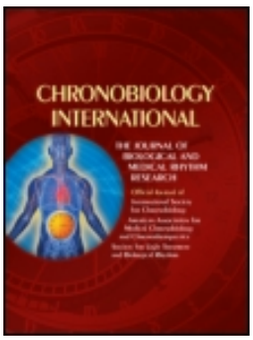

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Crosstalk Between Environmental Light and Internal Time in Humans

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Daily exposure to environmental light is the most important zeitgeber in humans, and all studied characteristics of light pattern (timing, intensity, rate of change, duration, and spectrum) influence the circadian system. However, and due to lack of current studies on environmental light exposure and its influence on the circadian system, the aim of this work is to determine the characteristics of a naturalistic regimen of light exposure and its relationship with the functioning of the human circadian system. Eighty-eight undergraduate students (18–23 yrs) were recruited in Murcia, Spain (latitude 38°01′N) to record wrist temperature (WT), light exposure, and sleep for 1 wk under free-living conditions. Light-exposure timing, rate of change, regularity, intensity, and contrast were calculated, and their effects on the sleep pattern and WT rhythm were then analyzed. In general, higher values for interdaily stability, relative amplitude, mean morning light, and light quality index (LQI) correlated with higher interdaily stability and relative amplitude, and phase advance in sleep plus greater stability in WT and phase advance of the WT circadian rhythm. On the other hand, a higher fragmentation of the light-exposure rhythm was associated with more fragmented sleep. Naturalistic studies using 24-h ambulatory light monitoring provide essential information about the main circadian system input, necessary for maintaining healthy circadian tuning. Correcting light-exposure patterns accordingly may help prevent or even reverse health problems associated with circadian disruption. (Author correspondence: angerol@um.es)

Keywords: Free-living conditions, Human circadian system, Light exposure, Light quality index, Sleep-wake cycle, Wrist temperature, 24-h ambulatory monitoring

INTRODUCTION

The mammalian circadian system is composed of a hierarchically organized network of structures responsible for generating circadian rhythms and synchronizing them to the environment. It includes a central pacemaker (suprachiasmatic nucleus of the hypothalamus, SCN), several peripheral clocks, and input and output pathways that are responsible for environmental entrainment and generating circadian rhythms in the organism, respectively (Buijs & Kalsbeek, 2001; Duguay & Cermakian, 2009; Strattmann & Schibler, 2006).

Under natural conditions, the SCN is reset every day by periodic light input from the retina through the retinohypothalamic tract (Güler et al., 2008; Moore et al., 2002), by means of cones, rods, and intrinsically photoreceptive melanopsin ganglion cells (Dijk & Archer, 2009; Güler et al., 2008). Although other periodic cues, such as scheduled exercise, social contacts, sleep habits, and feeding time, can also entrain the circadian system (Atkinson et al., 2007; Mendoza, 2007; Mistlberger & Skene, 2004), daily exposure to environmental light is the most important zeitgeber in humans (Brainard et al., 1997; Skene et al., 1999). Based on this, it may be that inappropriate light exposure is involved in the pathophysiology of circadian disorders, and, therefore, contributes to a misalignment of the endogenous circadian clock and the voluntary rest-activity cycle.

Light-pattern timing, intensity, rate of change, duration, and spectrum are the major characteristics relevant to circadian entrainment by light (Pauley, 2004). Under laboratory conditions, it is known that light pulses during the first part of the night or at the end of the night induce phase delay or phase advance of the circadian pacemaker, respectively (Khalsa et al., 2003). Moreover, insufficient light intensity during the day can cause phase instability or even free-running circadian rhythms (Gronfier et al., 2007; Middleton et al., 2002), a very important issue to consider in certain populations, such as the elderly (Turner & Mainster, 2008). The threshold luminance required to prevent free-running is normally higher in the elderly, due to crystalline lens transmittance decline and pupil area reduction (Turner & Mainster, 2008). In addition, young people with normal vision free-run with weak nonphotic zeitgebers

