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On light as an alerting stimulus at night

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Abstract. Light exposure at night increases alertness; however, it is not clear if light affects nocturnal alertness in the same way that it affects measures of circadian regulation. The purpose of this study was to determine if a previously established functional relationship between light and nocturnal melatonin suppression was the same as that relating light exposure and nocturnal alertness. Four levels of narrow-band blue light at the cornea were presented during nighttime sessions. The ratio of electroencephalographic alpha power density with eyes closed to eyes open (alpha attenuation coefficient, AAC) and the Norris mood scale were used. The AAC and ratings of alertness increased monotonically with irradiance and were highly correlated. Both measures of alertness were highly correlated with model predictions of nocturnal melatonin suppression for the same circadian light stimulus, consistent with the inference that the suprachiasmatic nuclei play an important role in nocturnal alertness as well as circadian regulation.

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INTRODUCTION

Circadian rhythms in humans, including rest-activity patterns, hormone production cycles, and variations in core body temperature, are regulated by the suprachiasmatic nuclei (SCN) (Moore-Ede et al. 1982). These rhythms can be influenced by exogenous factors, the most important of which is the 24-h pattern of light and dark, which is the primary synchronizer of the circadian clock to the solar day. Light and dark patterns are conveyed from the retina to the SCN *via* the retinohypothalamic tract (RHT) keeping the internal biological clock synchronized with the solar day. Depending upon when it is applied in the 24-h cycle, light can phase advance or phase delay human circadian rhythms. Light has also been shown to have an acute effect on neuroendocrine responses. Light applied at night can, for example, suppress the synthesis of melatonin, which is released at night and under conditions of darkness. Among other important functions, such as cell repair and reducing the rate of division of tumor cells, melatonin is an important hormone for synchronizing circadian responses throughout the body. Light can also increase objective and subjective measures of alertness (Badia et al. 1991, Cajochen et al. 2000, 2005, Lockley et al. 2006); however, the functional relationship between light stimuli and nocturnal alertness has never been compared to the functional relationship between light stimuli and circadian regulation.

Recently, Rea and coauthors (2005) developed a model for human circadian phototransduction, which has been used to predict the relative effectiveness of different light sources for stimulating human melatonin suppression at night. The model is consistent with recently published evidence from neurophysiology and neuroanatomy, and incorporates the intrinsically-photosensitive retinal ganglion cells (ipRGCs) as well as input from rod and cone photoreceptors. It takes into account the high absolute threshold to light as well as the spectral sensitivity of the human circadian system. Importantly too, it considers evidence for a phenomenon known as spectral opponency that underlies human color vision (Figueiro et al. 2004, 2005). Because the model was based on several sets of psychophysical data where nocturnal melatonin suppression was measured after brief (30 to 90 min) light exposures (Brainard et al. 2001, Figueiro et al. 2004, McIntyre et al. 1989, Rea et al. 2001, 2002, Thapan et al. 2001), it was specifically developed to generate quantitative predictions of nocturnal melatonin suppression after exposures to any light spectrum and any light level. Figueiro and colleagues (2006a) recently demonstrated that the model could successfully predict the relative effectiveness of two polychromatic, white light sources (F17T8/TL741, Philips and FO17/SkyWhite/ECO, OSRAM Sylvania) at different irradiances for acute suppression of nocturnal melatonin.

Although the mechanisms associated with the alerting effects of light are not fully understood, recent studies in neurophysiology and neuroanatomy have revealed the probable importance of the SCN for affecting wakefulness at night (Saper et al. 2005). The light-stimulated SCN appear to have a direct impact on alertness through efferent neurons to the dorsomedial nucleus of the hypothalamus (DMH). In turn, the DMH projects to several important areas of the brain that both enhance alertness and suppress sleep. The suppression of the soporific nocturnal hormone melatonin synthesized by the pineal gland by the SCN may also play a role in increasing alertness at night. Consistent then with many empirical observations that light increases both objective and subjective measures of alertness, a more fundamental understanding of the underlying neural pathways in the brain affecting alertness at night by light activation of the circadian system is rapidly emerging.

