Lighting Res. Technol. 2011; **0**: 1–12

Modelling the spectral sensitivity of the human circadian system

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Received 10 September 2011; Revised 21 October 2011; Accepted 29 October 2011

It is now well established that the spectral, spatial, temporal and absolute sensitivities of the human circadian system are very different from those of the human visual system. Although qualitative comparisons between the human circadian and visual systems can be made, there still remains some uncertainty in quantitatively predicting exactly how the circadian system will respond to different light exposures reaching the retina. This paper discusses attempts to model the spectral sensitivity of the circadian system. Each of the models discussed here varies in terms of its complexity and its consideration of retinal neuroanatomy and neurophysiology. Future testing to validate or improve any of these computational models will require a targeted hypothesis, as well as a suitably high level of experimental control before one model can be rejected in favour of another. Until specific hypotheses are formulated and tested, it would be premature to recommend international acceptance of any model or system of circadian photometry.

1. Introduction

Throughout the last decade, much attention has been given to the effects of light on the non-image forming (NIF) channels emanating from the retina. A variety of studies have elucidated the NIF effects of light on, for example, pupil light reflex,[1] performance and attention,[2–5] sleep quality in young and older adults[6,7] and hormone production.[8,9] Of particular interest, the retino-hypothalamic tract innervates the biological clock in the suprachiasmatic nuclei (SCN) in the hypothalamus of the brain. The SCN generates self-sustained rhythms that repeat at approximately 24 hours, but the natural light/dark pattern on the retina synchronises the timing of the SCN to the local, 24-hour solar day. Circadian rhythms orchestrated by the SCN are fundamental to all biological life on earth, controlling such diverse cycles as DNA repair, insulin production, performance and the sleep/wake cycle.[10] Without exposures to a regular 24-hour light/dark pattern, a wide variety of maladies can occur, from fatigue to breast cancer.[11] Given the importance of circadian rhythms to human health and well-being, lighting practice must begin to formally consider this non-visual effect of light.

It is now well established that the spectral, spatial, temporal and absolute sensitivities of the human circadian system are very different from those of the human visual system. Qualitatively, the human circadian system has a higher threshold for stimulation than the visual system, has a peak spectral sensitivity at shorter wavelengths, and probably responds much more slowly to a light stimulus.[8,9,12–14] Most importantly, the human circadian system responds to the same light stimulus in opposite ways depending upon the time of day; a light stimulus in the morning will advance the timing of the circadian clock, whereas the same light stimulus in the evening

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10.1177/1477153511430474

will delay the clock.[15] Quantitatively, however, there remains some uncertainty in predicting exactly how the circadian system will respond to different light exposures reaching the retina. Despite these uncertainties, the spectral sensitivity of the human circadian system to narrow-band light sources has been reasonably well established through empirical investigation.[8,9,16] Based upon nocturnal melatonin suppression by narrow-band light, it is now clear that the spectral sensitivity of the human circadian system peaks at approximately 460 nm, with a full-width half maximum of about 100 nm. The underlying retinal physiology is also becoming more clear, following the discovery of intrinsically photosensitive retinal ganglion cells (ipRGCs),[17] which are central to circadian system phototransduction, the process by which the retina converts light into neural signals for the SCN. Several lines of evidence also demonstrate that rods and cones participate in this phototransduction process by providing information to the ipRGCs,[18,19] but there is still a debate about the neural circuitry of the retina that underlies the spectral sensitivity of the human circadian system.[20]

This paper discusses attempts to model the spectral sensitivity of the circadian system. Each of the models discussed here varies in terms of its complexity and its consideration of retinal neuroanatomy and neurophysiology. Computational models of the human circadian system's spectral sensitivity are crucial to lighting practice because they can help guide development of new products, systems, and architectural design. These models are also useful for further solidifying our understanding of fundamental mechanisms, if they are used to generate *a priori* predictions for hypothesis testing. The results of systematic hypothesis testing lead to more robust computational models that provide more accurate predictions of the effects of light exposure on human health and well-being. In fact, this iterative process is the only way that science, as well as effective applications, can progress.

