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Quantifying light-dependent circadian disruption in humans and animal models

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Abstract

Although circadian disruption is an accepted term, little has been done to develop methods to quantify the degree of disruption or entrainment individual organisms actually exhibit in the field. A variety of behavioral, physiological and hormonal responses vary in amplitude over a 24-hour period and the degree to which these circadian rhythms are synchronized to the daily light-dark cycle can be quantified with a technique known as phasor analysis. Several studies have been carried out using phasor analysis in an attempt to measure circadian disruption exhibited by animals and by humans. To perform these studies, species-specific light measurement and light delivery technologies had to be developed based upon a fundamental understanding of circadian phototransduction mechanisms in the different species. When both nocturnal rodents and diurnal humans experienced different species-specific light-dark shift schedules, they showed, based upon phasor analysis of the light-dark and activity-rest patterns, similar levels of light-dependent circadian disruption. Indeed, both rodents and humans show monotonically increasing and quantitatively similar levels of light-dependent circadian disruption with increasing shift-nights per week. Thus, phasor analysis provides a method for quantifying circadian disruption in the field and in the laboratory as well as a bridge between ecological measurements of circadian entrainment in humans and parametric studies of circadian disruption in animal models, including nocturnal rodents.

Introduction

Much has been learned about the coupling of exogenous light exposure patterns to the timing of our endogenous biological rhythms (Van Someren & Nagtegaal, 2007). The natural 24-hour (h) light-dark cycle incident on our retinæ is the primary synchronizer of our cellular, physiological and behavioral rhythms to our local position on Earth (Appleman et al., 2013). Photoreceptors in the retinæ convert optical radiation into neural signals that are then processed by post-receptor neurons and carried over the retinohypothalamic tract (RHT) to our master biological clock in the suprachiasmatic nuclei (SCN). The processed neural signals reaching the SCN drive its efferent “clock-signaling” neurons that orchestrate the timing of the many peripheral clocks throughout the body (Panda & Hogenesch, 2004). These peripheral clocks then regulate the timing of our biological functions from mitotic cell division (You et al., 2005) to endocrine synthesis (Haus, 2007) to behavioral sleep (Edgar et

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al., 1993). It is also well established that variations from a regular, daily pattern of light and dark, as with shift work or rapid trans-meridian flight, can compromise the functionalities of our rhythmic biological functions and systems. The term “circadian disruption” has been coined to encompass a wide range of both acute and chronic decrements in performance, sleep, wellbeing and health. Here we have focused on quantifying circadian disruption as might be caused by irregular exposures to light over consecutive 24-h days or light-dark patterns that do not have a 24-h period.

Although much has been learned about light-dependent circadian disruption from basic studies in biology, controlled animal studies, and from epidemiological studies of humans, surprisingly little is known about the light-dark exposure patterns people *actually* experience. Although circadian disruption can be measured in a variety of ways, such as periodic sampling of saliva for melatonin concentration (Mirick & Davis, 2008) or of core body temperature (Satlin et al., 1995) field studies designed to measure circadian disruption often rely upon activity measurements because they are relatively inexpensive to obtain and they provide high density data. Activity statistics such as interdaily stability (IS) and intradaily variability (IV) (Van Someren et al., 1997) have been used with success to measure circadian disruption, but to characterize light-dependent circadian disruption in vulnerable populations such as shift workers (Straif et al., 2007) it is obviously necessary to measure the light-dark exposure patterns as well as the activity-rest patterns. Again, these light-dark patterns determine the time-dependent functionality of all biological systems, so to gain a deeper understanding of the significance of circadian disruption on performance, sleep, wellbeing and health in vulnerable populations such as shift workers, it is arguably necessary to deploy practical, calibrated devices for continuously measuring and recording the stimulus exposure patterns these individuals actually experience. To quantify circadian disruption then, it is necessary to measure both the stimulus to and the response from the circadian system. Ideally, the outcome measure would be one with little masking from other biological systems, such as core body temperature or melatonin synthesis, but practical field measurements of these “primary” outcome measures in the field are more difficult and usually more expensive than measurements of activity. Activity-rest patterns can be, and have been used (Ancoli-Israel et al., 2003; Carvalho-Bos et al., 2007; Dowling et al., 2005; Figueiro et al., 2012; Fontana Gasio et al., 2003; Hatfield et al., 2004; Huang et al., 2002; Miller et al., 2010; Rea et al., 2008; Van Someren et al., 1997; Van Someren et al., 1999) as practical, but not primary, outcome measures in field studies because the sleep-wake cycle is partially regulated by the circadian system (Dijk & Lockley, 2002).

