Circadian-Effective Light

Modeling spectral, spatial, and absolute sensitivities

All physiological and behavioral functions are regulated by a master clock in the suprachiasmatic nuclei (SCN). We normally eat, sleep, work, and play according to the 24-hour time of day. The SCN synchronizes and coordinates these biological functions to the 24-hour day. The master clock in the SCN is directly coupled with the retina and its periodicity is regulated by the light-dark pattern incident on the retina. How the retina converts light into neural signals for the clock is termed *circadian phototransduction*. The physical light stimulus that is transformed into neural signals through circadian phototransduction is termed *circadian-effective light*. To mathematically characterize and specify circadian-effective light in architectural applications, it is desirable to have a computational model of circadian phototransduction. This section describes one possible model.

Non-linearity of phototransduction mechanisms in biology

Any model of circadian phototransduction must consider potential non-linear neural responses to light. The univariance principle governing photopigments (Rushton 1972) simply cannot be expected to apply to neural channel responses like the one that converts optical radiation on the retina to timing signals in the SCN. Indeed, *all* phototransduction mechanisms affecting measurable physiological and behavioral responses from living creatures exhibit non-linear responses to light stimulation.

Threshold and saturation are two common forms of non-linearity. A threshold amount of light is usually needed to evoke a response; below that threshold, differences in the light stimuli amounts, spectra, and durations are irrelevant. Similarly, at response saturation, all light stimuli are equally effective. Below threshold or above saturation then, adding more or less light will have no differential effect on the neural channel response.

Response compression is another common form of non-linearity. Rarely does a phototransduction mechanism respond proportionally to the amount of light absorbed. Rather, to maintain a large dynamic range, incremental amounts of light produce incrementally smaller responses. Increases in perceived brightness, for example, can be expressed as a power function with an exponent of 1/3 (Stevens 1971) so doubling the amount of light evokes only a 26% increase in perceived brightness.

Color vision in insects and vertebrates exemplifies another form of non-linearity called subadditivity. Color vision depends upon at least two photoreceptors tuned to different parts of the spectrum. Bipolar neurons represent the second step, after the photoreceptors, in the neural channel that determines color vision. These bipolar neurons compute the difference between two types of photoreceptors (e.g., L- and M-cones), signaling a graded positive or negative (i.e., bipolar) response to light to the next step in the color vision channel. Since the two types of photoreceptors are tuned to different parts of the spectrum, *more* light in one part of the spectrum (long wavelengths) can *reduce* the magnitude of bipolar response to another part of the spectrum

(shorter wavelengths). All of these forms of non-linearity should be explicitly considered in defining circadian light.

Spectral

Measuring the direct impact of light and dark on entrainment by the human circadian clock is difficult and expensive to research, so much of what we know about circadian phototransduction comes from studies of the impact of light at night on the synthesis of the hormone melatonin. Among the neural signals emanating from the master clock to signal time of day, the SCN controls the synthesis of melatonin by the pineal gland. Melatonin circulates in the blood stream signaling time of day (specifically, nighttime) to every cell in the body. Melatonin is only produced at night *and* under dim light. At night, light absorbed by retinal photopigments signal the SCN which in turn signals the pineal gland to reduce or stop producing melatonin. Presumably, the phototransduction mechanism in the retina responsible for suppressing nocturnal melatonin is the same as that which entrains the circadian system throughout the 24-hour cycle of light and dark. The absolute sensitivities of the circadian system as measured by nocturnal melatonin suppression and by phase shifting of a circadian marker like minimum core body temperature are quite similar in humans (e.g., Zeitzer et al. 2000). Similarly, short-wavelength light is maximally effective for shifting circadian phase and for nocturnal melatonin suppression (Wright and Lack 2001), suggesting the spectral sensitivity is the same for both phenomena.

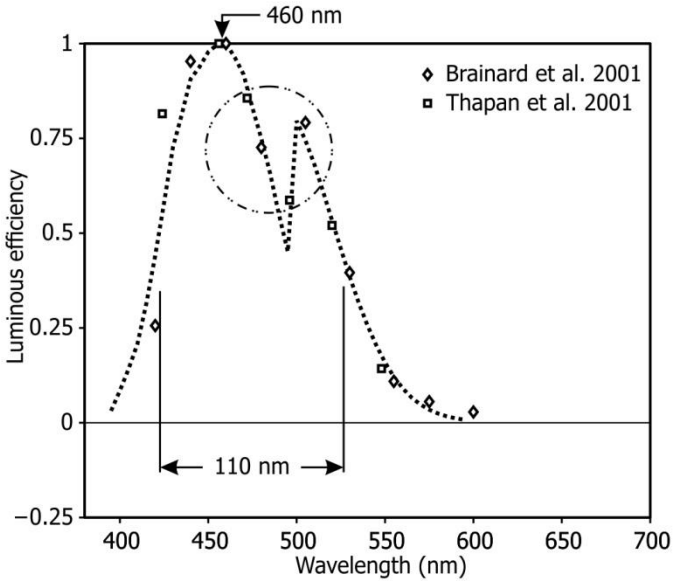
Some studies have shown differences in the impact of light exposure on nocturnal melatonin suppression and phase shifting (e.g., Hashimoto et al. 1996; Figueiro, Bierman et al. 2013). It is important to point out, however, that, absent invasive surgery, it is impossible to directly measure the spectral and absolute sensitivities of the human SCN to retinal light exposure. What can be measured psychophysically are the consequences of light exposure on downstream physiological mechanisms like nocturnal melatonin suppression and phase shifting. Considering that the SCN is constantly counting light-induced neural signals from the retina (e.g., Roenneberg et al. 2010) but recognizing that the protocols for assessing nocturnal melatonin suppression and phase shifting are differentially affected by the time of light exposure, it is impossible to unambiguously compare the spectral and absolute sensitivities of the SCN from the results of different protocols. Given the similarities in the spectral and the absolute responses to light, and accepting scientific parsimony without direct proof, it is assumed that the circadian phototransduction mechanisms are, at least to a first-order approximation, the same for melatonin suppression and phase shifting.

Empirically, nocturnal melatonin suppression in humans was shown in two independent studies to have a peak spectral sensitivity to narrowband light stimuli at 460 nm and a 110-nm wide absorption band at half-maximum sensitivity (Figure 1). These two psychophysical studies were conducted in much the same way using a constant-criterion method. Briefly, constant criterion methods are employed to deal with possible non-linear response characteristics of a biological system to variable amounts of a physical stimulus. A fixed response criterion is selected and the amount of a variable stimulus needed to reach that criterion is recorded. For these two studies, a fixed half-saturation criterion of nocturnal melatonin suppression (≈ 35%) was selected because this response was above threshold and below saturation; the corneal irradiance at each test

wavelength needed to reach that criterion was recorded. The reciprocal of the amount of irradiance at each wavelength needed to reach the constant criterion defined the spectral sensitivity of nocturnal melatonin suppression to narrowband light stimuli in both studies. Although both experiments are in good agreement over much of the wavelength range of sensitivity, there is an obvious discontinuity in the data sets at about 500 nm, not coincidently as will be discussed below, the wavelength that appears to the visual system as unique green (Figure 1). A light that appears unique green is neither 'blue' nor 'yellow' because the spectrally opponent blue versus yellow (b-y) color mechanism is physiologically unresponsive to that light. An analysis of the nocturnal melatonin suppression data, consistent with retinal neurophysiology, suggests that the b-y color channel defines the obvious discontinuity, and thus plays an important role in human circadian phototransduction.