1.1 Models of human circadian phototransduction

The first two attempts to model the spectral sensitivity of the human circadian system were based on the acute melatonin suppression data collected independently by Brainard *et al.*[8] and Thapan *et al.*[9] Although the experimental procedures in these studies were slightly different, both sets of investigators correctly employed a constant criterion method for deriving the spectral sensitivity of melatonin suppression by light at night. Table 1 and Figure 1 present these spectral efficiencies where the light stimulus is quantified in terms of irradiance at the cornea as determined graphically by Rea *et al.*[21] using a 35%

Table 1 Relative sensitivities at different peak wavelengths for melatonin suppression using a constant criterion response from Brainard *et al.*[8,16] and from Thapan *et al.*[9] For the Brainard *et al.* data, efficiencies at each wavelength were determined by digitising the published graphs of the dose–response functions for each narrow-band wavelength. The radiant power at the cornea needed to suppress nocturnal melatonin by 35% was estimated for each peak wavelength (P_λ). The corresponding data from Thapan *et al.*, given in quantum sensitivity units, were read off of the published graphs and converted to radiometric sensitivities. The minimum power needed to suppress the criterion amount of melatonin ($P_{\lambda\ \text{min power}}$) occurred at or near 460 nm for Brainard *et al.*[8] and for Thapan *et al.*[9] Relative sensitivity was estimated from the ratio ($P_{\lambda\ \text{min power}}$)/$P_\lambda$; these values are tabulated here and plotted in Figure 1

Brainard *et al.* (2001, 2008)		Thapan *et al.* (2001)	
Wavelength (nm)	Relative sensitivity	Wavelength (nm)	Relative sensitivity
420 (Brainard et al. 2001)	0.146	424	0.896
420 (Brainard et al. 2008)	0.219	456	1.000
440	0.993	474	0.814
460	1.000	494	0.535
480	0.704	520	0.481
505	0.727	548	0.144
530	0.345		
555	0.094		
575	0.065		
600	0.027		

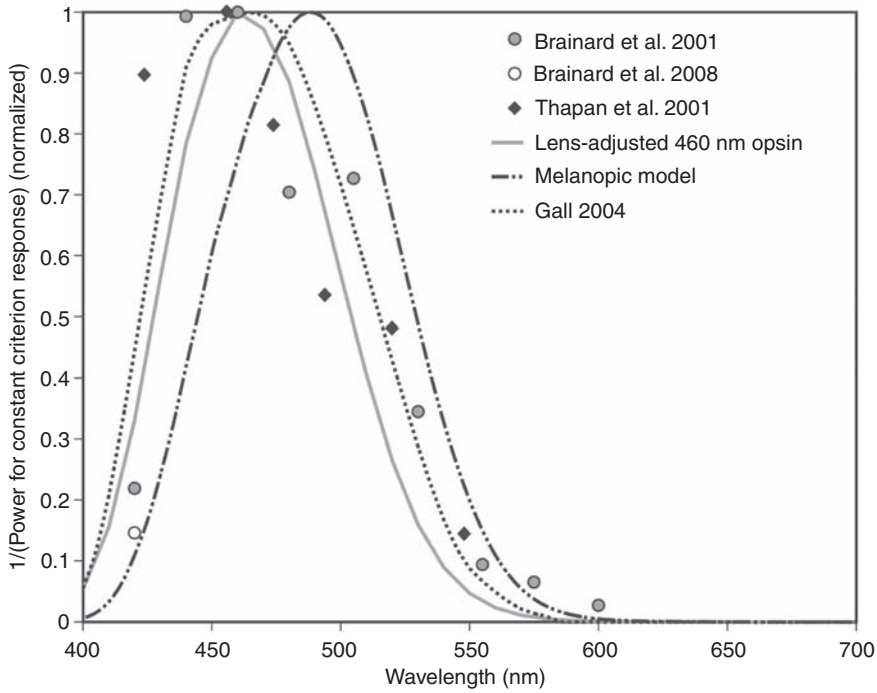

Figure 1 Two sets of estimates of the spectral sensitivity of the human circadian system to narrow-band spectra based upon nocturnal melatonin suppression[8,9,16] together with three additive weighting functions for corneal irradiance aimed at modelling the estimates, one based upon a single opsin ($\lambda_{max} = 460$ nm), another upon a single opsin (λ_{max} at approximately 488 nm), and one upon an arbitrary fit to the spectral sensitivity estimates.[23] The single-opsin functions have both been adjusted to account for crystalline lens transmission according to Wyszecki and Stiles[25]