The present paper brings together several lines of research and technology development aimed at characterizing light-dependent circadian disruption in human populations and in nocturnal rodents that often serve as models for health research. A previous field study aimed at quantifying circadian disruption in rotating-shift work nurses is summarized. A practical field device for measuring light-dark and activity-rest patterns exhibited by these nurses is also described together with phasor analysis, a method borrowed from signal processing to quantify circadian disruption. Finally, a recent study is summarized to demonstrate the utility of this approach for linking field measurements of light-dependent circadian disruption in diurnal humans to controlled experiments of light-dependent

circadian disruption using a nocturnal animal model. All human and animal studies conducted by our research team (Lighting Research Center, Rensselaer Polytechnic Institute) conform to international ethical standards (Portaluppi et al., 2010; World Medical Association, 2000).

Characterizing circadian light

In the 1980s, Ebihara and Tsuji showed that circadian entrainment was achieved in retinal-degenerated mice (Ebihara & Tsuji, 1980). In the 1990s, Foster and colleagues demonstrated that mice with severely degenerated classical photoreceptors exhibit normal circadian clock resetting by light (Foster et al., 1991). One of the explanations for these findings was the possibility that circadian photoentrainment was located outside the eye. However, this hypothesis was rejected after the demonstration that eye removal abolished circadian photoentrainment (Freedman et al., 1999) and reports that light shining at the back of the knees of humans, as had been proposed (Campbell & Murphy, 1998), could not entrain the circadian system (Lockley et al., 1998; Eastman et al., 2000). Although the eyes were needed for circadian entrainment, classical photoreceptors were not, strongly suggesting that a novel photoreceptor might exist in the retina. Consistent with these studies, Berson and colleagues (2002) identified a unique class of intrinsically photosensitive retinal ganglion cells (ipRGCs) in the mammalian retina. Unlike rods and cones, this photoreceptor is located in the retinal ganglion cell layer, depolarizes in response to light, is slower to respond compared to rods and cones, and has a peak spectral response at approximately 484 nanometers (nm). A novel opsin, melanopsin, was identified and drives the photosensitive response of the ipRGCs. Melanopsin protein is located in the cell bodies of these ganglion cells as well as in their axons and dendrites.

Although ipRGCs are central to circadian phototransduction, the classical photoreceptors (i.e., rods and cones) also contribute to this response in rodents (Hattar et al., 2003). Ruby and colleagues (2002) showed that melanopsin-deficient mice could still be entrained to light-dark cycles and were still able to show phase-shifting response to bright white light, although these responses were attenuated by approximately 40%, suggesting that although melanopsin is not essential for the SCN to receive light stimulus, it contributes significantly to the magnitude of the response. At the same time, Panda and colleagues (2003) demonstrated, using a monochromatic light of 480 nm (near the peak spectral response of the ipRGCs), that melanopsin-knockout mice had a 45% attenuation in phase-shifting response to two higher irradiances and an even greater attenuation at a lower irradiance. Consistently, Lucas and colleagues (2001) showed that in genetically manipulated mice in which the rods and cones are no longer photosensitive, pupil response to light is diminished at high irradiances. Finally, Hattar and colleagues (2003) showed that genetically manipulated mice lacking melanopsin, coupled with a rod/cone system that was unable to signal light, failed to show any pupil light reflex, did not entrain to the light-dark cycle, and showed no masking effect to light. A compilation of these studies suggests that melanopsin and classical photoreceptors (rods and cones) are involved in circadian phototransduction by light in rodents. Moreover, Aggelopoulos and Meissl (2000) showed through electrophysiological recordings that photic responses of SCN neurons are responding, at

least in part, to rod and cone input. Although it is likely that these findings can be extended to primates and humans, no similar studies to date have been conducted using primates.