Figure 1

Spectral sensitivity of nocturnal melatonin suppression for different narrowband spectra



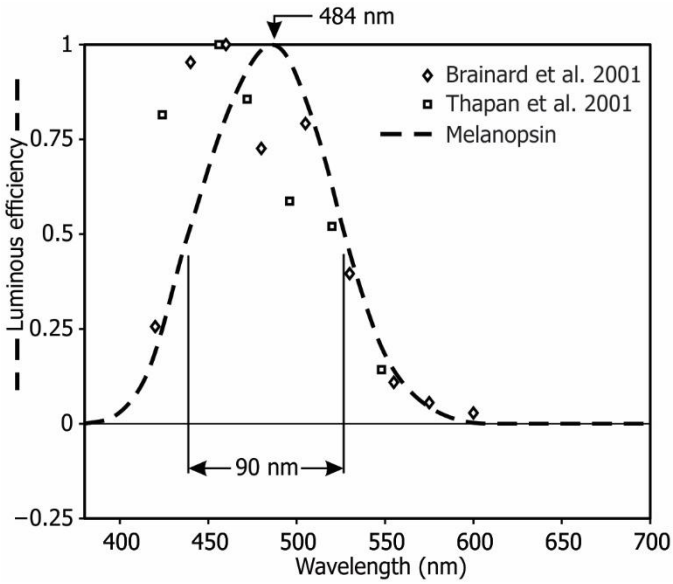
Results are shown from two studies (Brainard et al. 2001; Thapan et al. 2001), both using a constant criterion method for characterizing the spectral sensitivity of the human circadian system. Except for the circled spectral region, wavelengths near unique green (close to 500 nm), the results show good agreement with peak sensitivity at approximately 460 nm and a half-maximum sensitivity of about 110 nm. The dotted line represents predictions from the model of circadian phototransduction by Rea et al. (2005; 2012) described later in the text.

No single retinal photopigment exhibits the properties illustrated in Figure 1, including the photopigment melanopsin (Provencio et al. 1998) found in the intrinsically photosensitive retinal ganglion cells (ipRGCs) (Berson et al. 2002). Direct measurements of the action spectrum for melanopsin in human ipRGCs show a peak spectral sensitivity at approximately 479 nm (Bailes and Lucas 2013) and like all other known retinal photopigments has a half-maximum sensitivity bandwidth of about 95 nm; with pre-retinal filtering, primarily from the crystalline lens and

macula lutea, the peak sensitivity shifts to approximately 484 nm and the half-maximum sensitivity bandwidth is about 90 nm (Figure 2). *Prima facie* then, the empirical data rule out any simple spectral sensitivity model for nocturnal melatonin suppression based upon a single photopigment, including melanopsin. Logically, too, in an intact retina, no single photoreceptor, specifically ipRGCs, can be responsible for circadian phototransduction. Indeed, results from several electrophysiological experiments with vertebrates (Hattar et al. 2003; Belenky et al. 2003; Panda et al. 2003) show that, while ipRGC *efferent* (conducting) axons are the main conduit of light signals to the master clock, ipRGC *afferent* (receiving) dendrites receive indirect input from the more distal rods and cones. Therefore, a completely successful model of human circadian phototransduction must take into account all retinal photoreceptors and their supporting neural mechanisms and must be constrained by the known anatomy and physiology of the retina and brain (Kolb et al. 2004), including neural interactions under a wide range of operating conditions (Rea et al. 2005; Figueiro et al. 2008).

Figure 2

The action spectrum of the photopigment melanopsin after pre-retinal screening by the human crystalline lens



The in situ spectral sensitivity of melanopsin peaks at about 484 nm with a half-maximum sensitivity of about 90 nm (Open symbols are estimates of spectral sensitivity to narrow-band spectra from Brainard et al. 2001 and Thapan et al. 2001).

Equation 1 mathematically defines the modelled spectral sensitivity of the human circadian system. Circadian light (CL_A) from Rea et al. (2005; 2012) is a scale measured in terms of spectrally weighted (equation 1) flux per unit area. The subscript "A" reflects a method to convert from units of photopic illuminance to the spectrally weighted CL_A scale, where by definition, 1000 lx of CIE illuminant A equals 1000 on the CL_A scale.

Equation 1

$$CL_A = \begin{cases} 1548\left[\int Mc_\lambda E_\lambda \mathrm{d}\lambda + \left(a_{b-y}\left(\int \frac{S_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda - k\int \frac{V_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda\right) - a_{rod}\left(1 - e^{\frac{-\int V'_\lambda E_\lambda \mathrm{d}\lambda}{RodSat}}\right)\right)\right] & if \int \frac{S_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda - k\int \frac{V_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda > 0 \\ 1548\int Mc_\lambda E_\lambda \mathrm{d}\lambda & if \int \frac{S_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda - k\int \frac{V_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda \leq 0 \end{cases}$$

CL_A: circadian light. The constant, 1548, sets the normalization of CL_A so that 2856 K blackbody radiation at 1000 lux has a CL_A value of 1000.

E_λ: light source spectral irradiance distribution

Mc_λ: melanopsin (corrected for crystalline lens transmittance)

