Spectral Sensitivity of the Circadian System

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ABSTRACT

Light exposure regulates several circadian functions in normal humans including the sleep-wake cycle. Individuals with Alzheimer's Disease (AD) often do not have regular patterns of activity and rest, but, rather, experience random periods of sleep and agitation during both day and night. Bright light during the day and darkness at night has been shown to consolidate activity periods during the day and rest periods at night in AD patients. The important characteristics of bright light exposure (quantity, spectrum, distribution, timing and duration) for achieving these results in AD patients is not yet understood. Recent research has shown that moderate (~18 lx at the cornea) blue (~470 nm) light is effective at suppressing melatonin in normal humans.

It was hypothesized that blue light applied just before AD patients retire to their beds for the night would have a measurable impact on their behavior. A pilot study was conducted for 30 days in a senior health care facility using four individuals diagnosed with mild to moderate levels of dementia. Four AD patients were exposed to arrays of blue light from light emitting diodes (max wavelength = 470 nm) in two-hour sessions (18:00 to 20:00 hours) for 10 days. As a control, they were exposed to red light (max wavelength = 640 nm) in two-hour sessions for 10 days prior to the blue light exposure.

Despite the modest sample size, exposure to blue LEDs has shown to affect sleep quality and median body temperature peak of these AD patients. Median body temperature peak was delayed by approximately 2 hours after exposure to blue LEDs compared to exposure to red LEDs and sleep quality was improved. This pilot study demonstrated that light, especially LEDs, can be an important contribution to helping AD patients regulate their circadian functions.

Keywords: LED, health, circadian, sleep, spectral sensitivity

1. INTRODUCTION

Circadian rhythms are biological rhythms that repeat at approximately every 24 hours. In mammals, circadian rhythms are driven by a pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus of the brain. The SCN is a self-sustaining oscillator that maintains its daily activities for weeks even when isolated in culture. In humans, the SCN has an intrinsic period that is slightly greater than 24 hours, and the light/dark cycle is the main synchronizer of the SCN to the 24-hour solar day. Photic information is conveyed directly from the retina to the SCN via the retinohypothalamic tract (RHT) and indirectly via the intergeniculate leaflet (IGL).[1]

Among other physiological rhythms, the SCN controls the production of the pineal hormone melatonin. Melatonin is produced at night and under conditions of darkness. Melatonin is an output signal of the circadian clock and is able to convey circadian and photoperiodic information to various structures and organs that have melatonin receptors within the brain and throughout the body. Melatonin is known as the hormone of darkness, signaling nighttime to the body. Core body temperature (CBT) is also used as a marker for the circadian clock. CBT has an inverse relationship with melatonin, and CBT minimum occurs at night, between 03:00 and 05:00 hours, when melatonin levels are high.

In 1980, Lewy and colleagues showed that bright white light (2500 lux for 2 hours during the night between 02:00 and 04:00) suppressed human melatonin to daytime levels[2] and later showed that bright white light relieved symptoms of seasonal affective disorder (SAD). These discoveries were very important because they stimulated other clinical and applied research. Van Someren *et al.* has shown that exposing Alzheimer's disease (AD) patients to bright light during the day and darkness at night consolidated their rest/activity patterns;[3] Miller *et al.* showed that cycled light, instead of

continuous light, improved the growth rate of premature infants.[4] Badia *et al.*, Boyce *et al.*, and Figueiro *et al.* showed that bright light exposure at night increased brain activity, improved cognitive performance, and improved subjective alertness, respectively.[5, 6, 7]