Based on these published data, Rea and colleagues proposed a phototransduction model of the human circadian system (Rea et al., 2005; 2012). The model was developed within the constraints of physiologically plausible neural mechanisms in the retina, described above. The ipRGC is the central element in the phototransduction model, but a wealth of studies have shown that, after processing by post-receptor neurons, signals from rods and from cones also provide photic information to the SCN. The model takes into account these multi-channel inputs to circadian phototransduction, including the spectrally opponent blue versus yellow (b-y) color channel (Kaiser & Boynton, 1996). The b-y channel input to circadian phototransduction can result in a sub-additive response to polychromatic (white) light because short-wavelength and long-wavelength cone inputs to the b-y channel are subtracted. Thus, human circadian system response to polychromatic (white) lights cannot be predicted from a spectral sensitivity function determined from narrowband (colored) lights alone. Figure 1 illustrates the spectral and absolute sensitivities of the human model.

In 2005, Bullough and colleagues designed and implemented a unique cage lighting system to determine the spectral sensitivity of the murine circadian system and to directly test for additivity. From previous literature it was known that the murine retina contained rods and two cone types (Jacobs et al., 2004) and ipRGCs (Berson et al., 2002). The lighting system in each cage was comprised of green and blue light emitting diodes (LED) and a fluorescent source emitting ultraviolet (UV) radiation. These three sources were chosen to stimulate melanopsin in the ipRGCs, rhodopsin in rods and the known S-cone and M-cone photopigments. Figure 2 shows the absolute and spectral response function determined by Bullough and colleagues (2005) for the murine circadian system. Mice must have a qualitatively different circadian phototransduction mechanism in their retina. They are between 3000 and 10000 times more sensitive to light and they have less prominent color mechanisms than humans (Bullough et al., 2005).

The function developed by Bullough and colleagues (2005) was based upon a constant criterion phase shift to pulses of light of different intensities from each light source (two LEDs and the UV fluorescent lamp) and mathematically manipulating the relative contributions of the absorption spectra of the four known photopigments in the murine retina. To determine if the murine circadian system was additive, Bullough and colleagues delivered carefully controlled light pulses combining the radiances of two light sources that, when combined, should also provide a constant criterion phase shift response. That direct test supported the inference that the murine circadian system was strictly additive and that the spectral sensitivity in Figure 2 could be used as a luminous efficiency (additive) function for any spectral power distribution, monochromatic or polychromatic. This finding is consistent with previous results (Jacobs et al., 2004) demonstrating that mice have negligible color vision. Without a color mechanism, sub-additivity is less likely. Even though mice are nocturnal rodents without appreciable color vision, other nocturnal rodents that serve as animal models for health research (e.g., rats) appear to have rudimentary color vision and may demonstrate sub-additivity in circadian phototransduction. Certainly humans have color vision and, as already noted, have been shown to exhibit sub-additivity because the color

opponent mechanisms distal to the ganglion cell layer contribute to circadian phototransduction.

Measuring light and activity

Light is formally defined in terms of optical radiation effective for the human visual system. The photopic luminous efficiency function $V(\lambda)$, is used as part of the fundamental definition of light to convert radiometric quantities to photometric quantities (Commission International de l'Éclairage, 1978). The $V(\lambda)$ function with a peak response at 555 nm is nearly universally used to characterize and measure all visually effective optical radiation, but is actually based upon the spectral sensitivity of the foveal cones in the central visual field. All other spectral response functions, including that of the circadian system, are not formally recognized.

Because the spectral sensitivity of the human circadian system is different than the spectral sensitivity of the human foveal cones, we developed a light meter that was capable of measuring optical radiation for the circadian system. Figure 3 shows a Daysimeter similar to those used in several field studies where personal light-dark and activity-rest patterns were measured. The Daysimeter acquires light data using an integrated circuit (IC) light sensor array and activity data with single electronic sensor package containing three solid-state accelerometers. The digital data are stored in the on-board memory. The Daysimeter is calibrated in terms of the non-linear model of human circadian phototransduction (Rea et al., 2005; 2012; Figure 1). The peak spectral sensitivity is in the short-wavelength (blue) portion of the spectrum and the absolute light sensitivity is, in terms of conventional photopic response, approximately 0.2 lux and exhibits a linear response range up to approximately 65,000 (2^{16}) lux. Activity is measured in terms of the sum of the squared deviations from the mean value over a prescribed sampling interval. Power to the device comes from a small coin-cell battery. The Daysimeter can be deployed for several weeks, depending upon the sampling interval determined for an experiment. Additional details on the Daysimeter development, calibration, evaluation and deployment may be found in Figueiro et al. (2013b).