S_λ: S-cone fundamental

mp_λ: macular pigment transmittance

V_λ: photopic luminous efficiency function

V'_λ: scotopic luminous efficiency function

RodSat: half-saturation constant for bleaching rods = 6.5 W/m^2

k = 0.2616

$a_{b\text{-}y}$ = 0.700

a_{rod} = 3.300

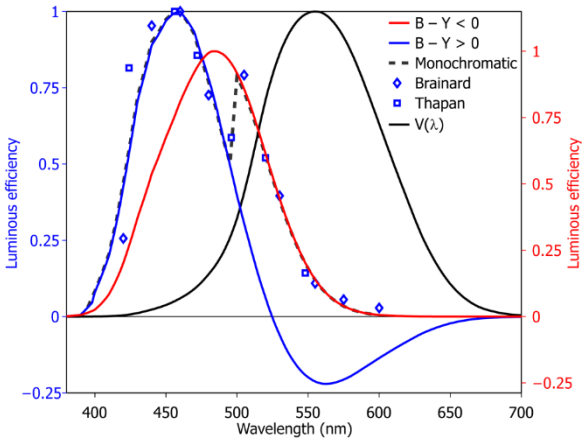
More details of the model can be found in other publications (Rea et al. 2005; 2012) but briefly, all known photoreceptors contribute to the spectral sensitivity of the circadian system. Rod bleaching controls the threshold for absolute sensitivity of cone contributions to the ipRGCs, so absolute light levels are expressed in units of CIE scotopic illuminance. As rods saturate, cones begin to provide input to the ipRGCs. However, cone signals are processed by the outerplexiform layer of the retina before reaching the ipRGCs. In particular, cone signals must be converted into spectrally opponent, blue versus yellow (b-y) or red versus green (r-g) signals by bipolar (depolarizing and hyperpolarizing) neurons before they can reach the next stage of neural processing. To fit the nocturnal melatonin suppression data from Brainard et al. (2001) and Thapan et al. (2001) and to be consistent with orthodox retinal neural physiology (Kolb et al. 2004), the modeled S-ON cone response (Kolb 2004) adds to the self-generated ipRGC response *only if* the b-y bipolar neuron depolarizes, signaling "blue" to the innerplexiform layer of the retina. If the b-y bipolar neuron generates a hyperpolarizing "yellow" response, the signal cannot be processed by the ipRGCs. The spectral response of the b-y mechanism is modeled by the difference between S-cone fundamental (Smith and Pokorny 1975) and the sum of the L- and M-cone response (i.e., V(λ)) after the spectral transmittance of the pre-retinal screening pigment, the macula lutea, (mp_λ) is removed under the assumption that the macula is a very small area of the luminous field in the studies by Brainard et al. (2001) and Thapan et al. (2001). It should be noted that Dacey et al. (2005) measured an S-OFF cone input to ipRGCs in primates. However, those data were recorded from the lateral geniculate nucleus (LGN), not the SCN. The ipRGCs responsible for input to the SCN are ON depolarizing ganglion cells and can only respond to ON depolarization inputs from more distal neurons, so functionally, an S-OFF response combined with an ipRGC response simply cannot fit the spectral sensitivity data from Brainard et al. (2001) and Thapan et al. (2001).

A special case exists when b-y = 0; these spectral power distributions that signal neither "blue" nor "yellow" by the b-y bipolar neurons are consciously seen as pure, or "unique" green (e.g.,

Pridmore 2013). To best fit the data from Brainard et al. (2001) and Thapan et al. (2001) (Figures 1 and 2), the wavelength associated with b-y = 0 in the model was at 497 nm for an absolute level of 300 scotopic lux at the cornea. As can be seen in Figure 3, there is a sudden transition in modeled spectral efficiency at 497 nm; CL_A efficiency at longer wavelengths is modeled by ipRGC-melanopsin spectral sensitivity alone whereas efficiency at shorter wavelengths reflects both ipRGC-melanopsin and S-cone spectral sensitivities.

Figure 3

Spectral sensitivity for monochromatic and for "cool" (b-y > 0) and "warm" (b-y < 0) polychromatic sources



The points in Figures 1 to 3 were derived from experiments using single, narrowband light stimuli, not broadband, polychromatic light sources used in architectural lighting. The model expressed in equation 1 nevertheless has implications for commercially available light sources as well as narrowband light sources. For these polychromatic sources, subadditivity becomes of central scientific interest because it is well established that the distal photoreceptors, processed by spectrally opponent bipolar neurons, are also part of the circadian phototransduction process. For this reason, three experiments were conducted to help determine how the circadian system might respond to polychromatic light sources.

For the first experiment (Figueiro et al. 2004), melatonin suppression was measured for two light sources, a blue LED and a clear mercury lamp; Figure 4 shows their spectral power distributions. This figure also includes a simple spectral envelope defined by the Brainard and Thapan points in Figures 1 and 3, like the spectral envelope proposed by Gall and Bieske (2004). Additively applying this spectral envelope to the two spectral power distributions yields 743 "circadian lux" at the cornea for the LED and 1525 "circadian lux" at the cornea for the mercury (Hg) source. Thus, using a simple additive model of the spectral sensitivity of circadian phototransduction for polychromatic light sources, the mercury lamp would be expected to suppress more melatonin at night than the LED. In fact, as shown in Figure 5, the opposite was true. A lower level of "circadian lux" resulted in more nocturnal melatonin suppression. We surmised, due to the well-established subadditive properties of the spectrally opponent b-y channel, that the long-

wavelength emissions of the mercury light source at 546, 577, and 579 nm reduced the effectiveness of the short-wavelength light at 405, 407, and 436 nm.

Figure 4

Spectral power distributions for the blue LED and the clear mercury (Hg) sources together with an empirical spectral sensitivity envelope for nocturnal melatonin suppression for individual narrowband sources. Adapted from Figueiro et al. 2004.

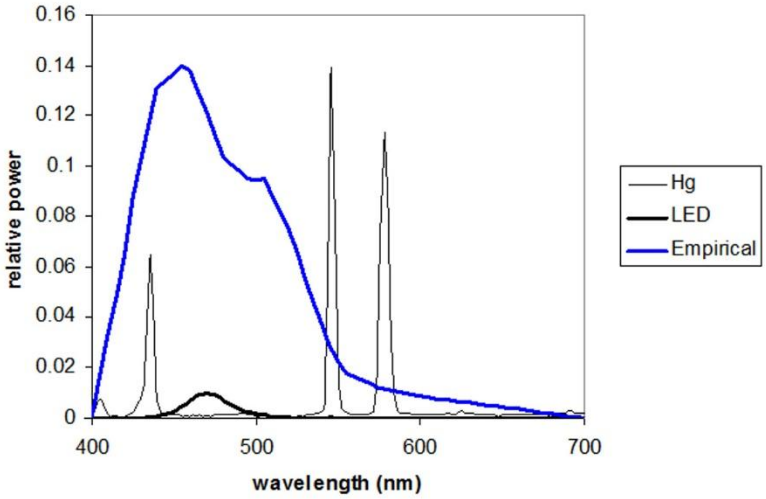
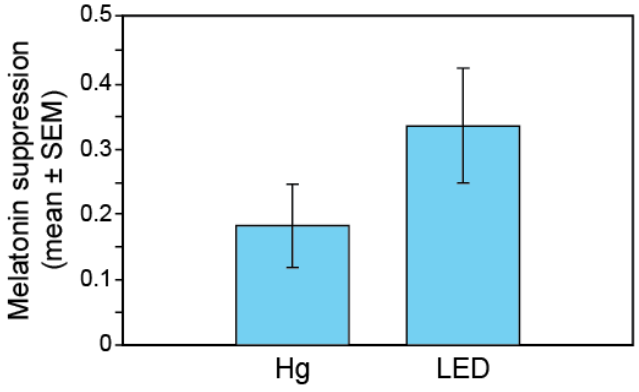


Figure 5

Nocturnal melatonin suppression following one-hour exposures to the blue LED and clear mercury (Hg) sources. Adapted from Figueiro et al. 2004.



To test this hypothesis, a second experiment (Figueiro et al. 2005) was conducted using the mercury light source. A simple 2 × 2, within-subjects design was employed. Subjects were

exposed to high and to low levels of the mercury lamp with and without filtering its long-wavelength emissions.

Figure 6

Relative spectral power distributions for the four experimental conditions, scaled for pupil area and lens transmission. Adapted from Figueiro et al. 2005.