With these recent findings, it is becoming more and more important to understand the characteristics of light (intensity, timing and duration, spatial distribution, and spectrum) that are effective for the circadian system. The characteristics that are ideal for vision are quite different than those that are maximally effective for the circadian system.[8] Certainly, we are years away from a complete understanding of the impact of light on circadian regulation, but an initial understanding of the effects of light on the circadian system can be helpful in paving the way to practical applications where the circadian system, as well as the visual system, are important. Examples of these applications include the effects of light on seasonal depression, alertness and performance of nightshift workers, sleep quality of older adults, including AD patients, growth of premature infants, and jet lag symptoms. This paper will briefly discuss intensity, timing, duration, and spatial distribution as they relate to the circadian system, but will focus on spectrum and how, by tailoring the spectral power distribution (SPD) to the circadian system, light can be effectively used to mitigate the effects of one of the many circadian disorders, sleep quality of AD patients. Ultimately, the goal of this paper is to show how a better understanding of the stimulus can lead to more effective practical lighting applications for the circadian system.

1.1 Intensity[9-13]

Typical light levels found in office environments (500 lux from white light on the workplane) are more than sufficient for the visual system to process most alpha-numeric information. One hour exposure to this same white light, however, is barely sufficient to stimulate the circadian photobiological system. While the melatonin suppression curve to the far right in Figure 1 shows that illuminances of around 100 to 200 lx (at the eye) from "full-spectrum" lamps measured at the eye can suppress melatonin to some degree, it also demonstrates how close typical office light levels are to the threshold for melatonin suppression. For the purpose of this paper, it is assumed that suppression of nocturnal melatonin is indication of circadian-related responses. While threshold levels for the circadian system are on the order of 10^{12} photons,[9, 10] Figure 1 shows that visual task performance requires several orders of magnitude less light. In fact, the threshold limit for detectability in complete darkness is several magnitudes even lower than for visual performance.[11]

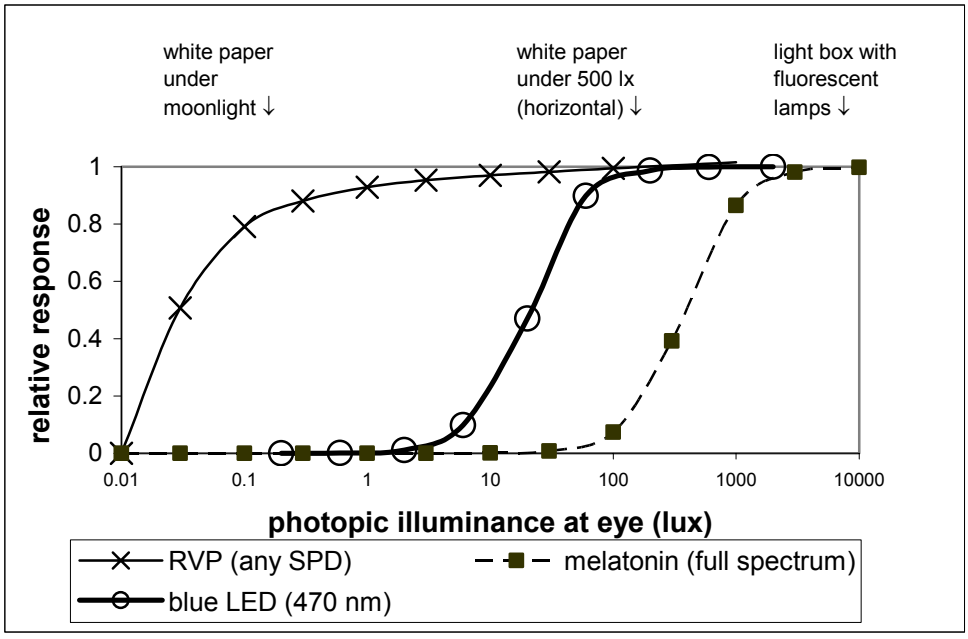

Figure 1: Relative visual performance[12] and relative melatonin suppression[13] as a function of illuminance (from "full spectrum" fluorescent lamps and blue LEDs) at the eye (relative suppression after one hour of light exposure is shown). Adapted and modified from Rea *et al.*[8]

1.2 Duration and timing

Operation of the visual system does not vary significantly on timing of light exposure; it responds to a light stimulus at any time of the day or night. Depending on the timing of light exposure,[14] however, light can phase advance or phase delay the biological clock,[15] or it can have no effect at all. Phase advance resets the clock to an earlier time and phase delay resets the clock to a later time. Because our clock's natural rhythm is a bit longer than 24 hours, we need to advance it every morning in order to be synchronized to the solar day.