Phasor analysis

The light-dark and activity-rest patterns recorded by the Daysimeter can be used to quantify the degree of light-dependent circadian disruption exhibited by individuals using a technique known as phasor analysis. Phasor analysis as applied to measure circadian entrainment and disruption has been described elsewhere (Rea et al., 2008) but, briefly, the relationship between the 24-h light-dark exposure pattern, the stimulus, and the rest-activity pattern, the response, can be quantified in terms of the phase and the magnitude of their *joint* circular correlation function. The joint circular correlation function is determined by calculating correlations (r , not r^2) between the entire, continuously repeating time series of light-dark exposure data and the entire, continuously repeating time series of rest-activity data as one time series is rotated with respect to the other. Upon each incremental rotation of one time series with respect to the other a new correlation value is determined. A high, positive value of r is obtained when the two time series are in phase and a high, negative value of r is

obtained when they are counter-phased. For a well entrained individual, the circular correlation function is smooth and well characterized by an oscillating sine function with a period of 24-h; for a disrupted individual the amplitude of the 24-h oscillation is much smaller and the circular correlation function includes many more high-frequency components (i.e., it is less smooth). To quantify the relative strength of the circadian contribution to the circular correlation function, it is next decomposed into its Fourier components from which the 24-h frequency component can be isolated and then graphically represented by a vector, called a phasor. The vector length, or phasor magnitude, represents the amount of synchrony between the light-dark and activity-rest patterns measured by the Daysimeter. The greater the phasor magnitude, the stronger the coupling between the light-dark stimulus pattern and the activity-rest response pattern and, thus, the greater the light-dependent circadian entrainment. The vector angle, or phasor angle, reflects the phase relationship between the 24-h light-dark exposure pattern and the 24-h activity-rest pattern. For diurnal species the phasor angle is, by convention, positive and is negative for nocturnal species.

Human and mouse data

As part of the larger Nurses' Health Study II, 138 nurses volunteered to participate in a field study; both dayshift and rotating-shift nurses were recruited (Miller et al., 2010). Each nurse wore a Daysimeter for seven consecutive days while awake and not showering; while asleep, subjects were required to place the Daysimeter on a nearby table or in a drawer. For dayshift nurses the Daysimeter was always in the dark while they were asleep. For rotating shift nurses, however, the Daysimeter often recorded light while asleep that would not penetrate their closed eyelids and reach the retina (Bierman et al., 2011). For those cases, the light data were removed before analysis to better represent the actual retinal light exposure. The rotating-shift nurses worked from one to five nights over the recording period. Reported here are the data from 47 dayshift (DS), 23 rotating-shift nurses who worked one night per week (RS1) and 16 rotating-shift nurses who worked three consecutive nights per week (RS3).

In a light-tight laboratory, 24 male C57BL/6 mice were individually housed in cages containing a running wheel connected to a wheel monitoring system. A green (peak wavelength: 519 nm, full width half maximum [FWHM] bandwidth: 40 nm) LED lighting system was developed for the study; 4 $\mu\text{W}/\text{cm}^2$ of diffuse light could be delivered to the center of each cage floor. In a within-subjects design, every mouse was exposed to one of three lighting schedules for two consecutive weeks. The lighting patterns simulated a dayshift (DS)¹ schedule (12 h light:12 h dark), a one-night-per-week rotating-shift schedule, and a three-nights-per-week rotating-shift schedule. For the rotating-shift schedules, the 12-h light and 12-h dark phases were reversed for one (RS1) or for three consecutive (RS3) 24-h days per week.

¹But was obviously a "night" shift for the nocturnal mice.

The bridge

Phasor analysis was used to quantify light-dependent circadian disruption in humans and in mice based upon the calibrated (both for humans and for mice) light-dark and activity-rest patterns. Figure 4 shows the vector-averaged phasors for nurses and for mice (left panel) together with individual phasor magnitudes for nurses and for mice; the phasor magnitudes are plotted as a function of the number of night shifts per week (right panel). The differences in phasor angles for nurses and for mice reflect the different photic niche of each species. Diurnal humans are active during the day and asleep at night whereas nocturnal mice are active during the dark phase and resting during the light phase. Phasor magnitudes, our measure of light-dependent circadian disruption, are remarkably similar for the two species when exposed to the same light-dark exposure pattern. These findings support the inference that phasor magnitudes can be used to bridge human studies of circadian disruption in the field with animal model studies of circadian disruption in tightly controlled laboratory settings. It must be stressed however, that this can only be accomplished with calibrated, species-specific light and activity measurements where these calibrations depend upon a clear understanding of the circadian phototransduction mechanisms in those species.