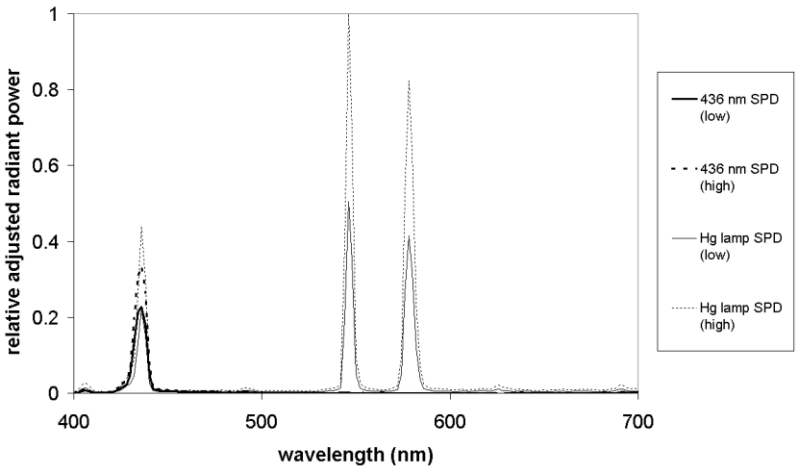
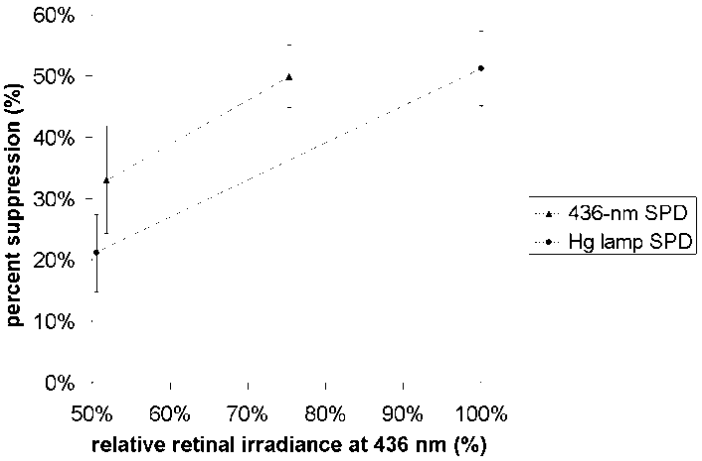


Figure 6 shows the spectral power distributions of the four light stimuli. As can be seen in Figure 7, increasing the amount of light for the filtered and for the unfiltered light produced more suppression, as expected. However, the filtered light produced *more* suppression than the unfiltered light, directly supporting the conclusion that subadditivity plays an important role in circadian phototransduction. Again, the most likely candidate for this phenomenon is the spectrally opponent b-y channel response in the retina. To further test this hypothesis, a third test of subadditivity was undertaken.

Figure 7

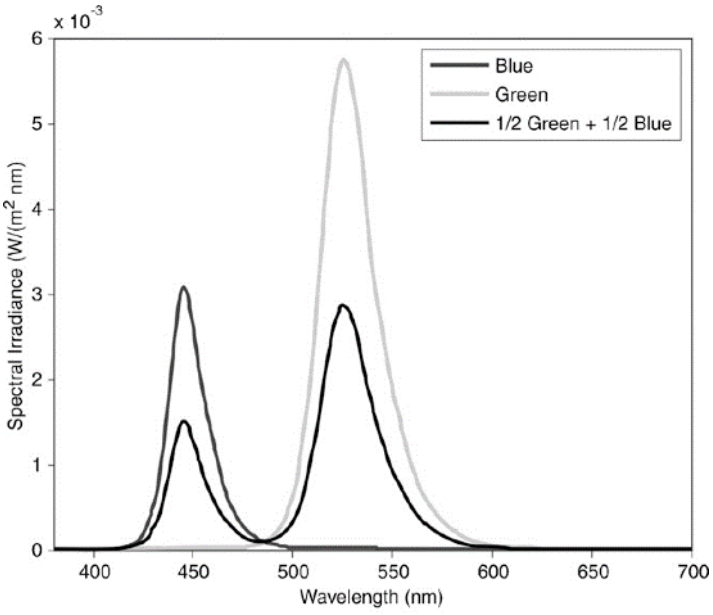
Nocturnal melatonin suppression plotted as a function of the relative radiant power at 436 nm for each experimental condition. Adapted from Figueiro et al. 2005.



A dichoptic experiment was undertaken (Figueiro et al. 2008) whereby light stimuli were separately applied to each of the two eyes simultaneously. Figure 8 shows the spectral power distributions of the three light stimuli used in the experiment. As shown in the upper portion of Figure 9, for two experimental conditions the blue and the green lights were presented separately and simultaneously to the two eyes. For this within-subjects design, both blue to the left eye and green to the right eye as well as blue to the right eye and green to the left eye were presented for one hour to determine if the model could predict nocturnal melatonin suppression *as if the blue and the green lights were independent stimuli*. An additive response was predicted because the hypothesized subadditive, spectrally opponent mechanism is in the retina and the two light stimuli could not interact in the neural channel response. The third condition provided the same total radiant power as the first two experimental conditions to both eyes, but both eyes were now given polychromatic, blue and green lights, where the two light stimuli could interact in the retina. In other words, adding the green light to the blue light in each retina would reduce their independent effectiveness for suppressing nocturnal melatonin production. As can be seen in Figure 9, the model predicted all three experimental conditions.

Figure 8

Corneal illuminances (lx) and irradiances (W/m^2) for the light stimuli. From Figueiro et al. 2008.

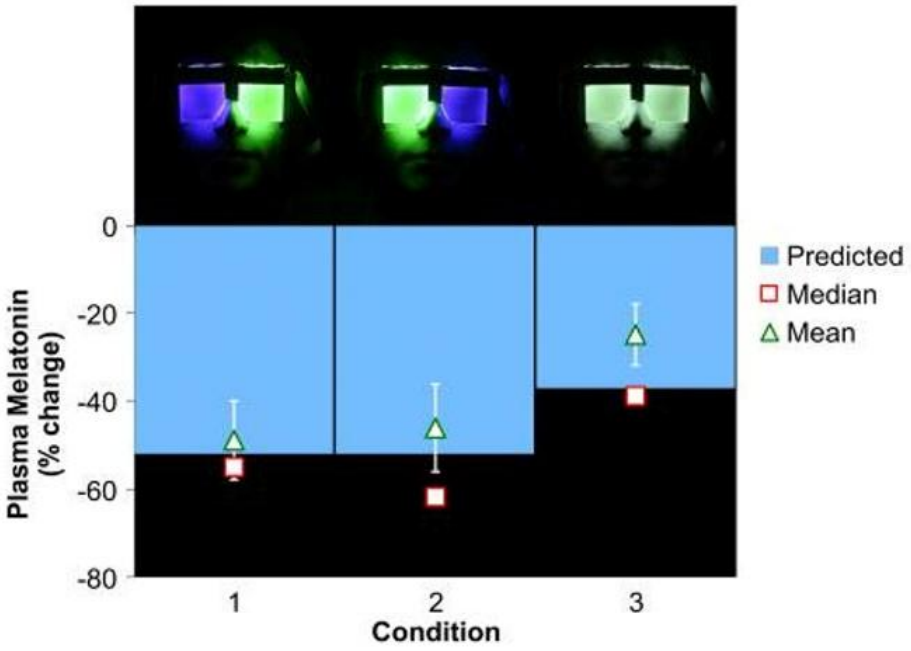


Monocular Stimulus	Illuminance (lux)	Irradiance (W/m^2)
Blue	3.0	0.077
Green	113.2	0.211
1/2 Blue + 1/2 Green	57.7	0.142

Total irradiances at both eyes was the same for all three experimental conditions.