suppression criterion from the dose–response functions in the original publications. It should be noted that Brainard *et al.*[16] published an additional dose–response function for 420 nm and, using the same methods as Rea *et al.*,[21] we estimated the spectral sensitivity of the human circadian system at this wavelength; this spectral efficiency is also included in Table 1 and Figure 1. Brainard *et al.*[8] and Thapan *et al.*[9] both fitted their respective sensitivity estimates using a single, hypothetical opsin with peak sensitivity at or near 460 nm. Figure 1 shows a single-opsin sensitivity function modified to account for crystalline lens transmission comparable to those used by Brainard *et al.*[8] and Thapan *et al.*[9] Figure 2 shows the residual errors of the 460-nm, single-opsin model as a function of wavelength; residual error is defined as the absolute difference between the measured sensitivity at a given wavelength and the modelled sensitivity at that wavelength. The 460-nm, single-opsin model does not appear to adequately characterise the set of empirical data at wavelengths shorter and longer than 460 nm.

Subsequent studies have cast doubt on the physiological accuracy of these first attempts at modelling the spectral sensitivity of the human circadian system because there is no known photopigment in the retina with peak sensitivity at or near 460 nm. Melanopsin, the photopigment in the ipRGCs, is now known to be the primary photopigment for circadian phototransduction and has a peak sensitivity at or near 480 nm.[17,22] Recently, Enezi *et al.*[20] proposed a single-opsin, 'melanopic' spectral

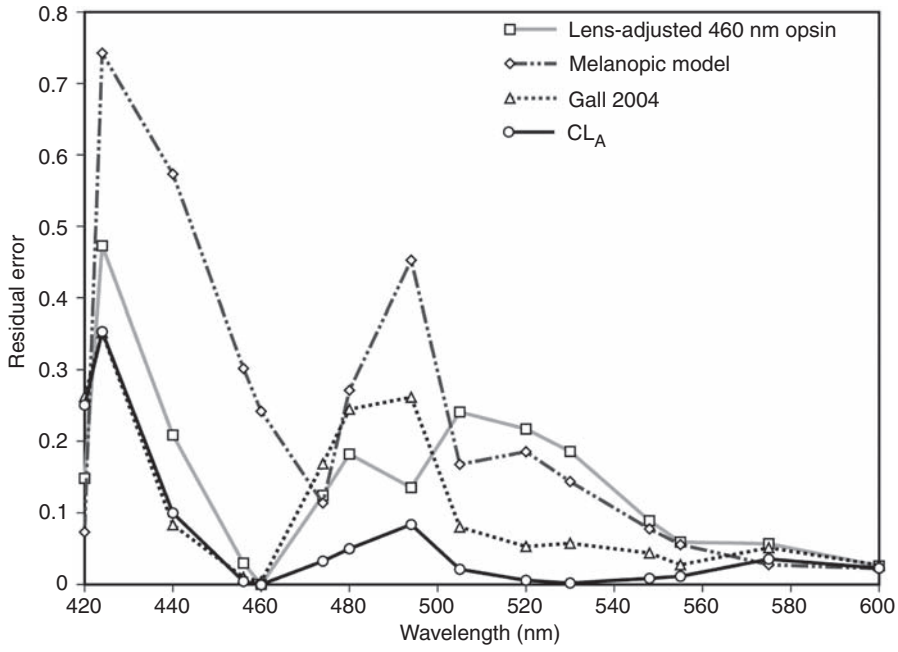

Figure 2 Residual errors from four estimates of the spectral sensitivity of the human circadian system to narrow-band spectra. Residual errors are were defined as the absolute differences between the measured sensitivity at a given wavelength and the estimated sensitivity at that same wavelength. The mean residual error for the lens-adjusted 460-nm opsin model, the melanopic model, the Gall[23] function, and the CL_A model are 0.14, 0.23, 0.12 and 0.06, respectively

sensitivity function (Figure 1), based upon the now well-established spectral absorption of melanopsin. Based upon original data from genetically manipulated mice, they argued that a single opsin peaking close to 480 nm can account for mouse pupil responses to light exposure as well as phase shifting to a light pulse. They argue further that, by extension, once corrected for human lens absorption, their single-opsin melanopic model can also explain the spectral sensitivity of the human circadian system. Their melanopic function is included in Figure 1, but does not appear to characterise the set of empirical data well; this conclusion is reinforced by the residual error plot (Figure 2).