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and room light intensities <200 lux (Middleton et al., 2002). Similarly, astronauts show free-running rhythms with light exposures <80 lux (Gronfier et al., 2007). Regarding the duration of bright-light exposure, it is interesting to note that young adults from industrialized areas rarely receive more than 20–120 min of daily light exposure >1000 lux (Espiritu et al., 1994; Hebert et al., 1998; Savides et al., 1986), whereas in the elderly exposure time is only ~30–60% of this value (Campbell et al., 1988; Mishima et al., 2001). Some studies show that progressive appearance of light (similar to natural dawn) may be more effective than "square-wave" light onset (Kavanau, 1962; Tang et al., 1999). It seems the biological clock is not only sensitive to the level of light luminance, but also to its rate of change. Finally, the synchronizing power of light is dependent on its light spectrum, with light enriched in blue wavelengths (460–480 nm) being more effective than wavelengths outside this band (Rahman et al., 2008).

Several circadian rhythms under the control of the SCN are commonly used to evaluate the status of the circadian system. These rhythms, called circadian marker rhythms, serve to characterize the timing of the internal temporal order. A marker rhythm should be able to be easily measured over long periods using noninvasive methods. The most frequent human marker rhythms include salivary melatonin or cortisol, urinary 6-sulfatoxymelatonin, actimetry, and core body temperature (CBT) (Mormont et al., 2002; Van Someren, 2000). Recent evidence suggests sleepiness may be more closely linked to increased peripheral skin temperature than to a core temperature drop, and distal skin temperature seems to be correlated and phase-advanced with respect to CBT, suggesting heat loss from extremities may drive the circadian CBT rhythm (Krauchi et al., 2000; Ortiz-Tudela et al., 2010; Sarabia et al., 2008). The wrist temperature (WT), recorded on the radial artery on the nondominant hand, circadian rhythm exhibits an inverse phase relationship with CBT, and it has recently being proposed as a noninvasive, robust, and easy-to-register index of the circadian system (Ortiz-Tudela et al., 2010; Sarabia et al., 2008). WT rhythm integrates endogenous and exogenous influences, thus presenting considerable advantages for evaluating the effects of synchronizing agents, such as light exposure, on circadian function.

To date, most studies dealing with the effects of light exposure on the circadian system have been conducted under strict laboratory-controlled conditions, using light stimuli that are too far from the natural light characteristics; thus, naturalistic studies, using 24-h ambulatory light monitoring, may provide very important information about the characteristics of the light-dark cycle that are essential to the maintenance of a healthy circadian system. In fact, this is one of the first studies to simultaneously register the main input (light exposure) of the circadian system, along with two markers of circadian function, WT and sleep patterns, for a duration of 1 wk. Considering the importance of light as a zeitgeber and the lack of current studies on light exposure in healthy young subjects and its influence on circadian rhythms, the aim of this work is to determine, for the very first time, the characteristics of a naturalistic light-exposure regimen and its relationship with the human circadian system, as assessed by WT and sleep diary recordings.

MATERIALS AND METHODS

Subjects

For the present study, 88 undergraduate volunteers (36 males and 52 females, 18–23 yrs of age) residing in Murcia, Spain (latitude 38°01′N) were recruited. All recordings were made in November. The mean ± SEM environmental temperature was 12.3°C ± 0.4°C (mean maximum temperature 19°C ± 0.6°C, mean minimum temperature 7.4°C ± 0.4°C), with sunrise occurring between 07:31 and 07:54 h, and sunset between 17:46 and 18:03 h (data obtained from the University of Murcia's weather station: https://estacion.um.es/). Participants were instructed to complete a sleep diary designed by the Chronobiology Laboratory at the University of Murcia, and they were encouraged to maintain their normal lifestyle. The diary compiled information regarding sleep onset, sleep offset, and the time and duration of naps. The study abides by the bioethical principles set out by the Declaration of Helsinki. Data from the volunteers were included in a database and were protected according to Spanish Law 15/1999 of 13th December 1999. All participants received adequate information about the study characteristics and signed an informed consent form before their inclusion in the study (Portaluppi et al., 2010).