Figure 9

Photographs of the three light stimuli (upper) together with the predicted and observed suppression of nocturnal melatonin (lower). From Figueiro et al. 2008.

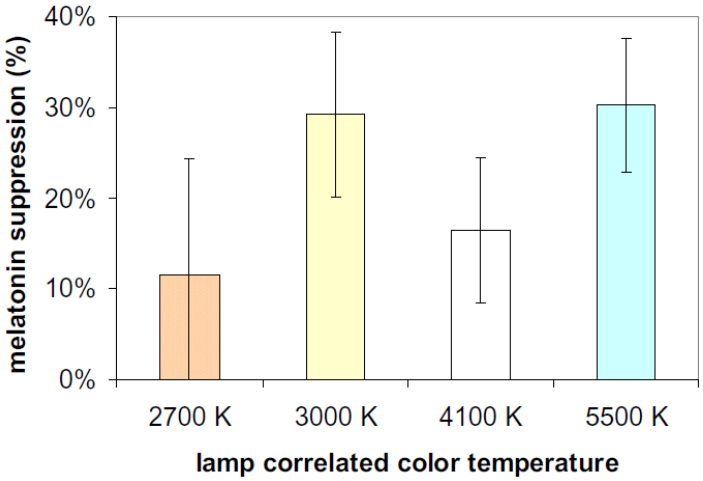


These three experiments show very clearly that subadditivity, formed by conventional and well-known mechanisms in the retina, plays a role in circadian phototransduction. More practically, these studies imply that it is incorrect to infer that "blue enriched" light sources will always be more effective than "warmer" sources with lower CCT. Figure 10 illustrates how subadditivity compromises this simple inference. In this study (Rea et al. 2006), nocturnal melatonin suppression was measured after subjects viewed the interior of a white box illuminated by one of four commercially available light sources, each with a different CCT. As can be readily seen, the 3000 K light source suppressed more melatonin than the "cooler" 4100 K light source. In fact, this particular 3000 K light source suppressed as much melatonin as the "much cooler" 5500 K light source.

In general then, under controlled viewing conditions like those employed in all of these studies, subadditivity must be taken into account to make *a priori* predictions of nocturnal melatonin suppression from polychromatic light sources.

Figure 10

Nocturnal melatonin suppression following one-hour exposures to four fluorescent, polychromatic light sources of different correlated color temperatures. Adapted from Rea et al. 2006.

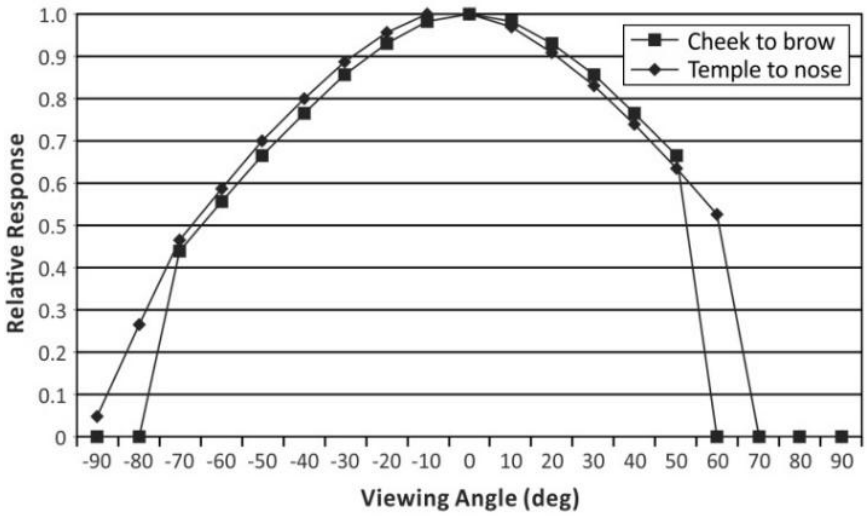


Spatial

A model of the optics of the eye (Van Derlofske et al. 2000; 2002) shows that light rays entering the eye along the central axis are most effective for reaching the retina, so light presented on the central axis will be more efficient at reaching the retina than the same light presented from above, below, or to the sides of the line of sight. Figure 11 shows the spatial sensitivity of the model for two cross sections, one temporal to nasal and one brow to cheek, on a linear scale. The abscissa represents the source angle relative to the optical axis of the eye, and the ordinate represents the relative amount of flux incident on the retina. The response curves differ slightly from a cosine distribution. They start slightly narrower than a cosine function as would be used in a good quality illuminance meter at small angles and become slightly wider than a cosine at large angles. The shape of this function is largely dictated by the apparent size of the pupil and by the path length of the light travelling through the ocular media. The sharp cut-off at high angles is mostly due to vignetting and light blocking by the facial structures. Only in the temporal direction, where the facial structure is not a factor, does vignetting in the eye itself become important. Within the eye, vignetting is due to light blocking by the edge of the iris and the lens. The distribution is also slightly shifted along the abscissa, due to the nasal shift of the pupil. These differences amount to a discrepancy of up to 6% in the total integrated response for a completely uniform illuminance distribution (e.g., Ganzfeld) compared to a cosine corrected illuminance meter.

Figure 11

Retinal spatial response function with facial cut-off. Negative angles represent the directions toward the cheek and temple (after Van Derlofske 2000).



The literature suggests that the ipRGCs form a photosensitive loose net throughout the retina except in the central fovea (Hatori and Panda 2010). Although ipRGC dendrites are absent in the fovea, they envelope the circular fovea pit (Jusuf et al. 2007), approximately 1° visual angle in diameter, where the S-cones and corresponding b-y color opponent mechanisms are largely found (de Monastario et al. 1985). From Figure 4 it is clear that light entering the eye will be maximally effective along the central axis despite the relatively small, "circadian-blind" foveal pit.