A number of studies have compared the relative effectiveness of monochromatic lights for stimulating the circadian system, both in terms of nocturnal melatonin suppression and phase shifting (Brainard et al. 2001, Lockley et al. 2003, Thapan et al. 2001, Warman et al. 2003, Wright and Lack 2001, Wright et al. 2004). Since the SCN is central to circadian response and since it is strongly implicated in affecting nocturnal arousal, it was natural to suppose that short-wavelength (blue) light (Brainard et al. 2001, Rea et al. 2002, Thapan et al. 2001) might be an efficacious alerting stimulus at night. Indeed, blue light has been recently shown to exert an alerting effect at night, measured both objectively [e.g., electroencephalogram (EEG), reaction times, heart rate] and subjectively (e.g., rating questionnaires) (Cajochen et al. 2005, Revell et al. 2005). Lockley and others (2006) also showed that subjects exposed to blue light (460 nm) with dilated pupils had significantly lower subjective sleepiness ratings, decreased auditory reaction times, greater attention, decreased EEG power density in the delta-theta range (0.5 to 5.5 Hz) [commonly associated with sleepiness (Hugdahl 1995)] and increased EEG power density in the high-alpha range

(~10 Hz) than those exposed to the same photon densities of a 555-nm monochromatic light.

Although previous studies have shown that blue light can have alerting effects in humans at night, no study has established a functional relationship between different levels of blue light exposure and alertness. More importantly and more generally, none of the studies to date have tested *a priori* predictions of the effectiveness of different light stimuli for modulating levels of nocturnal alertness. The ability to make quantitative predictions of the effectiveness of different light stimuli for stimulating alertness is important because a quantitative understanding of this functional relationship could then be used to help design comfortable, cost-effective lighting systems for night-shift applications where performance is very important. One approach to the problem would be to present different light spectra at different irradiances and determine the spectral and absolute sensitivities of light-induced nocturnal alertness. Another, more elegant way, would be to determine if the model of circadian phototransduction developed by Rea and colleagues (2005) could be used to predict the impact of light on alertness at night because it already incorporates spectral and absolute sensitivities to light as a stimulus for circadian regulation. This more parsimonious approach to the problem would, at the very least, justify a much more extensive study of the absolute and spectral sensitivities of nocturnal alertness to light. In this paper then, we set out to determine if the model of circadian phototransduction developed by Rea and others (2005) could be used to quantitatively characterize the photic stimulus for light-induced nocturnal alertness.

METHODS

Eight subjects participated in the study, which ran from 00:00 to 08:30 on two nights (four subjects per night). Before accepting subjects for the experiment, they were screened for sleep habits according to their responses on the Munich ChronoType Questionnaire (Roenneberg et al. 2003); subjects that were extremely early (before 6:00) or late risers (after 10:00) were excluded from selection. Selected subjects were asked to avoid sleeping and to refrain from caffeine intake after 10:00 the day of the study. Upon arrival to the laboratory, subjects signed an informed consent form approved by Rensselaer's Institutional Review Board, and also performed the Ishihara (1993) test for color blindness as well as a visual acuity test. One male subject demonstrated pronounced color blindness and, as determined later, highly unusual EEG patterns. His data were excluded from subsequent analyses. Therefore, data from seven subjects, four males (20–54 years, median = 34.5) and three females (26–41 years, median = 30), were used in all analyses.

Table I

Lighting conditions used in the experiment

Illuminance at cornea (lx)	Irradiance at cornea (W/m^2)	Photon density at cornea ($photons/cm^2/s$)
5	0.05	1.2×10^{13}
10	0.1	2.4×10^{13}
20	0.2	4.8×10^{13}
40	0.4	9.6×10^{13}

Four arrays of blue light emitting diodes (λ_{max}=470 nm) (iCove, Color Kinetics) mounted inside the front face of light-integrating boxes delivered diffuse blue illumination ranging from 5 to 40 lx (0.05 to 0.4 W/m^2) at the subjects' corneas (see Table I for the light levels), as measured with a calibrated and well-characterized illuminance meter (Model P30SC0, LMT) and a laboratory grade sprectro-radiometer.

The boxes, placed on small tables 0.76 m above the floor, measured 0.6 × 0.6 × 0.6 m. The inside of the boxes were painted matte white. A chin rest was clamped to the bottom of a square 0.45 m × 0.45 m aperture cut into the front of the box so that the subjects' head position remained fixed during the exposure sessions. A 0.3 m × 0.3 m aperture was cut in the back of the box so that a numerical verification task (Rea 1981) could be presented to subjects on a display monitor during the exposure sessions. A red filter (Roscolux #32, Rosco) was placed over the monitor screen throughout the experiment to minimize circadian stimulation by the light emitted from the computer screen. The vertical illuminance from the filtered computer screen alone was 0.8 lx at the eye.