Furthermore, the visual system responds to a light stimulus very quickly (less than 1 second).[16] The duration of light exposure needed to suppress melatonin is longer than the duration of light exposure needed to activate the visual system; suppression of melatonin content in the bloodstream is measurable at approximately 10 minutes after bright light exposure was initiated.[2]

1.3 Spatial distribution

For the visual system, light distribution is critical to visual performance. For example, the accurate rendition of the patterns of light and dark on this page are necessary to identify the words on this page. The circadian system does not respond to these patterns, only the overall amount of light reaching the retina.[17, 18]

1.4 Spectrum

Early studies of melatonin suppression by light in rats[19] found that the spectral sensitivity of this response peaked around 500 nm, consistent with the spectral sensitivity of rod photoreceptors. Preliminary data in humans[20] reinforced the possible role of rods [having a scotopic, V'(λ), spectral sensitivity peaking at 507 nm] in circadian phototransduction. Subsequent studies, however, have shown that the peak spectral sensitivity of the circadian system is even shorter than that of rods, around 460 nm.[9, 10, 21] This spectral sensitivity is very different than the spectral sensitivity of the fovea, used to perform nearly all of our "visual work" (e.g., reading). Although fewer than 1% of the photoreceptors in the retina are found in the fovea, nearly 80% of our visual cortex is devoted to processing information received in our central vision.[22] The fovea is dominated by L and M cones, which dominate the spectral sensitivity of the photopic luminous efficiency function, V(λ). The mechanisms underlying this spectral sensitivity function are not yet fully understood, and may involve novel photopigments in retinal ganglion cells,[23] probably in combination with traditional photoreceptors. Indeed, Rea *et al.*[21] noted that the data of Brainard *et al.*[9] and Thapan *et al.*[10] could be explained through a function they named C(λ) (Figure 2), a combination of rod and S cone spectral sensitivity. Consistent with this observation, Chiquet *et al.* found that the width of the action spectrum they derived for human melatonin suppression was wider than would be expected if a single opsin photopigment were the responsible mechanism.[24]

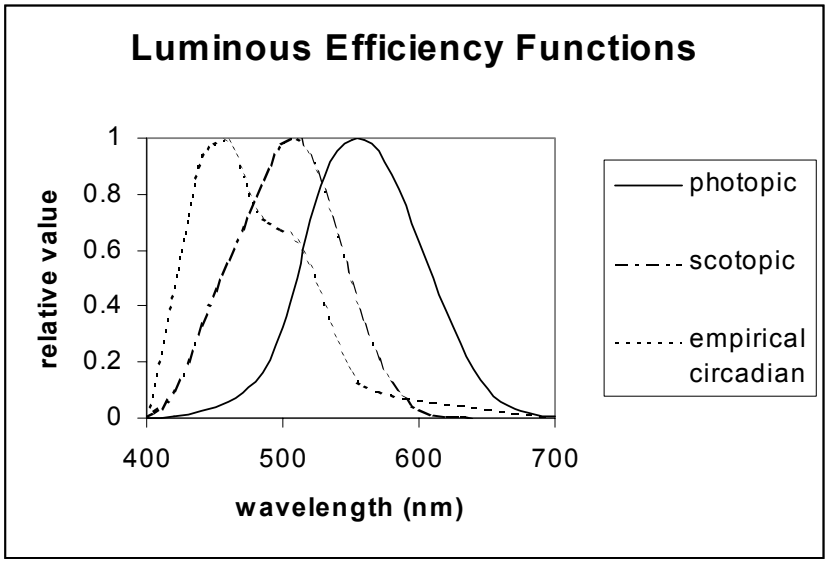

Figure 2: A luminous efficiency function for photopic, scotopic, and circadian responses; the latter is based on Brainard *et al*. and Thapan *et al*.[9, 10] Adapted from Rea *et al*.[21]