Notwithstanding the well-described spatial distribution of light entering the eye, there is some evidence in the literature that different quadrants of the retina are differentially sensitive to circadian-effective light. In other words, the sensitivity of the retina to circadian-effective light is not uniform across the retina. Gaddy et al. (1992) reported that light from a visor which provided illumination to the inferior retina was *less* effective at the same photopic illuminance than the same illuminance (presumably on the cornea) from a light box viewed directly by the foveae. Although the spectral irradiance distributions from the two light sources and subject groups were confounded in this early study, the results suggest that shading from the brow might attenuate the amount of light incident on the retina when the light source is above the line of sight. In contrast to these results, the same laboratory (Glickman et al. 2003) reported that the inferior retina was *more* sensitive to light exposure than the superior retina, both of which were less effective than the light stimulating both the superior and inferior retinae at the same corneal illuminance when viewed directly. This study employed a within-subjects design and the spectra were the same for the different viewing conditions.

Although not consistent with the earlier results from their laboratory, the later findings from Glickman and colleagues are consistent with an earlier study by Lasko et al. (1999). These authors compared 500 lx from the same light box presented in the upper and lower visual fields. Like Glickman and colleagues, they found that the light source presented in the upper visual field (inferior retina) was more effective than the light source presented in the lower visual field. Unfortunately, unlike Glickman and colleagues, this earlier study by Lasko and colleagues did not compare the effects of the light box seen on-axis at the same corneal illuminance.

Visser et al. (1999), and later Rüger et al. (2005) from the same laboratory, looked at the impact of light presented to the nasal and temporal retinae. The authors conclude from the results of both studies that the nasal retina is more sensitive to circadian-effective light than the temporal retina. A problem with these two studies, however, is that the optics of the eye is not considered (Figure 4). It is likely that their apparatus, due to baffling of the ambient lighting in the laboratory, simply allowed more light to enter the eye from the temporal field (nasal retina) than from the nasal field (temporal retina). These results do not necessarily mean that the retina is isotropic with respect to circadian-effective light stimulation, but, in practice, it is likely that light entering the eye from the temporal field will be more effective than light entering the eye from the nasal field due to shading by the nose. It also should be noted, in contrast to the findings from Glickman and colleagues, that Rüger and colleagues showed that the inferior and superior retinae were equally sensitive to light entering the eye from the both the temporal and the nasal fields. Thus, there remains quite a bit of uncertainty with regard to spatial sensitivity of the retina to circadian-effective light stimulation, once corrected for the optics of the eye.

Absolute

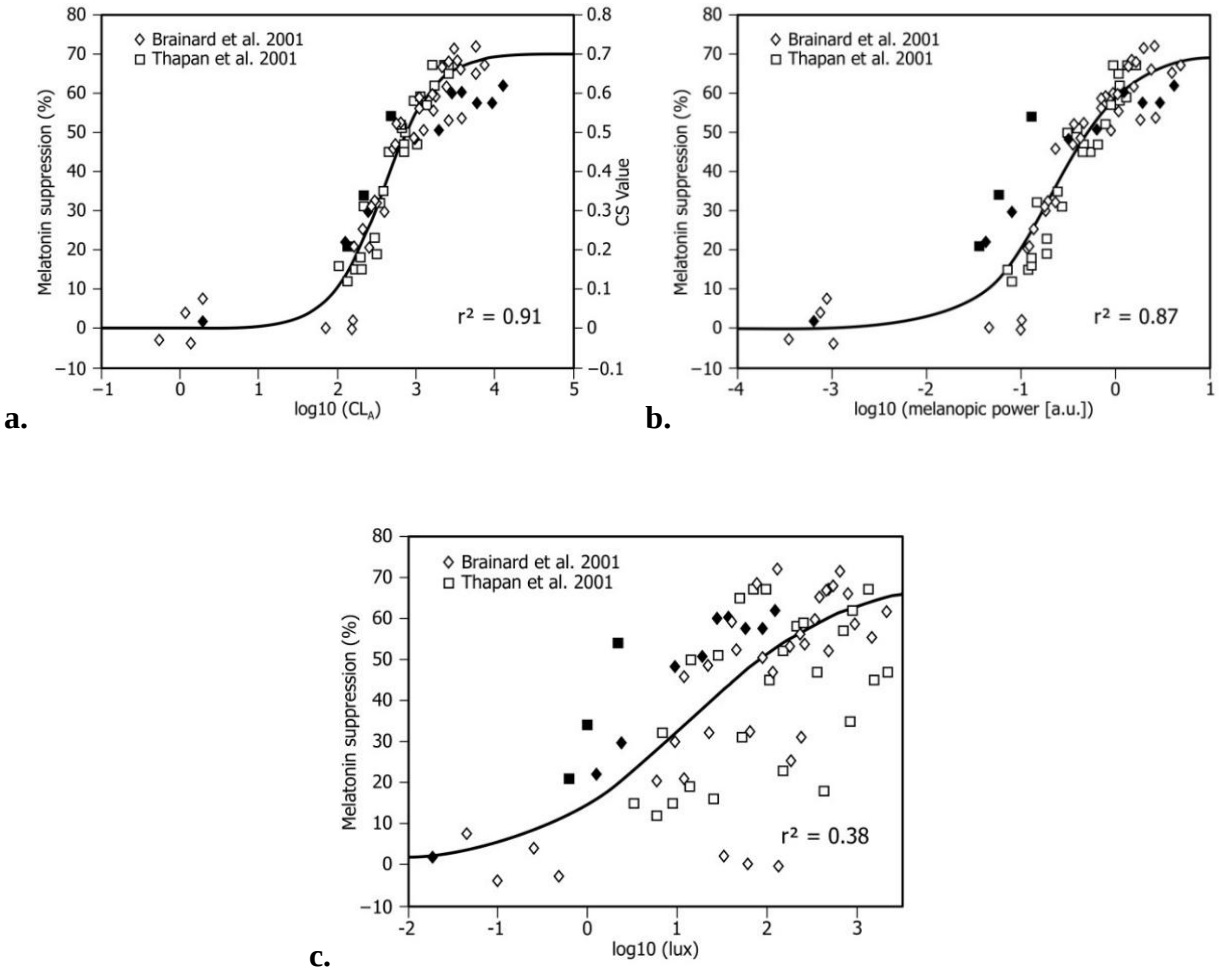
A complete model of circadian phototransduction must consider how the amount of light incident on the retina affects the response of the circadian system from threshold, the first measurable response to light, to saturation, the maximum output of the system. Equation 2 provides the functional relationship between $\log_{10}$ CL_A and circadian stimulus (CS), which is equivalent to nocturnal melatonin suppression in percent. This equation was developed in part from the data from Brainard et al. (2001) and Thapan et al., (2001) that each used to estimate the spectral sensitivity of nocturnal melatonin suppression to narrowband spectra presented in Figures 1 – 3. The three panels in Figure 12 show those nocturnal melatonin suppression data for every combination of wavelength and irradiance level from those two studies.

Equation 2

$$CS = 0.7 - \frac{0.7}{1 + \left(\frac{CL_A}{355.7}\right)^{1.1026}}$$

Figure 12

Nocturnal melatonin suppression for different narrowband spectra plotted as a function of $\log_{10}$ CL_A (a; equation 1), $\log_{10}$ 'melanopic lux' (b; in arbitrary units, a.u.) and $\log_{10}$ photopic illuminance (c).