Environmental Light-Exposure Recording

All subjects were required to wear a HOBO Pendant Temperature/Light Data Logger UA-002-64 (Onset Computer, Bourne, Massachusetts, USA) on a lanyard close to their eyes to record light exposure. According to the manufacturer's specifications, the data logger has a measurement range between 0 and 320,000 lux, memory capacity for up to 28,000 values taken at regular, previously programmed intervals (in our case, every 30 s), and light-spectrum wavelength recording capacity of 150–1200 nm, which is broader than the sensitivity of the human eye. In order to validate the light sensor, a LX 101 lux meter (3E NDT; Pasadena, Texas, USA) was used to make a set of simultaneous recordings in different environments (data not shown). Readings from both devices demonstrated a strong, significant positive correlation at different intensities ($r = 0.997$, $p < .01$). A high degree of repeatability of sensor measurements was observed when recordings were simultaneously performed with two different HOBO sensors ($r = 0.998$, $p < .01$). Participants were instructed to wear the lux meter over clothing and to leave it on the bedside table during sleep. To compare the light exposure of our subjects to the natural sunlight cycle, environmental light intensity was

recorded for 1 wk in the same area and for the same experimental period. To do this, a HOBO sensor was placed outdoors, facing North in a shady location to avoid direct light irradiance.

Wrist Skin-Temperature Measurement

In addition to the HOBO sensor, all subjects wore a Thermochron iButton DS1921H (Maxim Integrated Products, Sunnyvale, California, USA) for WT measurement with a precision of ±0.125°C. This temperature sensor was placed on the wrist of the nondominant hand over the radial artery and isolated from the environmental temperature by means of a double-sided cotton sport wrist band, as previously described (Sarabia et al., 2008). The sensor was programmed to sample every 10 min throughout the entire week. Both the light and temperature sensors were worn simultaneously, as shown in Figure 1.

Data Analysis

To facilitate the determination of light exposure, the presence/absence of natural light (solar day and night, respectively), and the light-intensity analysis, the following ranges were established: very dim light (<10 lux), indoor dim light (10–500 lux), indoor bright light (500–1000 lux), and outdoor bright light (>1000 lux), as described in a previously conducted study (Turner & Mainster, 2008). Environmental light intensities in lux were converted into logarithmic units and averaged every 10 min to allow comparisons with temperature data.

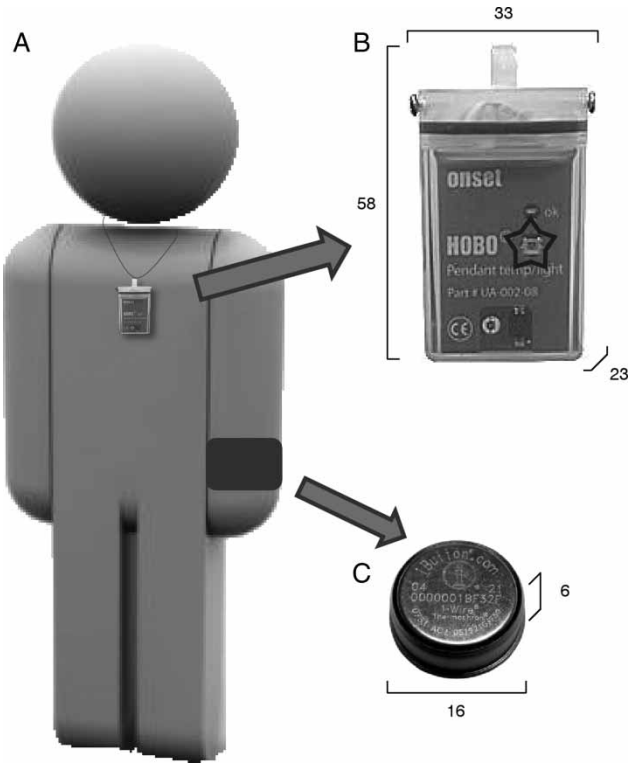

FIGURE 1. Body location of light and temperature sensors. The light-data logger is hung around the neck on a lanyard, and the temperature-data logger is placed on the wrist of the nondominant hand (A). B shows the HOBO-data logger, with a mark indicating the exact position of the light sensor. The iButton data logger is shown in C. Sensor measurements are expressed in millimeters.