The spectral sensitivity of circadian responses in comparison to visual responses [approximated by V(λ)] helps to explain the seemingly large variations in the amount of light necessary to stimulate the circadian system. It has been reported recently that an illuminance of 8 lx at the eye can phase shift melatonin production rhythms.[25] This illuminance corresponds, however, to two narrow wavelength bands of "blue" light peaking at 436 and 456 nm, very close to the peak spectral sensitivity of the C(λ) function. Photometric convention stipulates that the luminous efficacy of light at 555 nm is equal to 683 lm/W.[26] Thus, 8 lx characterized with V(λ) from the short-wavelength source (assuming peaks of equal height) used by Warman *et al.*[25] is equivalent to 830 lx characterized with C(λ). The equivalent circadian stimulus from a 3000K fluorescent lamp would result in an illuminance of 490 lx characterized with V(λ). Conventional photometry based on V(λ) can therefore be misleading when comparing two light sources' effects on the circadian system. Figure 3 shows the SPDs of a 3000K fluorescent lamp and the short-wavelength source, scaled to provide equal stimulation to the circadian system as defined by C(λ). This result is corroborated by recent data from our laboratory, which have demonstrated significant suppression of nocturnal melatonin from just 18 lx from blue LEDs (λ_{max} = 470 nm).

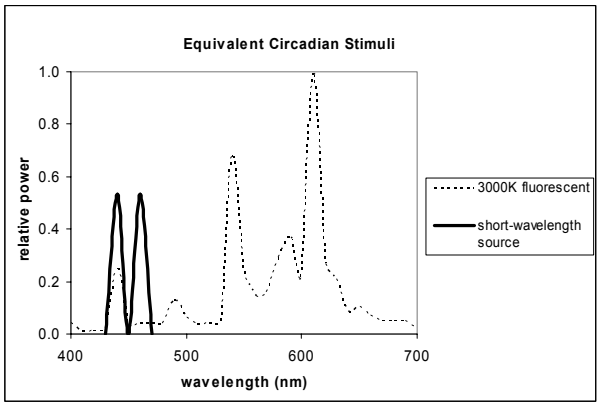

Figure 3: Relative spectral power distributions of a 3000K fluorescent lamp and a short-wavelength source for equivalent circadian effect.

These findings are significant because they show how light sources that have been designed to meet the needs of the visual system, like the 3000K fluorescent lamp, are not very effective in activating the circadian system. Light sources with maximum emission at the short wavelengths will have a greater impact on the circadian system than light sources with maximum emission at longer wavelengths.

1.5 Applications

Based on our knowledge of advanced lighting technologies, our understanding of sensory neurophysiology and psychophysics, and how lighting characteristics affect both the visual and the circadian systems, we undertook a pilot study to determine if exposure to modest levels of blue light from light-emitting diodes (LEDs) could have a measurable impacts on circadian responses in one population with well-documented circadian disruptions.

2. METHODS

The 30-day study was conducted in February and March of 2002 in a senior health care facility in Clifton Park, New York. The experiment was approved by Rensselaer's Institutional Review Board (IRB), and consent forms were signed by the caregivers, family members, and patients (two out of four were able to sign). Four AD patients exhibiting a wide range of symptoms, from very mild to severe, participated in the study. Patients followed their normal routine except they were brought to a common room for two hours between 18:00 and 20:00 hours. This two-hour period was just prior to the time they were normally taken to their rooms to sleep for the night. The common room was furnished with a couch, a table and chairs, a television, and some reading materials and games. The room was illuminated to approximately 300 lux (lx) on the table by ceiling fixtures containing fluorescent lamps. Two experimenters interacted with the four patients during the evening two-hour sessions.