The data from Brainard et al. (2001) and Thapan et al. (2001) were used to estimate the spectral sensitivity of nocturnal melatonin suppression to narrowband spectra in Figure 1. The filled diamonds represent the 440-nm data from Brainard et al. (2001) and the filled squares represent the 424-nm data from Thapan et al. (2001); see text for an explanation of their significance.

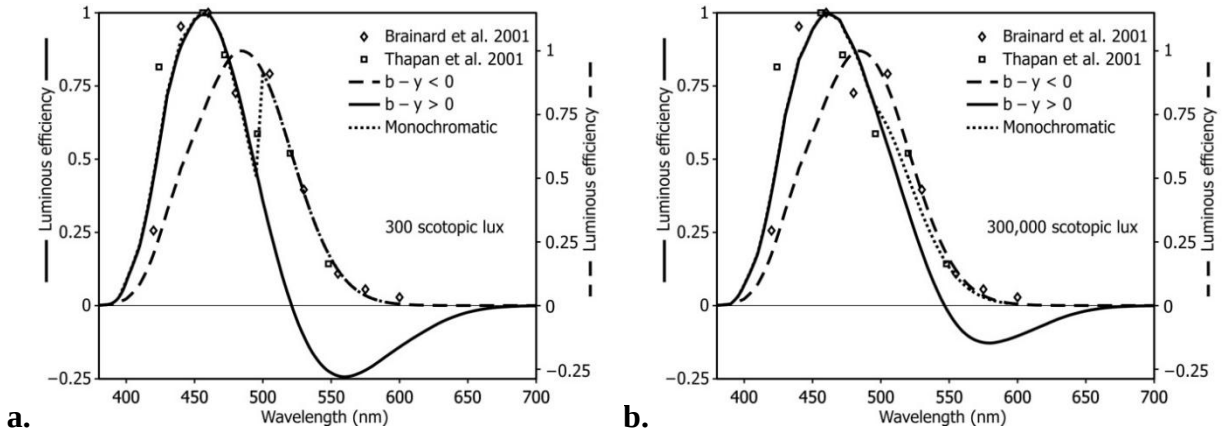
Figure 12 shows the same data, but plotted as a function of $\log_{10}$ CL_A (Figure 12a), $\log_{10}$ melanopsin-weighted irradiance (arbitrary units) (Figure 12b), and $\log_{10}$ photopic illuminance (Figure 12c). Among these three possible characterizations of circadian-effective light for the human circadian system, CL_A best characterizes the spectral sensitivity of the nocturnal melatonin suppression data. Clearly, photopic illuminance is a poor rectifying variable for characterizing circadian-effective light. And although the overall residual error is incrementally

smaller with CL_A ($r^2 = 0.91$) than with melanopsin-weighted irradiance ($r^2 = 0.87$), it is important to note that the regression errors in Figure 12b are *systematically* larger than those in Figure 12a for the short-wavelength data (solid symbols for 424 and 440 nm). Thus, the functional impact of light sources with a high proportion of short-wavelength radiation (i.e., 'cool' light sources) will be systematically underestimated using a metric based upon melanopsin-weighted irradiance.

Spectral sensitivity of a neural system may change with the amount of light incident on the retina because a single photopigment cannot possibly represent the dynamic operating characteristics of the neural mechanisms underlying circadian phototransduction. Figures 13a and 13b illustrate the modeled change in spectral sensitivity at different scotopic illuminance levels where control of cone input is based upon the amount of rod saturation; at higher light levels, rods exhibit less control, thereby affecting CL_A spectral sensitivity.

Figure 13

The spectral sensitivity of the human circadian system at two light levels, (a) 300 scotopic lux at the cornea and (b) 300,000 scotopic lux.

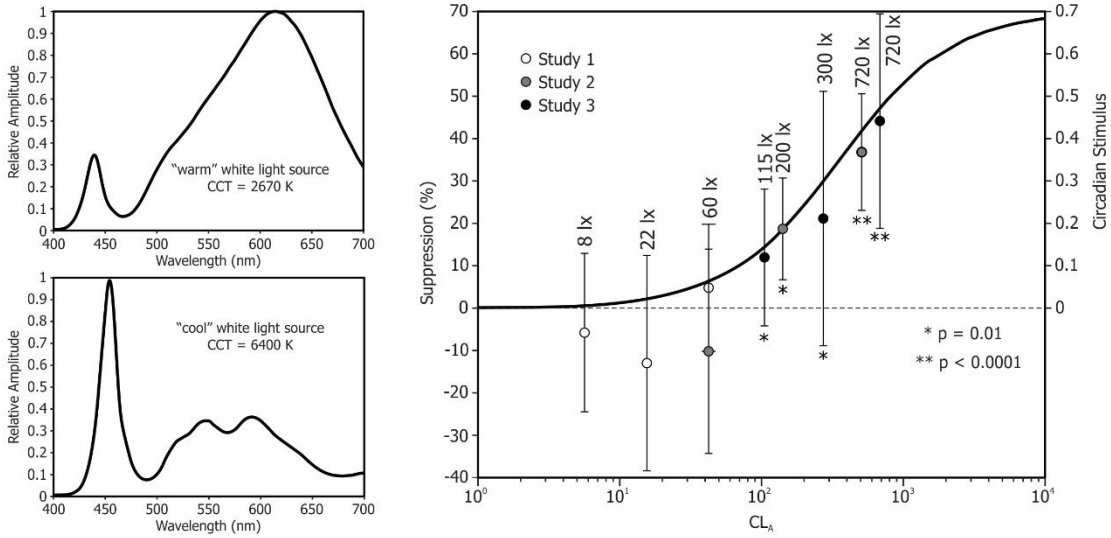


For 'cool' sources where the b-y mechanism signals 'blue' (b-y>0), the spectral sensitivity of the system is defined by the solid line, including a subadditive region of the spectrum where the spectral power from a light source subtracts from the overall response of the system. For 'warm' sources where the b-y mechanism signals 'yellow' (b-y<0), the spectral sensitivity is defined by the dashed line, the pre-retinal filtered melanopsin (Figure 2). It is worth pointing out that the measured spectral sensitivities in (a) are well described by the two-state model (equation 1) at 300 scotopic lux (also shown in Figure 1) but much less so in (b) at 300,000 scotopic lux (dotted lines in both graphs). At 300 scotopic lux, the circadian system is operating midway between threshold and saturation, consistent with the operating range of the circadian system where a constant criterion method can be successfully applied for determining spectral sensitivity. At 300,000 scotopic lux, the system is operating at or near saturation where a constant criterion method cannot be used to determine spectral sensitivity. Thus, the modeled response in (b) (dotted line) poorly fits the empirical data collected at a much lower light level.

Figure 12a illustrates the relationship between log CL_A and CS for narrowband light sources while Figure 14 shows empirically measured nocturnal melatonin suppression (left ordinate) for commercially available 'warm-white' and 'cool-white' polychromatic light sources. Model predictions of CS (right ordinate) are also shown. It should be emphasized that the CS model predictions (solid line) were *not* fitted to the empirical suppression data for the 'white' light sources. Rather, Figure 14 serves to illustrate the validity of the circadian phototransduction model (Equations 1 and 2) for predicting nocturnal melatonin suppression from polychromatic sources that might be engineered for architectural lighting.