Even prior to the discovery of the ipRGC and its photopigment, melanopsin, there were clear hints from the empirical spectral sensitivity plots that circadian phototransduction cannot be predicted from the spectral sensitivity of a single opsin.[13] First, the envelope of spectral sensitivity defined by the empirical estimates is wider than that of a single opsin. Indeed, it is difficult to conclude that either single-opsin model in Figure 1 can predict the human circadian system response to narrow-band light stimuli, at least as measured by acute melatonin suppression. Furthermore, if the spectral sensitivity estimates by Brainard *et al.*[8,16] and Thapan *et al.*[9] are to be accepted, there is evidence in both sets for a discontinuity in the spectral sensitivity estimates between about 470 and 530 nm (Figure 1), suggesting involvement of neural mechanisms receiving input from different photopigments. Consistently, Hattar *et al.*[18] demonstrated that multiple photopigments contribute to circadian phototransduction in mammals. Subsequent studies demonstrated that although ipRGCs are the primary photoreceptors for circadian phototransduction, they

receive input from the classical rod and cone photoreceptors.[19] Since rod and cone photoreceptors cannot directly connect to the ipRGCs, they must do so through neural connections with bipolar, horizontal and amacrine cells. Perhaps then, it is not surprising that single-opsin models of the spectral sensitivity of the human circadian system are inadequate at characterising the empirical data in Figure 1.

Obviating considerations of specific photopigments and their neural connections, Gall[23] used a simple, arbitrary model to characterise the empirical spectral sensitivity estimates from Brainard *et al.*[8] and Thapan *et al.*[9] This model has been actively discussed for use in a system of circadian photometry.[24] While the Gall function (although it appears to have been derived in quantum units rather than radiant power units) is similar to orthodox luminous efficiency functions in that it is wider than one based on a single opsin, it ignores the discontinuities in both sets of estimates between about 470 and 530 nm (Figure 1). As a result, the Gall function misses the estimated spectral sensitivities at wavelengths shorter than and just longer than 460 nm, as shown in Figure 2. Generally, however, the Gall function fits the set of empirical spectral sensitivity estimates from Brainard *et al.*[8,16] and Thapan *et al.*[9] better than either single-opsin model.

1.2. A non-linear model

A model of human circadian phototransduction was published in 2005 for both narrow-band and polychromatic light sources.[21] The model was constrained by the known photopigments and the known neuroanatomy and physiology of the human retina, and assumed that the published spectral sensitivity estimates from Brainard *et al.*[8] and Thapan *et al.*[9] were valid. Subsequent work from our laboratory has specifically tested the validity of including a subadditive, spectral opponent input to the ipRGC from the blue–yellow (b–y) channel as implied by the known neuroanatomy and neurophysiology of colour vision formation in the human retina.[26] This aspect of the model includes shunting inhibition and a one-way, diode-like signal path whereby only depolarising input from the short-wavelength, S-cone bipolar to the ipRGCs is possible. When receiving depolarising input from the S-cone bipolar, the overall circadian response through the ipRGC is modulated by rod-dominated, shunting inhibition from AII amacrine cells. This shunting inhibition is switched off with a hyperpolarising 'yellow' response from the S-cone bipolar; thus, due to a one-way, depolarising input pathway, only the intrinsic sensitivity of the ipRGC contributes to the circadian response for 'yellow' stimuli. This process leads to the sharp discontinuity in the modelled spectral sensitivity to narrow-band stimuli near the b–y spectrally opponent cross-point (≈507 nm). For more information about the model, studies done by Rea *et al.*[21,27] can be referred.

Since 2005, several modifications to the model have been considered and are introduced here to reflect our current refinements of the circadian light (CL_A) calculations. As additional empirical data are collected, new refinements are likely to be proposed.

- Lens spectral transmittance is now explicitly included in the ipRGC melanopsin sensitivity (Mc_λ); it was already an implicit part of the other photosensitive inputs to the model: the S-cone fundamental by Smith and Pokorny[28] and the photopic luminous efficiency function (V_λ) established by CIE.[29] This approach provides for specifying the stimulus in terms of the corneal spectral irradiance.
- The b–y channel response in the original model utilised the S-cone fundamental and V_λ, both of which are based on foveally viewed stimuli, whereas the peripheral retina probably contains most of the photoreceptors and neural circuitry associated with circadian phototransduction. These two photosensitive inputs to the original

model implicitly included spectral attenuation by the macular pigment. To better represent the spectral sensitivities of these inputs to the model from the peripheral retina, macular pigment spectral absorption was removed from the refined model. Both the S-cone fundamental and V_λ were divided by the macular pigment spectral transmittance values obtained from in vitro optical density measurements of the macular pigment.[30]