WT data were filtered to eliminate artifacts, such as those produced by temporarily removing the temperature sensor. Sleep-wake information was converted into binary values by assigning a value of 1 when the subjects declared they were asleep and 0 when awake. Mean WT, sleep, and light-exposure patterns were calculated per individual and group. Sleep probability indicates the percentage of individuals asleep at any given time, as already described (Sarabia et al., 2008).

To characterize WT, light exposure, and declared sleep rhythms, a nonparametrical analysis was performed. This analysis determined the following parameters: interdaily stability (the constancy of the 24-h rhythmic pattern over days, IS); intradaily variability (rhythm fragmentation, IV); average in 10-min intervals for the 5 h with the maximum temperature (M5) and its timing (TM5); average in 10-min intervals for the 10 h with the minimum temperature (L10) and its respective timing (TL10), and the relative amplitude (RA), which was determined by the difference between M5 and L10 divided by the sum of M5 and L10 as previously done by Van Someren et al. (1999). For sleep, in addition to the time of sleep onset and offset, the duration and time of the sleep midpoint were also calculated. With respect to light exposure, we calculated the mean intensity (MI) over the entire 24-h period, as well as the mean light intensity during the morning (08:00 to 15:50 h), evening (16:00 to 23:50 h), and night (00:00 to 07:50 h).

In order to classify individuals according to their circadian system functionality, we used a new scoring index, the circadian function index (CFI), which was previously proposed by our laboratory (Ortiz-Tudela et al., 2010). This index was calculated by averaging three nonparametric indices (IS, IV, and RA) for temperature and sleep data. Before averaging, all these indices were normalized between 0 and 1, (IV was inverted, since its values are opposite to those for IS and RA). Accordingly, the CFI oscillates between 0 (gaussian noise) and 1 (a sinusoidal wave).

Similarly, we propose a new index for evaluating the quality of light exposure during the day, which we call the light quality index (LQI). This index considers the time spent in >500 lux, minus the time spent in <10 lux, divided by the time spent in >500 lux plus the time spent at <10 lux, and oscillates between +1 (all daytime exposed to >500 lux) and −1 (all daytime exposed to <10 lux).

Changes in WT associated with acute changes in light exposure were examined by correlating positive and negative changes in light intensity (in logarithmic interval units: 0–1, 1–2, 2–3, and 3–4) with the corresponding changes in WT for a given time point in 12 subjects chosen randomly (6 men and 6 women). In order to eliminate the influence of sleep and body position, the sleep

periods and 30 min before and after sleep were excluded from the analysis. All these spontaneous changes in light exposure were balanced among subjects, and a correlation analysis was then performed between the rate of change for light intensity and that for WT. To determine the long-term effects of light exposure on circadian rhythmicity, Pearson correlations were calculated between each of the light-dark cycle features (IS, IV, RA, MI, morning, evening, and night light exposure, and LQI) and sleep probability (IS, IV, RA, CFI, and sleep midpoint) and WT (IS, IV, RA, CFI, and TM5) parameters. In addition, a classification of individuals according to the light-pattern features that most affected their sleep and WT rhythms was performed. For this purpose, we first classified subjects into quartiles based on their individual light-dark pattern stability, morning light exposure, day/night contrast (or RA for light), and LQI. The corresponding 24-h mean waveform (for temperature, sleep, and light) per quartile was then calculated. The first quartile (Q1) represents the lowest values, whereas the fourth quartile (Q4) represents the highest values. Similarly, we also classified the subjects according to their WT pattern quartiles and analyzed their light-pattern characteristics.