From 00:00 to 00:50, subjects were fitted with electrodes (Ag-AgCl) placed on the scalp according to the International 10-20 system (American Electroencephalographic Society 1991) at locations Pz/Oz, O1 and O2, and referenced to electrodes attached to the earlobes (A1, A2). The EEG recording system (Active Two, BioSemi) used a sampling rate of 1 024 Hz. Data were preprocessed using a digital, finite impulse

response (FIR) bandpass filter of order 2000 with low and high cutoff frequencies of 1 and 40 Hz, respectively, followed by an out-of-bounds (± 30 μV threshold) test to reject epochs that were contaminated by muscle or eye-movement artifacts.

Following every 50-min exposure to one of the blue light conditions, EEG measurements were taken while the subject was looking at a mark on the back wall of the integrating box. Measurement periods lasted 6 min and followed the procedures used for the alpha attenuation test (AAT) (Alloway et al. 1997, Hagiwara et al. 1997, Stampi et al. 1995). This test uses the alpha attenuation coefficient (AAC), defined as the ratio of mean total alpha power (8 to 12 Hz) recorded while the subjects' eyes are closed to mean total alpha power recorded while subjects' eyes are open. An increase in AAC indicates a higher alertness level. EEG data were obtained during three cycles of 1-min periods of eyes open and 1-min periods of eyes closed over a 6-min period. Following administration of the AAT, subjects reported their subjective alertness using a modified version of the 'drowsy/alert' question on the Norris (1971) mood scale, scored using a seven-point scale (–3 = drowsy, +3 = alert) rather than the continuous rating scale originally used by Norris.

Subjects were exposed to all four blue light levels in one night. The blue light exposure levels were counterbalanced across four different subjects on both nights of the experiment. Alternating between the four blue light exposures, subjects were seated for one hour in a room dimly and diffusely illuminated (15 to 50 lx at the cornea) with a 3500 K compact fluorescent lamp (one uplight fixture with two PLC/26W/35/4P, Philips lamps). Subjects were never permitted to sleep during the experimental session. Due to technical problems, it was not possible to collect data from one subject during the 5 lx condition. The elimination of all the data for one subject and the data at 5 lx for another subject affected the counterbalancing of the experimental design. However, as will be discussed later, this probably had little effect on the results.

Spectral analyses of the EEG data were conducted by dividing preprocessed time series data into 5-s-long epochs with 0% overlap. A Blackman window was applied to each epoch and then fast Fourier transforms (FFT) to compute spectral power density. The resulting spectral power density was then re-sampled to a 0.5-Hz spectral resolution. The 5-s-long epochs for each 1-min measurement period (up to 12, following out-of-bounds processing) with eyes open or closed were then combined to form 1-min epochs for each channel and each subject.

RESULTS

Figure 1 shows the average power density values in the alpha region (8 to 12 Hz) when the eyes were open and when they were closed following 50 min. exposures to each of the four blue light levels for each subject and measurement channel. Figure 2 shows the AAC values calculated from the means of the ratios of alpha power with eyes closed (for 1 min) and open (for 1 min) for each pair of 1-min epochs (Stampi et al. 1995). (It should be noted that because the distribution of alpha power values was asymmetrical, the ratios of the average eyes-closed and -open values in Figure 1 are not equal to the mean AAC values in Fig. 2). AAC increased monotonically with blue light levels from 5 lx to 40 lx. A one-way analysis of variance (ANOVA) revealed a nearly-significant (P=0.06) main effect of illuminance for AAC. Limited pairwise comparisons (McGuigan 1997) between the 5-lx and other conditions using one-tailed Student's t-tests revealed statistically significant differences in AAC between 5 and 20 lx (P<0.01) and between 5 and 40 lx (P<0.01). We do not believe that these statistically significant results are an artifact of the improper counterbalancing because for the two sets of data lost at 5 lx, one subject was presented this light level first, while the other saw it last.

Figure 3 shows the mean subjective ratings for the 'drowsy/alert' question on the Norris mood scale for

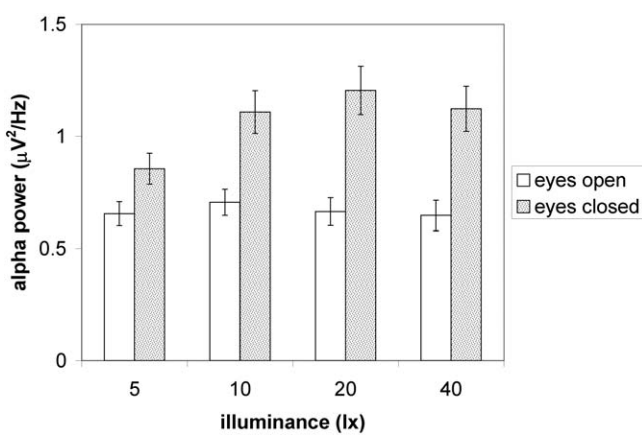

Fig. 1. Mean power density values (± SEM) for each subject and measurement channel in the alpha region (8 to 12 Hz) when the eyes were open and when they were closed following 50 min exposures to each of the four blue light levels

