical day–night cycles.

Ocular aging and inadequate environmental illumination limit nonvisual photoreception. Common morbidities often assumed to be age-related inevitabilities may result in part from light-deficiency-induced SCN signal output dampening that may produce chronodisruption and possible hyperactivation of the HPA axis and stress cascade. Chronic chronodisruption may increase the risks of insomnia, depression, cognitive impairment, dementia, inflammation, obesity, metabolic syndrome, cardiovascular disease and premature mortality. Interactions are complex, but light deficiency may be a common causative factor. We suggest that chronic SCN dysfunction could account for the strong association of blindness and visual loss with early mortality. Sighted, non-shift working individuals may also be at risk for chronodisruption from pRGC light deficiency even if light exposures are otherwise properly timed. These risks would increase with aging due to progressive loss of retinal illumination caused by decreasing pupillary area and crystalline lens transmission. Morbidity may be decreased and quality of life improved by (1) lifestyle changes that increase sunlight exposure, (2) light supplementation and natural lighting in homes and buildings, (3) cataract surgery, and (4) exogenous melatonin entrainment for totally blind individuals lacking pRGC photoreception.

### Practice points

- 1) Nonvisual light deficiency cannot be perceived consciously. Typical residential illuminance is too low for circadian needs even in young adults. Properly timed exposure to sunlight or other bright light sources is vital for mental and physical well-being in all age groups.<sup>11</sup> Optimal intensity and timing of environmental light exposure depend on many individual-specific variables including length of the endogenous circadian period, lens transmittance, pupillary diameter, integrity of pRGC photoreceptor populations and prior light history. In general, several hours of at least 2500 lux of blue-weighted light exposure (ideally sunlight) starting early in the morning benefit most people. Bright light immediately and directly enhances cognition, alertness, performance and mood, so bright environments throughout the day provide additional benefits, especially for middle-aged or older adults.
- 2) Progressive, age-related losses in circadian photoreception potentially occur in everyone, regardless of their visual acuity.<sup>11</sup> It may be possible to maintain youthful circadian photoreception with adequate daily outdoor daylight exposure or by using adequately bright and properly timed indoor lighting to compensate for age-related losses in pupillary area, crystalline lens transmittance and perhaps pRGC populations.<sup>11</sup>
- 3) Bright, properly timed light exposures are helpful for managing symptoms of circadian dysfunction including insomnia, depression, reduced cognitive function and fatigue. These exposures may help normalize signs of chronodisruption including depressed hormonal amplitudes, increased ACTH, CRH or cortisol levels, and loss of normal daily core body temperature rhythms.
- 4) Evolution is probably responsible for the fact that skylight's spectrum and intensity are optimal for pRGC photoreception. Normal environmental light exposure<sup>180,184</sup> and cataract surgery<sup>181</sup> do not increase the risk of age-related macular degeneration. Direct sun gazing is hazardous, especially near midday.<sup>183,184</sup> Solar UV-B radiation (280–320 nm) is a risk factor for cataractogenesis.<sup>186</sup> Phakic children and adults should wear a brimmed hat and UV-protective lenses in bright outdoor environments near midday.<sup>179,183,185</sup>

## Research agenda

Future research should address the following issues.

- 1) The effect of cataract extraction on nonvisual photoreception requires further investigation. Nocturnal melatonin suppression and other nonvisual effects could be compared in aged-matched phakic and pseudophakic subjects. Alternatively patients could serve as their own controls after cataract surgery has been performed in the first eye if monocular light exposures were utilized and melatonin suppression were compared in the pseudophakic versus phakic eye (recognizing that the percentage of melatonin suppression from monocular light exposure may be less than bilateral ones).<sup>187</sup> Additional objective parameters that could provide further insight into the effect of cataract surgery on circadian photoreception include body temperature, cortisol, melatonin, markers of inflammation, glucose metabolism, lipids, blood pressure, objective sleep quality and cognitive function. Environmental light exposure, pupil diameter, and IOL transmission should be carefully controlled, as well as other parameters potentially affecting clinical outcomes such as patients' medications, diet, pupillary area, IOL type, dietary supplementation, smoking, alcohol consumption, shift work, recent multi-time zone travel, daily time outdoors, season of testing, geographical latitude, and measured environmental light exposure. Potential differences between UV- and blue-blocking IOLs should be explored especially with regards to cognitive performance, insomnia and subjective mood.
- 2) Alzheimer's disease patients should be studied to see if pseudophakia affects the incidence, severity and progression of their disease and its frequently comorbid sleep-wake disturbances.
- 3) Noninvasive, convenient, cost effective methods for testing pRGC function and viability would be extremely useful. These tests would be valuable in determining if pRGC function itself declines with aging and whether losses are affected by different systemic or ocular diseases.
- 4) People with visual impairment have early mortality. Chronodisruption in visually blind people may improve with exogenous melatonin, but this therapy may be suboptimal and/or unnecessary for individuals with intact pRGC photoreception. Visually impaired patients with intact pRGC photoreception should be monitored for laboratory evidence of chronodisruption and to determine if these parameters improve with effective environmental light exposure.
- 5) Research caveats: Optimal human sensitivity for melatonin suppression was not determined until 2001<sup>5</sup> and pRGCs were not identified until 2002.<sup>1,188</sup> Prior to these discoveries traditional rod and/or cone photoreceptors were assumed to mediate all photic effects. The photopic "lux" is the most widely used unit for quantifying illuminance. This unit is a photometric term characterizing how effectively a light exposure elicits cone-mediated (bright light) vision. A scotopic lux is also defined for rod-mediated (dim light) vision but there is no international standard "circadian lux" unit for accurately characterizing a light source's nonvisual pRGC spectral (luminous) efficiency. Care should be taken in comparing broad spectrum and monochromatic wavelength results until a standardized circadian lux unit has been adopted. Many circadian studies fail to (1) perform or describe ophthalmic screening of test subjects or (2) control for critical parameters such as lens transmission and pupillary area. Some investigations exclude

subjects with cataract but then consider phakic and pseudophakic patients to be equivalent despite the markedly increased retinal illuminances provided by IOLs. Studies on "blind" subjects typically fail to specify their definition of blindness. Therefore, subjects might be "legally blind" (markedly impaired visual acuity or visual field in both eyes), "visually blind" (no conscious light perception but with intact pRGC photoreception) or "totally blind" (no visual or nonvisual photoreception). Pharmacological pupillary dilation increases retinal illumination and therefore circadian efficiency significantly.<sup>92</sup> Additionally, the use of chin rests with light source-directed fixation<sup>91</sup> during exposures produce results that markedly overestimates light efficiency and underestimates light requirements for circadian effects in normal environmental exposures. Study protocols vary widely and many fail to specify fundamental light exposure parameters such as the spectrum of the light source used. Finally, there are critical differences among species in circadian sensitivity making extrapolation of experimental animal data to clinical circumstances highly problematic. For example, nocturnal rodents may be 1000 to 10,000 times more sensitive to light than diurnal humans, and their peak spectral sensitivity (~480 nm) is roughly 20 nm longer (redder) than that of humans (460 nm).<sup>10,189,190</sup>

## Conflict of interest statement

The authors have no proprietary interests in any manufacturers or products. The authors received no funding for this research. Dr. Turner and Dr. Van Someren have no personal competing interests. Dr. Mainster is a consultant for Abbott Medical Optics, Iridex and Ocular Instruments Corporations.

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