All data are expressed as mean ± SEM. The data were processed using Microsoft Office Excel 2007, and all statistical analyses (repeated-measures analysis of variance [ANOVA] followed by post hoc pairwise comparisons using a Bonferroni test and Pearson correlations using Bonferroni correction) were performed with SPSS version 15.0 (SPSS, Chicago, Illinois, USA). Values of $p < .01$, or $p < .001$ for Pearson correlations, were considered to be statistically significant.

RESULTS

Light-Exposure Pattern

A weekly record and its corresponding mean waveform from a representative subject are shown in Figure 2. WT showed a characteristic rhythm with stable values above 34.5°C during sleep time, and low and highly variable values during the active period. The light intensity and timing of exposure during the day also displayed a very high variability, with values of up to 70,000 lux, but the resting period was mostly spent in darkness. In addition, a high degree of irregularity for sleep onset, offset, and duration can be observed.

Figure 3 represents the average 24-h mean patterns for light exposure, environmental light cycle, WT, and sleep probability, averaged over 7 days. WT exhibited a daily rhythm that matched the sleep probability rhythm. Maximum mean light exposure during the natural day was ~200 lux, which is much lower than the maximum potential light exposure in the shade (10,000 lux). On the contrary, light intensities were stronger than natural during the evening and night. Light exposure seemed to show a roughly inverse relationship to WT. WT increased in anticipation of sleep onset, maintained a high level during the sleep period, and then dropped immediately after awakening. A secondary peak was observed in the afternoon, whereas the 24-h minimum occurred between 20:00 and 22.00 h, a period known as the "wake maintenance zone," due to the low probability of finding adults asleep at that time. The light-exposure pattern showed values <10 lux between 00:00 and 08:00 h, >100 lux at midday, and in the range of 10–100 lux during both the morning (08:10 to 12:30 h) and evening (16:00 to 00:00 h), all of which are consistent with artificial light and/or lighting inside buildings.

Table 1 shows the main characteristics of the 24-h patterns in light exposure, WT, and sleep. Minimum light-exposure values were recorded at 04:35 ± 00:05 h, coinciding with TM5 and midpoint of sleep.

Short-Term Effects of Light Exposure

A common feature of natural light exposure is the very high variability in light intensity hitting the retina. Using the spontaneous changes in light exposure, it was possible to analyze the influence of acute light changes on WT. Figure 4 shows two examples that demonstrate this association. In the case depicted in panel A, when light intensity decreased, WT immediately increased. Similarly, panel B shows how a transient increase in light intensity was mirrored by a decrease in WT that was also transient. Using these spontaneous changes in light exposure, selected in a balanced manner among subjects and considering only the wakefulness period, a significant inverse relationship between rate of change in light exposure and rate of change in WT (Figure 4C), with a slope of –0.42°C per logarithmic unit of light intensity, was obtained.

Long-Term Effects of Light Exposure

Duration of Light Exposure

As shown in Table 2, individuals spent most of their time at low light intensities. In fact, on average over the 24-h period, they exposed themselves to intensities of <500 lux for 21 h 27 min ± 23 min, and to intensities >1000 lux for only 1 h 43 min ± 16 min. But what is more important, during the photophase of the natural day, the subjects only received 1 h 18 min of bright light, whereas they were exposed to >1000 lux for 26 min during the scotophase of the natural day. This short diurnal bright-light exposure period occurs in addition to relatively long exposures (2 h 46 min) to intensities <10 lux during the natural day.

Association Between Long-Term Light Exposure, WT, and Sleep

Significant correlations were found between light exposure and WT rhythmic parameters. The CFI for WT indicates that the light-pattern feature that is associated with better WT rhythmicity is IS ($r = 0.304$, $p < .05$). Light exposure IS and RA were positively correlated with wrist temperature IS ($r = 0.394$, $p < .01$ and $r =$