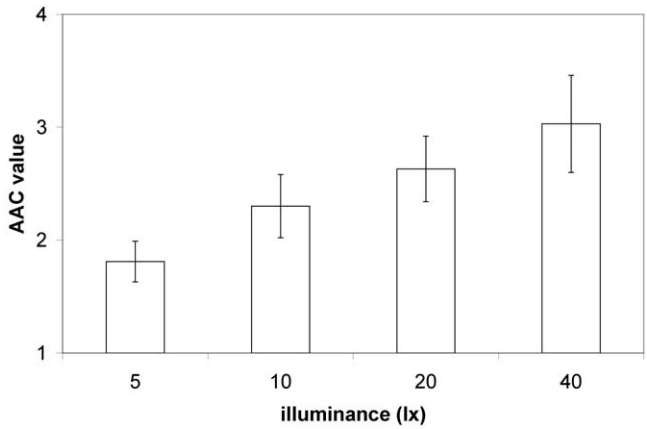

Fig. 2. Mean AAC values (± SEM) for each light level, calculated from the mean of ratios of the alpha power with eyes closed to eyes open, for each pair of 1-min measurement epochs

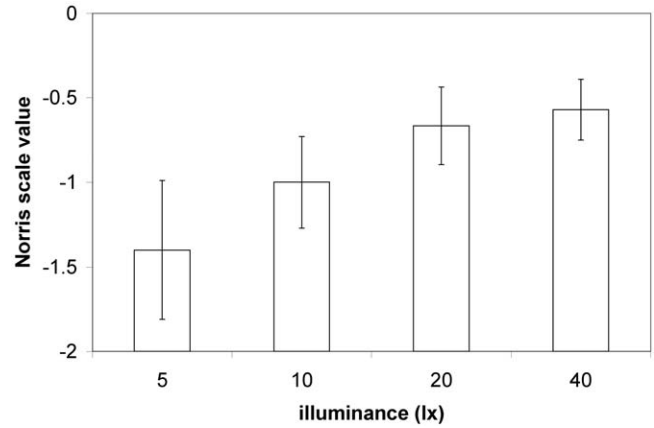

Fig. 3. Mean subjective alertness ratings (± SEM) using the modified Norris (1971) mood scale for each light level

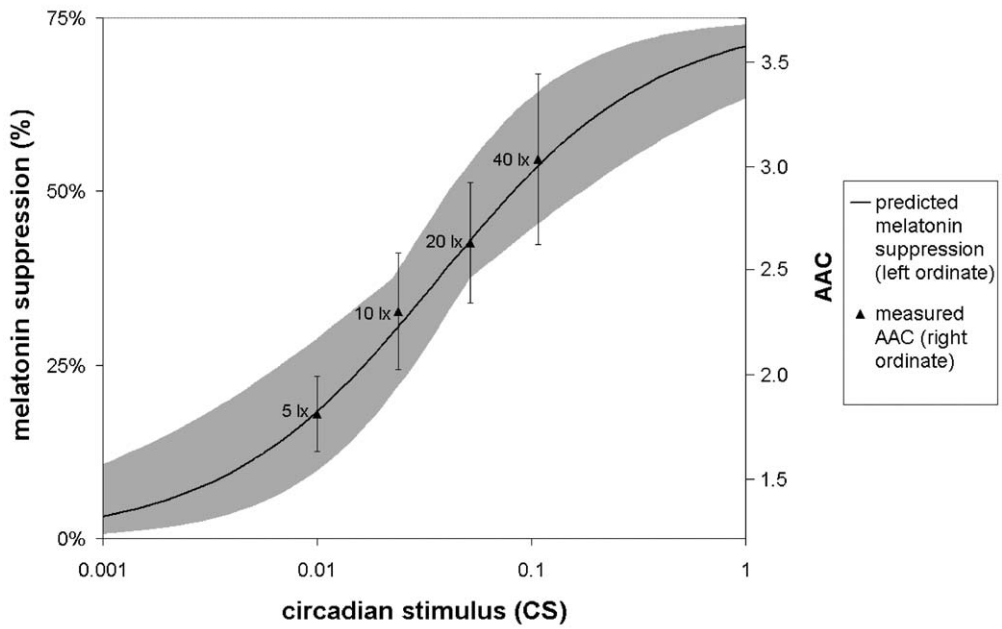

Fig. 4. Predictions of nocturnal melatonin suppression (solid line and shaded area representing 95% confidence intervals for predictions, left ordinate) (Figueiro et al. 2006b) and measured AAC values ± SEM (triangles, right ordinate) for each light level used in the present study. It should be noted that no additional transformation of abscissa values were necessary to compare melatonin suppression with AAC values for this experiment.

each lighting condition. A one-way ANOVA did not reveal a statistically significant effect of light level on subjective ratings, but the ratings were highly (r^2=0.95) and significantly (P<0.05) correlated with the AAC values across illuminance. Thus, the functional relationship between light exposure and subjective measure of alertness converges with the functional relationship between light exposure and objective measure of alertness, as would be expected if these two measures shared the same underlying phototransduction mechanism.