After 10 days of acclimation to the two-hour sessions, patients were exposed to tabletop light fixtures containing red LEDs each evening for 10 days (see Figures 4a and 4b). These light fixtures produced approximately 30 lx at the cornea of the patients, although this value could not be rigidly controlled due to random sleep periods, agitation and absence from the room due to other unrelated, clinical conditions. The red-light exposure condition was introduced as a control because red light at this illuminance should not be effective in activating the circadian system. The red-light exposure was followed by 10 days of blue-light exposure, again producing approximately 30 lx at the cornea of the patients from a tabletop light fixture. It was expected that this condition would be effective for activating the circadian system. These expectations concerning the different light exposures were based upon calculations using the $C(\lambda)$.[21]

Tympanic temperatures and observations of sleep were obtained from nurses during the last four nights of the red-light, blue-light, ambient-only lighting conditions. These data were obtained at approximately 22:00, 00:00, 02:00, 04:00 and 06:00 hours from all four patients. Two patients, one with very mild symptoms and one with severe symptoms, were fitted with wrist-worn devices that measured activity during the 30-day study.

Figure 4a and 4b: Experimental Design and Apparatus.

3. RESULTS

The results obtained with this pilot study were very encouraging. Even though the data were variable, we found the following:

- Patients slept better between 02:00 and 04:00 hours after blue-light exposure compared to red-light exposure (Figure 5).
- Blue-light exposure delayed the decline of their body temperatures by approximately 2 hours compared to red-light exposure (Figure 6).
- The two patients that wore the wrist activity monitors showed more activity during daylight than at night, with peak activity shifting to midday. The ratio of activities during the day to those at night (light/dark ratio) increased, which means that they were more awake during the day and more asleep at night. (Table 1)

Repeated Measures Analysis of Variance (ANOVA) were conducted for both dependent variables: sleep and temperature. A statistically significant time by lighting conditions interaction was found for amount of sleep ($p = 0.0027$). The percentages of time subjects were found asleep at 02:00 and at 04:00 hours were significantly greater ($p = 0.046$ and $p = 0.013$, respectively) after exposure to blue light than after exposure to red light. An almost statistically significant time by lighting conditions interaction was found for tympanic temperature ($p = 0.08$).

Together, these findings indicated that exposure to blue light consolidated their rest/activity periods and sleep relative to the exposure to red light or typical ambient lighting. Tailoring intensity, spectrum, timing, duration, and distribution of light might be a clinically effective treatment for consolidating rest/activity rhythms of AD patients, which can also benefit caregivers in institutions and at home.

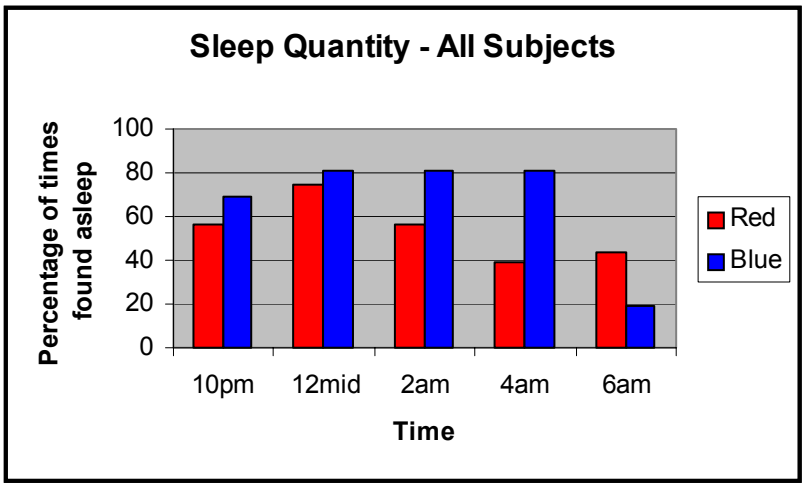

Figure 5: Sleep quantity for all subjects. Subjects slept better between 02:00 and 04:00 hours after blue-light exposure (bars at right) compared to red-light exposure (bars at left).