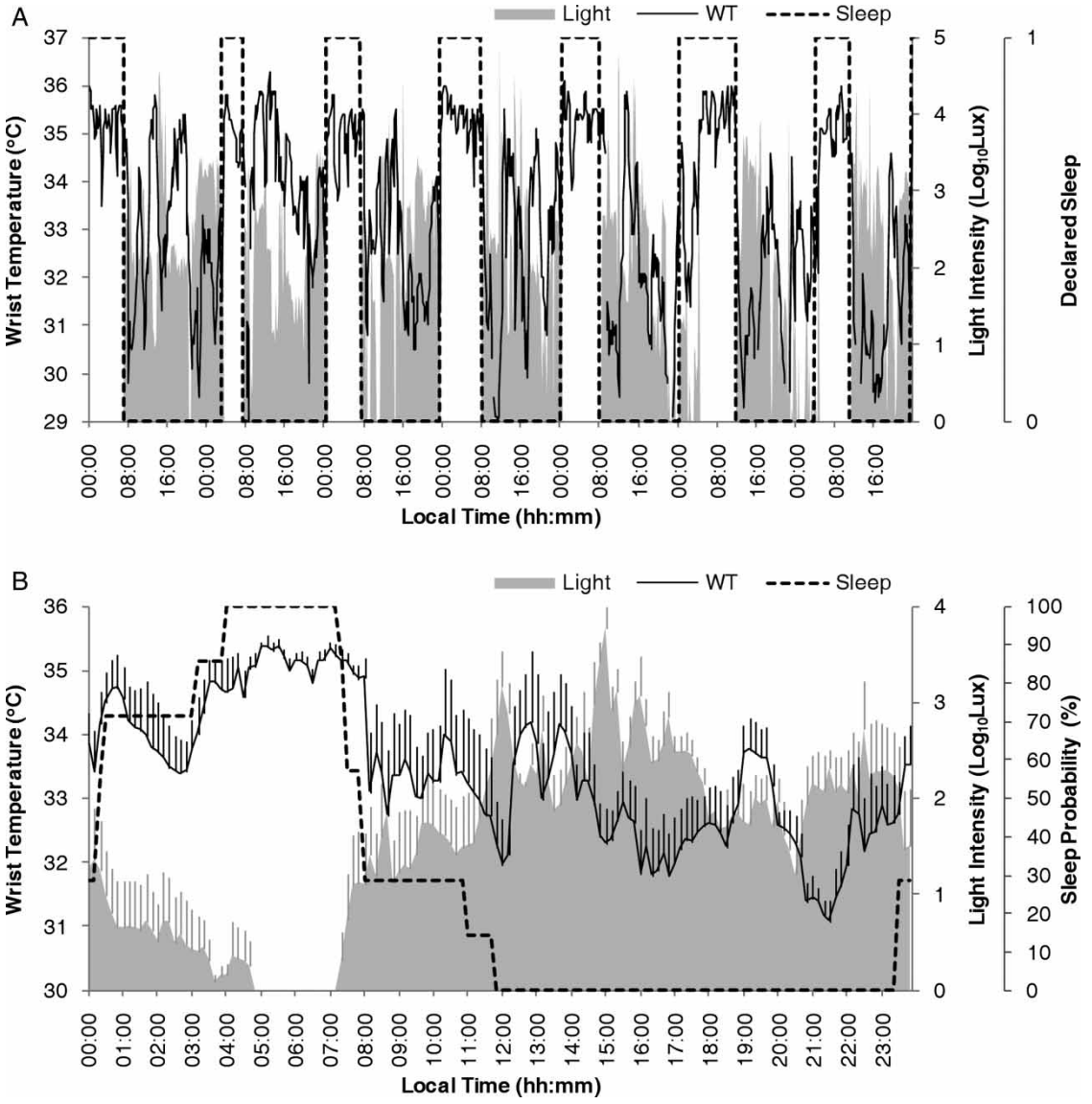

FIGURE 2. Individual wrist temperature, light intensity, and sleep pattern from a representative subject. One week of continuous recordings (A) and daily mean waveforms (B) for wrist temperature (black line), light intensity (grey area), and sleep probability (dotted line) from a representative subject. In the latter case, the values are expressed as mean ± SEM.