Of particular importance, the functional relationships between light and objective and subjective measures of nocturnal alertness both show a strong convergence with predictions of nocturnal melatonin suppression (Fig. 4). As described previously (Figueiro et al. 2006b), those predictions were obtained by combining a four-parameter

logistic function from Zeitzer and coauthors (2000), representing light-induced nocturnal melatonin suppression from threshold to saturation, with the amount of circadian light stimulus calculated from the model of circadian phototransduction by Rea and colleagues (2005). It should be stressed that for this analysis we did not make any *post-hoc* transformations to the circadian stimulus (CS) values from the model. This analysis therefore supports the inference that both the spectral and absolute sensitivities for nocturnal melatonin suppression are homologous with the spectral and absolute sensitivities for light-induced nocturnal alertness. Although nocturnal melatonin suppression and light-induced nocturnal alertness are undoubtedly separate neural phenomena with their own biophysical processes, they do both share a common neural relay site, the SCN (Saper et al. 2005), and, based upon this analysis, common phototransduction mechanisms in the retina. In other words, "light" for nocturnal melatonin suppression appears to have the same functional characteristics as "light" for nocturnal alertness.

DISCUSSION

The present results extend those from recent investigations of alertness following blue light exposure (Cajochen et al. 2005, Lockley et al. 2006) by demonstrating that there is a monotonic dose response relationship between blue light exposures and alertness, measured both objectively (AAC) and subjectively (Norris Scale).

As shown in Fig. 4, a very strong positive correlation (r^2=0.998) between the four AAC values obtained in this study and predicted levels of nocturnal melatonin suppression following approximately 1-h exposures to light was found, suggesting an SCN participation in light-induced nocturnal alertness. Saper and others (2005) have shown that the efferent pathways from the SCN to the hypothalamus driving alertness and sleep suppression are anatomically distinct from the pathway leading to the pineal gland responsible for melatonin synthesis. They have shown that the SCN have some projections to the ventrolateral preoptic nucleus (VLPO), which promotes sleep or the orexin neurons, which promotes alertness. Orexins are produced in the lateral hypothalamus and are important in promoting and sustaining wakefulness by projecting to areas in the brain that govern arousal and alertness. The majority of the SCN output are, however, directed toward the subparaventricular zone (SPZ) and the DMH. Lesions to the ventral SPZ disrupt circadian rhythms of sleep and wakefulness. Lesions to the DMH, which also receives input from the SPZ and is one of the major sources of input to the VLPO and orexin neurons, also diminishes circadian rhythms of sleep and wakefulness. In fact, animals with DMH lesions sleep about one hour more each day and have less activity. It seems like the DMH is needed for conveying SCN information to the sleep/wake regulatory system.

Although the SCN clearly have input to the pineal gland and melatonin production through a separate pathway than the circadian control of sleep, the very strong positive correlation between nocturnal melatonin suppression and AAC to the same blue-light stimulus is consistent with the findings from Saper and colleagues that the SCN play a role in both effects.

Importantly, these results strongly suggest that the model of circadian phototransduction developed by Rea and colleagues can be used to accurately characterize the photic stimulus for light-induced nocturnal alertness for any light level and any spectrum. As mentioned above, this suggestion is based upon the convergence of recent neuroanatomical studies (Saper et al. 2005) with the extremely tight correlations between subjective and objective measures of alertness and predictions of nocturnal melatonin suppression shown here (Fig. 4).

CONCLUSION

The results presented here do not prove causality but do suggest that the SCN affect both objective and subjective measures of alertness. Certainly it is important to extend this modest study of light-induced nocturnal alertness by testing a wider range of photic stimuli, but it now appears increasingly likely that the phototransduction mechanisms in the retina providing input to the SCN for nocturnal melatonin suppression are the same as those providing input to light-induced nocturnal alertness. And whereas it might be premature to offer specific recommendations for using light to improve alertness at night, the path toward lighting specifications now appears much clearer.

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