Figure 14

Nocturnal melatonin suppression from one-hour exposures to two polychromatic sources (left panels) at different corneal photopic illuminance levels as a function of CL_A.



Means and standard deviations are plotted from three independent studies conducted at different times. Studies 1 and 2 (Rea and Figueiro 2013) used the 'warm' white light source and study 3 used the 'cool' white light source. It should be noted that the data from study 3 are unpublished; however, they were collected using apparatus, methods and procedures identical to those used in studies 1 and 2.

Applications research

Despite the uncertainties in the biophysics of circadian phototransduction as well as those associated with accurate characterization of the functional stimulus, there is empirical support for the inference that daytime light exposure specified in terms of light equivalent to 30% suppression of melatonin at night (i.e., CS = 0.30) will have a positive effect on people in terms of promoting sleep at night, reduced sleepiness during the day and possible amelioration of depressive symptoms. Specifically, this amount of circadian-effective light has been used successfully to relate light exposure to clinically-relevant outcome measures in several

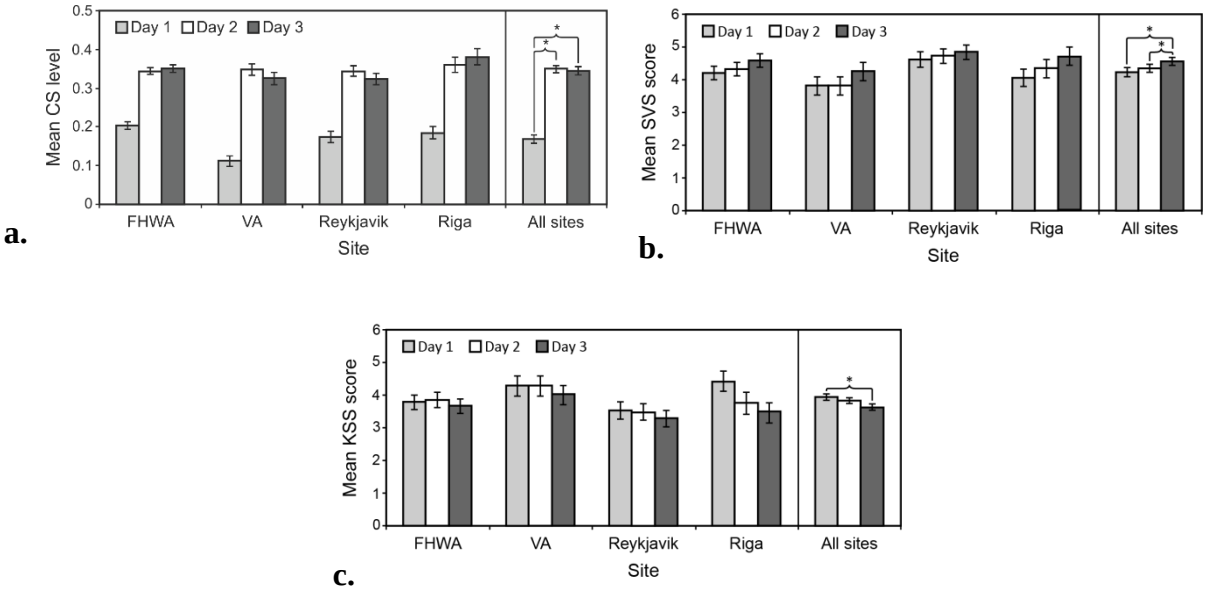
laboratory studies, including three studies using self-luminous displays (Wood et al. 2013; Figueiro and Overington 2016; Figueiro et al. 2011), and in several more specialized field studies, including nuclear submarines (Young et al. 2015), senior facilities for persons with Alzheimer's disease (Figueiro et al. 2014, 2016), and offices (Figueiro, Steverson et al. 2015; Figueiro and Rea 2016).

In the laboratory studies, light stimuli from self-luminous displays were measured using the Daysimeter (Bierman et al. 2005; Figueiro, Hamner et al. 2013), a calibrated device placed near the cornea during the experiment. Wood et al. (2013) showed that melatonin suppression at night from self-luminous displays after subjects were using the devices for one hour was predicted to be, on average, 3%. The actual average measured melatonin suppression was also 3%. Other studies predicting the efficacy of light exposure have been less successful. In one study of delivering light through closed eyelids while subjects were asleep (Figueiro, Bierman and Rea 2013), an estimate had been made of eyelid transmission from a previous study (Bierman et al. 2011) to set a light dose. From that estimate, a steady green-light (λ_{max} = 527 nm) dose (131 W/m^2 for one hour) was delivered that should have suppressed melatonin by 38% while subjects slept at night. The model predictions significantly underestimated the observed melatonin suppression of 56%. The large discrepancy was likely due to an error in estimating eyelid transmission for the light source, but this is not known for certain.

For the field applications, a light exposure equivalent to CS = 0.30 was hypothesized to be enough to promote entrainment in various populations, and as a result of this increased entrainment, sleep, mood and behavior would be improved. In three published studies (Figueiro et al. 2014, 2016; Figueiro, Hunter et al. 2015), Figueiro and colleagues showed that exposing older adults with Alzheimer's disease to a dose equivalent to, or higher than CS = 0.30 from the time of waking to 6:00 PM improved sleep quality, increased sleep duration, and reduced symptoms of depression and agitation. Similarly, Young et al. (2015) showed that exposing submariners to a lighting installation delivering a similar light dose increased measures of circadian entrainment (increased total melatonin in first morning urine void), increased sleep efficiency, as measured by actigraphy, and reduced self-reports of sleepiness during the shift. Finally, recent data from Figueiro and Rea (2016) showed that office workers in summer months had greater sleep duration and efficiency than in winter months. During the summer months, the average measured light values were close to those equivalent to CS = 0.30 while the average light exposure in winter months was very near threshold. Recent data from close to 200 subjects working in four different buildings in Europe, Iceland, and North America showed that, compared to those receiving light exposures of CS = 0.15 or less in the morning hours (between 8:00 AM and noon), office workers who receive a CS = 0.30 or more during the morning hours (Figure 15a) reported having better subjective feelings of vitality (Subjective Vitality Scale [SVS], Figure 15b) and were less sleepy at work (Karolinska Sleepiness Scale [KSS], Figure 15c). These sleep related outcome measures are very important to employers and employees alike, suggesting that "bright" circadian-effective light during the day can help people sleep better at night and perhaps, because they are less sleepy, enhance productivity during the day.

Figure 15

Average illuminance at the occupants' corneas in four different spaces, before and after intervention (CS; a) together with associated subjective measures of vitality (SVS; b) and sleepiness (KSS; c).



It seems reasonable to conclude from these application studies that continuous morning light exposures to CS = 0.3 for an extended duration (e.g., 2 hours) is a practical circadian-effective lighting design criterion for day-active individuals.

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