0.326, $p < .05$, respectively). In addition, higher light intensities during the morning were correlated with phase advance (measured as TM5) in WT ($r = -0.311$, $p < .05$)

Highly significant correlations were also observed between most of the light parameters and the sleep declared by subjects (Table 3). In contrast with the positive, significant correlation between light-exposure parameters (IS, RA, MI, morning, evening, and LQI) and the sleep IS and CFI, intradaily variability in the light pattern and light at night were associated with worse sleep characteristics. It has been proposed that the WT rhythm shows a clear relationship with a well-established marker rhythm: the sleep-wake cycle. In agreement with this, a statistically significant correlation was observed between WT and sleep IS, CFI, and phase markers (Table 4).

To further analyze the influence of light intensity on circadian system functionality, the four light-exposure parameters that showed the most significant association with sleep and WT were used as criteria for classifying individuals into quartiles, and then to calculate their corresponding WT and sleep average mean waveform. However, and to facilitate comparison, only the first and fourth quartiles (Q1 and Q4) for light-exposure patterns are shown. The first classification criterion was light IS (Figure 5A). The light patterns for subjects with the highest and lowest light IS values are shown in Figure 5B. Sleep and WT rhythms for those same subjects are shown in Figure 5C and D, respectively. The highest degree of light regularity (Q4) was associated with higher values for both IS (0.75 ± 0.02 vs. 0.60 ± 0.03, $p < .001$) and RA (1.00 ± 0.00 vs. 0.99 ± 0.01, $p < .05$) in the sleep pattern, along with a phase advance in sleep

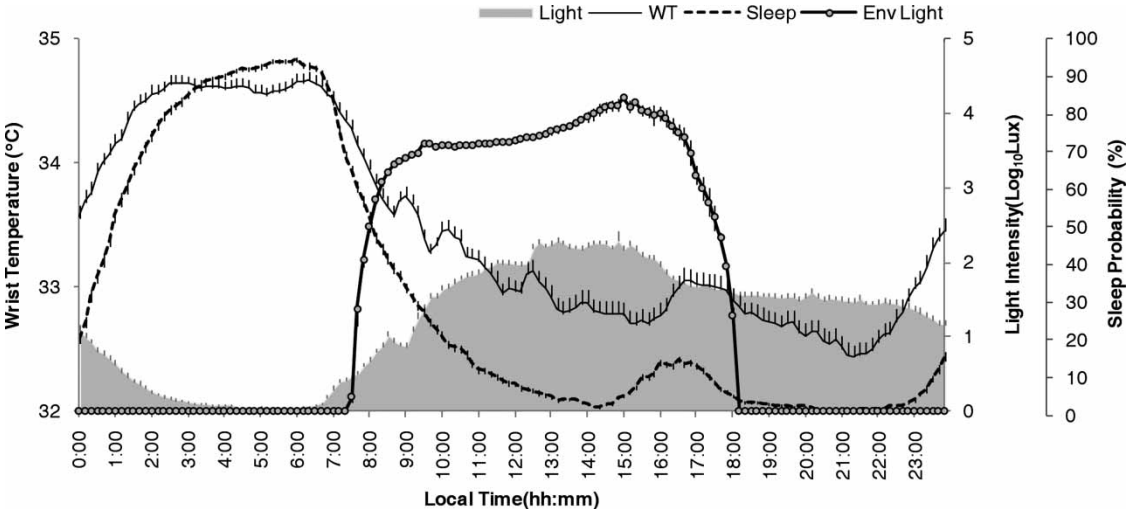

FIGURE 3. Average mean waveforms for wrist temperature, light intensity, and sleep pattern. Average daily evolution of light exposure (grey area), wirst temperature (black line), sleep pattern (dotted line), and environmental light (grey circles) for all experimental subjects (n = 88). The data shown have been obtained by averaging all individual mean waveforms. All variables are expressed as mean ± SEM.