- Threshold constants for the ipRGC and the b–y response functions, b_1 and b_2, respectively, have been dropped in the revised formulation. Empirical data for suppression values less than 15% were not included in the original model formulation. Since there is still uncertainty regarding the threshold for nocturnal melatonin suppression, these constants were dropped to simplify the model.
- The constant a_1 has been dropped from the original model equations, again, for simplicity and the other constants have been adjusted to reflect that change. For clarity, the original designations for the remaining two constants, a_2 and a_3, have been changed to a_{b-y} and a_{rod}, respectively.
- The value of k has been set so the crosspoint of the b–y channel is at 507 nm, consistent with independent estimates of unique green.[31] For wavelengths longer than 507 nm, the spectral sensitivity of the model is based upon melanopsin only, due to the one-way, depolarising input pathway from the S-cone bipolar cells.

Equation (1) reflects these changes in the revised model. Figure 3 shows the revised model predictions for the empirical spectral sensitivity estimates from Brainard *et al.*[8,16] and Thapan *et al.*[9]

$$CL_A = \begin{cases} 1622\left[\int Mc_\lambda E_\lambda \mathrm{d}\lambda + \left(a_{\mathrm{b-y}}\left(\int \frac{S_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda - k\int \frac{V_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda\right) - a_{rod}\left(1 - e^{\frac{-\int V'_\lambda E_\lambda \mathrm{d}\lambda}{\mathrm{RodSat}}}\right)\right)\right] \\ \qquad if \int \frac{S_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda - k\int \frac{V_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda \geq 0 \\ 1622\int Mc_\lambda E_\lambda \mathrm{d}\lambda \quad if \int \frac{S_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda - k\int \frac{V_\lambda}{mp_\lambda} E_\lambda \mathrm{d}\lambda < 0 \end{cases} \quad (1)$$

where

CL_A: Circadian light. The constant, 1622, 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) sensitivity[25]
S_λ: S-cone fundamental[28]
mp_λ: macular pigment transmittance[30]
V_λ: Photopic luminous efficiency function[29]
V'_λ: Scotopic luminous efficiency function[29]
RodSat: Half-saturation constant for bleaching rods = 6.5 W/m^2 [21]
$k = 0.2616$
$a_{b-y} = 0.6201$
$a_{rod} = 3.2347$

2. Comparison of model predictions

Based upon basic retinal neuroanatomy and neurophysiology and upon the fits to the empirical spectral sensitivity estimates in Figure 1, single-opsin models are likely inadequate for characterising the spectral sensitivity of the human circadian system. The Gall model was developed without regard to any underlying physiology, and predicts circadian

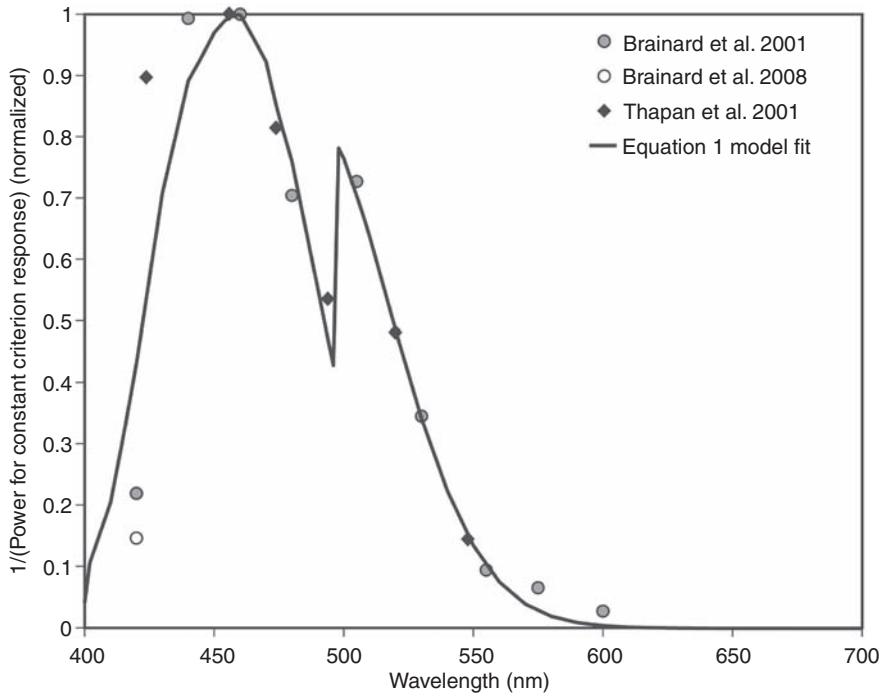

Figure 3 The spectral sensitivity estimates from Brainard *et al.*[8,16] and Thapan *et al.*[9] together with model predictions based upon Equation (1)