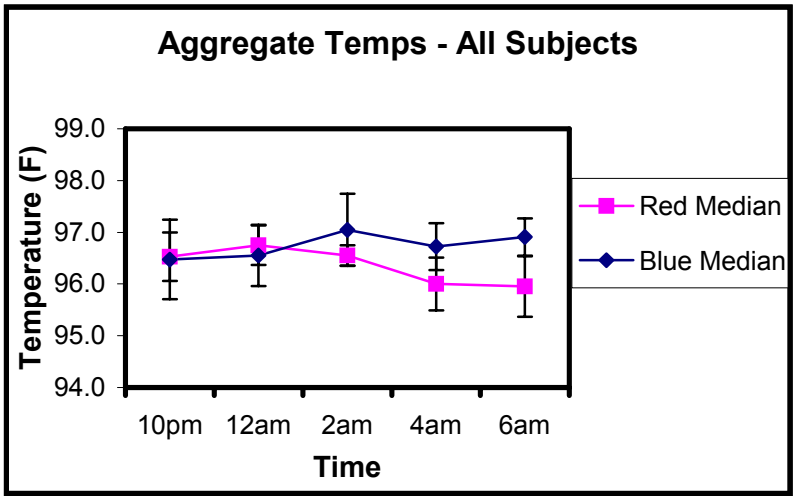

Figure 6: Aggregate temperatures for all 4 subjects. Decline of body temperature was delayed by approximately 2 hours, which is consistent with the timing of the light exposure.

	Subject 1 Blue Led	**Subject 1 Red Led**	**Subject 2 Blue Led**	**Subject 2 Red Led**
Light/dark ratio	2.24	2.13	1.20	0.99
Cosine peak	11:40	12:20	11:40	04:00

Table 1: Light/dark ratio (light period from 06:00 to 20:00 hrs and dark period from 20:00 hrs to 06:00 hrs) is the ratio of activity recorded during the light period (day) to the activity recorded during the dark period (night). A higher ratio indicates relatively more activity during the day than during the night and better consolidation of rest/activity rhythms. Cosine peak time is the estimated time for peak activity during the 24 h day.

4. DISCUSSION

The results presented here show that tailoring intensity, spectrum, timing, duration, and distribution of light has a great potential to serve as a non-pharmacological tool to help AD patients consolidate their rest/activity patterns and sleep better at night, which will also promote health and well-being of their caregivers. Similar results can be achieved by using white broadband spectra light, but this type of lighting usually has to be of a higher intensity, or applied for longer periods of time. The relative low levels needed from the blue LEDs used in this pilot study show the importance of understanding all lighting characteristics, especially intensity and spectrum. Higher intensities can be a source of glare and become very uncomfortable for AD patients to use. The subjects in the pilot study reported that the blue LEDs were "pleasant" to look at when room lights were on. Furthermore, understanding the likely circadian phase of AD patients enabled application of this light at the appropriate time (evening) to consolidate rest/activity patterns of these patients. Longer periods of time can be impractical, considering that it is very hard to maintain AD patients in a room for periods much longer than two hours.

These findings are very encouraging, but it is necessary to replicate these findings in a larger population before blue-light treatment can be recommended to help mitigate one of the many symptoms of AD. Replication of this pilot study is also important because it can be used to inform the design of multi-institutional clinical trials that will further expand understanding of the effectiveness of blue-light exposure on consolidating the rest/activity rhythms of people with AD. More important, it seems likely that the use of blue-light treatment can be extended to any application related to the circadian system. A better understanding of the stimulus should also help to effectively alleviate seasonal depression, improve performance of nightshift workers, increase growth of premature infants, and minimize jet lag. Once the specification of the stimulus is well understood, the likelihood of success in using light as a non-pharmacological means of alleviating the effects of circadian disruption in each of these applications is much greater.

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