The future

A great deal of research and development has been undertaken to accurately characterize “circadian light” for humans and for nocturnal rodents. We are also now able to measure light-dependent circadian disruption in humans living their normal lives and are able to quantify light-dependent circadian disruption in different species (Figueiro & Rea, 2010; Figueiro et al., 2013a; Figueiro et al., 2012; Radetsky et al., 2013; Rea et al., 2014). Through the Daysimeter technology and supporting science, we are now able to relate ecological measurements of human light-dependent circadian disruption to controlled laboratory studies of the impact of light-dependent circadian disruption in animal models (Radetsky et al., 2013). For example, animal models for diabetes (e.g., Rees & Alcolado, 2005) or for breast cancer (e.g., Fantozzi & Christofori, 2006) would be subjected to light-dark patterns emulating those experienced by human shift-workers. The onset time and the rate of disease progression in the animal models could then be more readily linked to actual human shift-work experience. This approach potentially links the epidemiological findings with humans (Schernhammer et al., 2006; Hansen & Stevens, 2011) to the basic genetic and exposure biology studies with animal models (Filipski et al., 2004; 2006; Blask et al., 2005). Indeed, without a bridge like the one described in the present paper it would be impossible to make comparisons between these two domains of science.

Developing a basic understanding of circadian phototransduction and the impact of light-dependent circadian disruption on health, performance and wellbeing is important, but we also need to translate that science into clinical treatments and general lighting applications (e.g., schools). We have already demonstrated that by applying controlled light exposures, it is possible to control circadian phase (Appleman et al., 2013). We have also demonstrated that we can apply light through closed eyelids to stimulate the circadian system as measured by phase change (Figueiro et al., 2013a). We are some years away from routine application of light therapy for sleep disorders, jet lag and chronotherapy (Hrushesky et al., 2004), but

some of the critical science has been completed and the technologies for translating that science into practice seem well on their way to product commercialization.

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Figure 1.

Presented in the left panel is the modeled spectral sensitivity of the human circadian system for narrowband and for polychromatic lights. Model predictions were based upon nocturnal melatonin suppression to narrowband light stimuli in two different studies (Brainard et al., 2001; 2008; Thapan et al., 2001) and constrained by neuroanatomy and neurophysiology of the human retina (Rea et al., 2005; 2012). Presented in the right panel is the functional relationship ($r^2 = 0.91$) between the spectrally weighted levels of circadian light (CL_A) and the measured levels of nocturnal melatonin suppression for the different amounts of narrowband light stimuli used in various published studies (Brainard et al., 2001; 2008; Thapan et al., 2001; Figueiro et al., 2011; West et al., 2011). Circadian stimulus (CS), the modeled circadian system response for any CL_A level, is operationally defined as being proportional to nocturnal melatonin suppression after 1 h exposure with a fixed, 2.3 mm diameter pupil. Also shown are modeled levels of response to different photopic illuminance levels (in lux) at the cornea for an incandescent source (2856 K) and a daylight source (D65). Adapted from Rea et al., 2005; 2012.

Figure 2.

Presented in the left panel is the modeled spectral sensitivity of the murine circadian system for narrowband and for polychromatic lights based upon light-induced changes in circadian phase for wheel running activity. Presented in the right panel is the functional relationship ($r^2 = 0.80$) between the spectrally weighted levels of circadian light for the mouse and the measured changes in circadian phase following 30 minute exposures to different amounts of narrowband light stimuli. Adapted from Bullough et al., 2005.

Figure 3.
The Daysimeter for measuring calibrated light-dark exposure patterns and activity-rest patterns.

Figure 4.

Presented in the left panel are vector-averaged phasors for nurses who participated in a one-week, field study using the Daysimeter and for mice housed in a controlled laboratory study where wheel-running activity was measured. Shown are average phasors for dayshift nurses (DS), rotating-shift nurses who worked one night per week (RS1) and rotating-shift nurses who worked three consecutive nights per week (RS3) together with average phasors for mice placed on a 12-h light:12-h dark “dayshift” schedule (DS), mice placed on a simulated one-night per week rotating-shift schedule (RS1) and mice placed on a simulated three consecutive nights per week rotating-shift schedule (RS3). In the right panel individual phasor magnitudes for nurses and for mice are plotted as a function of the number of night shifts per week. Adapted from Radetsky et al., 2013.