system response to very short (<470 nm) and rather long (>510 nm) narrow-band spectra nearly as well as the more complicated, non-linear models represented by Equation (1). Therefore, meaningful differences between the two model predictions for narrow-band spectra will probably only be found between 470 and 510 nm, as illustrated in Figure 2. From a lighting application perspective, however, exposures to narrow-band spectra are not commonly encountered. Of more importance for application are predictions for polychromatic 'white' light sources used for general illumination. Differences between the two model predictions diverge significantly for polychromatic light sources. This is not a result of the closeness in matching the responses for narrow-band sources, but rather, is due to the non-linear aspects of the Rea *et al.* model (i.e. spectral opponency and shunting inhibition) *versus* the linear Gall function. Figure 4 shows predictions of the relative effectiveness of different polychromatic light sources at a corneal illuminance of 300 lux for suppressing nocturnal melatonin as a function of correlated colour temperature (CCT) based upon the Gall function and upon the model represented by Equation (1). Since the Gall function does not predict absolute response, relative predictions from this additive spectral sensitivity function were normalised to be the same as the model prediction from Rea *et al.*[27] for a reference source (CIE Illuminant A) providing a corneal irradiance of 300 lux. As is readily apparent from Figure 4, the predictions of the relative effectiveness of the different light sources for stimulating the human circadian system can be the same or they can be quite different depending on the spectrum of the light source, laying the foundation for specific hypothesis testing. This is an important point. *Post hoc*

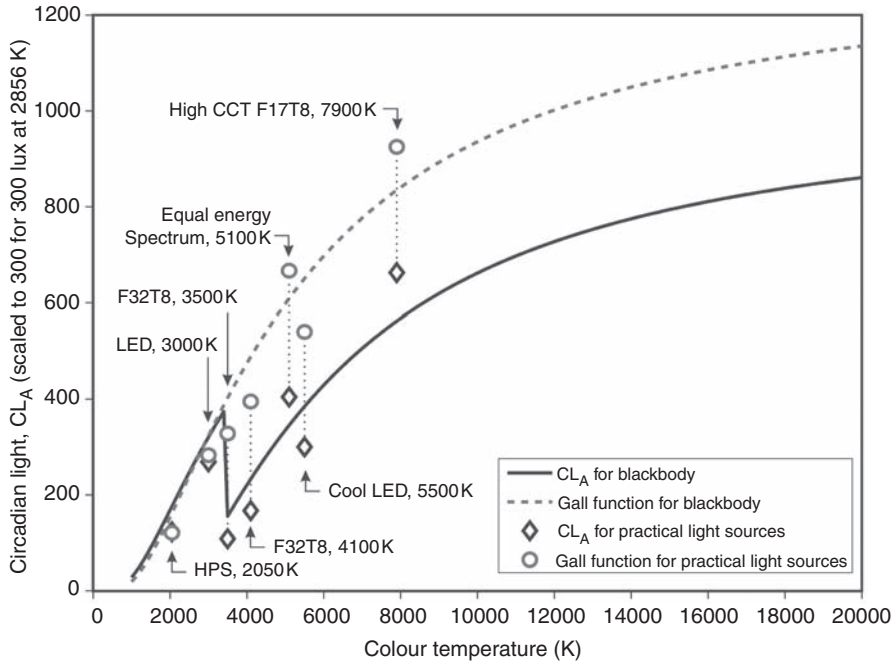

Figure 4 A comparison of the relative effectiveness of 300 lux corneal illuminance for different light sources of different CCTs and for a blackbody radiator at different colour temperatures for circadian system stimulation as predicted from the Gall function and from Equation (1)

curve-fitting of melatonin suppression data and a comparison of residuals will be of little value for validating or improving any computational model because systematic and random errors in the sampled data are treated equally in a statistical regression. This is perhaps illustrated best from Figure 2. Although the mean residual errors for the Gall model are slightly larger than those from the non-linear model described here, meaningful and systematic differences between the two model predictions are mainly between 470 and 510 nm. Thus, a useful comparison of model predictions will require a targeted hypothesis as well as a suitably high level of experimental control before one model can be rejected in favour of another. In other words, new experiments specifically designed to compare model predictions like those in Figure 4 will be needed.

3. Discussion

Orthodox photometry, based upon the photopic luminous efficiency function, V_λ, has been used for many years with some success at specifying the visual stimulus for lighting practice. Indeed, all current lighting standards for illuminance, luminous intensity and luminous flux are based upon V_λ. The ubiquity of V_λ is, however, strangely at odds with what is known about the human visual system's brightness response to light. V_λ is an additive function based upon the spectral sensitivity of just two of the three cone types. Brightness perception is a distinctly non-linear response to light governed by all three cone types,[25,32] and most likely, a class of ipRGCs.[20,27,33] It is becoming increasingly clear that a similar contrast may emerge for the specification of light for NIF systems. As discussed here,

simple models of the spectral sensitivity of the human circadian system are at odds with the empirical data and with the known neuroanatomy and neurophysiology of the retina. Metrological precision is, in principle, independent of biophysical accuracy; however, if a system of circadian photometry is to be developed, it will be necessary to consider the trade-off between practical utility and scientific accuracy, as has been the case for orthodox photometry.

Towards this end, it is first necessary to consider model predictions that are based upon the same radiometric units. Some of the results from Brainard *et al.*[8] and Thapan *et al.*[9] were based on stimuli specified in terms of irradiance (e.g. $\mu W/cm^{2)}$, and other results in terms of quanta (e.g. photons/cm^2/s). The conversion from one unit to the other is simple; therefore, it is certainly possible to combine spectral efficiency estimates from different experiments based upon these units, as is in Table 1 and Figure 1. However, care must be exercised to combine spectral efficiency estimates based upon the same units because the shape of a spectral efficiency curve based upon irradiance will differ from one based upon quanta. This artefact arises because efficiency is defined in terms of the wavelength requiring the least amount of power or quanta to produce a criterion effect; that wavelength requiring the least amount of power or quanta is the peak of the spectral efficiency curve. The peak wavelength will differ, however, depending upon whether the stimuli were defined in terms of power or quanta. For example, the peak of the photopic luminous efficiency function, V_λ, is at 555 nm when based upon units of irradiance, but at 550 nm when based upon quanta. Errors will therefore occur when combining or comparing spectral efficiency functions based upon different radiometric units. The likelihood of such errors increases when the radiometric units used to calculate spectral efficiency are not explicitly given. Orthodox photometry has been based upon units of irradiance, so a system of circadian photometry is likely to be based upon irradiance as well.

More substantively related to the goals of gaining greater accuracy in specifying the light stimulus and of considering the need for homology between photometry and biophysics, is the relatively high amount of uncertainty in predicting the response of the human circadian system to narrow-band light sources between about 470 and 510 nm. There is also high uncertainty in predicting the effectiveness of practical polychromatic light sources, as illustrated in Figure 4. This figure makes clear that it will be important to directly compare model predictions for white light sources below and above about 4000 K. If a simple, additive function can properly rank order practical light sources in terms of their impact on the human circadian system (e.g. nocturnal melatonin suppression), a more complicated, albeit physiologically more correct, non-linear system of circadian photometry may not be necessary.

Until specific hypotheses like the ones posed above are formulated and tested, however, it would be premature to recommend international acceptance of any model or system of circadian photometry. Given explicit, quantitative predictions of nocturnal melatonin suppression from different models of circadian system spectral sensitivity and given the practical implications for the development and regulation of electric light sources used for general illumination, such data would, in principle, be straightforward to obtain and would be extremely valuable for establishing a system of circadian photometry for architectural and clinical applications.

Finally, it is worth noting that the models used to predict the effects of light sources on the circadian system (e.g. like those in Figure 4) are based on acute melatonin suppression by light at night. Although there is no compelling reason to believe that circadian phototransduction for acute melatonin suppression is

different than that for phase shifting or circadian entrainment,[34] there may, nevertheless, be different neural processes underlying these two outcome measures.

Acknowledgements

The authors are grateful to Dieter Lang at OSRAM, and to Dipl.-Ing. Sohéil Moghtader at Deutsches Institut für Normung for their support. The authors also thank Lighting Research Center colleagues Dennis Guyon and Ines Martinović for their assistance with this manuscript.

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