TABLE 1. Mean values for light exposure, temperature, and sleep pattern characteristics

Light Exposure		Temperature		Sleep	
IS	0.53 ±0.10	IS	0.45 ±0.02	IS	0.69 ±0.01
IV	0.25 ±0.07	IV	0.18 ±0.01	IV	0.08 ±0.00
RA	0.94 ±0.07	RA	0.03 ±0.00	RA	0.99 ±0.00
Ml	1.22 ±0.22	CFI	0.58 ±0.01	CFI	0.88 ±0.00
Morning	1.84 ±0.31	TM5	04:21 ±00:09	Onset	01:16 ±00:30
Evening	1.56 ±0.40	TL10	17:21 ±00:14	Offset	08:40 ±00:37
Night	0.28 ±0.16	M5	34.76 ±0.06	Midpoint	04:58 ±00:29
LQI	-0.18 ±0.31	L10	32.61 ±0.09	Duration	07:31 ±00:37

Main characteristics for light exposure, wrist temperature, and sleep 24-h patterns: interdaily stability (IS), intradaily variability (IV), relative amplitude (RA), and circadian function index (CFI). In light-exposure pattern, MI indicates mean intensity throughout the 24-h period; Morning, Evening, and Night indicate the mean light exposure between 08:00 and 15:50 h, 16:00 and 23:50 h, and 00:00 and 07:50 h, respectively; LQI is the value for the light quality index. Wrist temperature rhythm uses the midpoint of the 5 h of maximum values (TM5) and the midpoint of the 10 h of minimum values (TL10) as phase markers, and its mean value (M5 and L10, respectively). Sleep-wake pattern Onset and Offset indicate night sleep start and end; Duration and Midpoint of the night sleep are indicated as duration and midpoint, respectively. All the values are expressed as mean ± SEM.

midpoint (04:35 ± 00:10 h vs. 05:41 ± 00:12 h, $p < .001$). In addition, the Q4 group presented higher values for IS (0.56 ± 0.03 vs. 0.41 ± 0.03, $p < .001$), RA (0.04 ± 0.00 vs. 0.03 ± 0.00, $p < .05$), CFI (0.67 ± 0.02 vs. 0.56 ± 0.02, $p < .01$), and reduction in IV (0.12 ± 0.01 vs. 0.18 ± 0.02, $p < .01$) for WT, as compared to Q1 subjects.

Studies involving both laboratory and free-living conditions have shown the timing of bright-light exposure to be a key factor for circadian synchronization. Figure 6 shows light exposure, sleep, and WT daily patterns for individuals classified according to the morning-light intensity they received between 08:00 and 16:00 h (Figure 6A). Light-exposure waveforms for both quartiles (Q1 and Q4) are shown in Figure 6B. Stronger morning-light exposure was associated with higher IS (0.76 ± 0.02 vs. 0.61 ± 0.03, $p < .001$), RA (1.00 ± 0.00 vs. 0.99 ± 0.00, $p < .01$), and CFI (0.91 ± 0.01 vs. 0.85 ± 0.01, $p < .001$) values of sleep patterns (Figure 6C), as well as phase advance measured in terms of sleep midpoint (04:21 ± 00:09 h vs. 05:53 ± 00:11 h, $p < .001$). Similarly, stronger morning light was associated with a WT phase advance measured at the midpoint of M5 (03:47 ± 00:12 h vs. 05:19 ± 00:22 h, $p < .001$) (Figure 6D).

Another important characteristic of the light-dark exposure that affects WT and sleep rhythms is RA, or the contrast between daytime and nighttime light. In Figure 7, subjects are classified into quartiles according to their RA light-exposure value (Figure 7A). The corresponding Q1 and Q4 light-exposure rhythms are shown in Figure 7B. The high day-night contrast of Q4 was associated with higher IS (0.78 ± 0.02 vs. 0.60 ± 0.03, $p < .001$), RA (1.00 ± 0.00 vs. 0.99 ± 0.01, $p < .05$), and CFI (0.91 ± 0.01 vs. 0.85 ± 0.01, $p < .001$), plus lower sleep IV (0.09 ± 0.00 vs. 0.08 ± 0.00, $p < .05$), and phase advance in sleep midpoint (04:37 ± 00:10 h vs. 05:33 ± 00:11 h, $p < .001$) (Figure 7C). In the case of WT

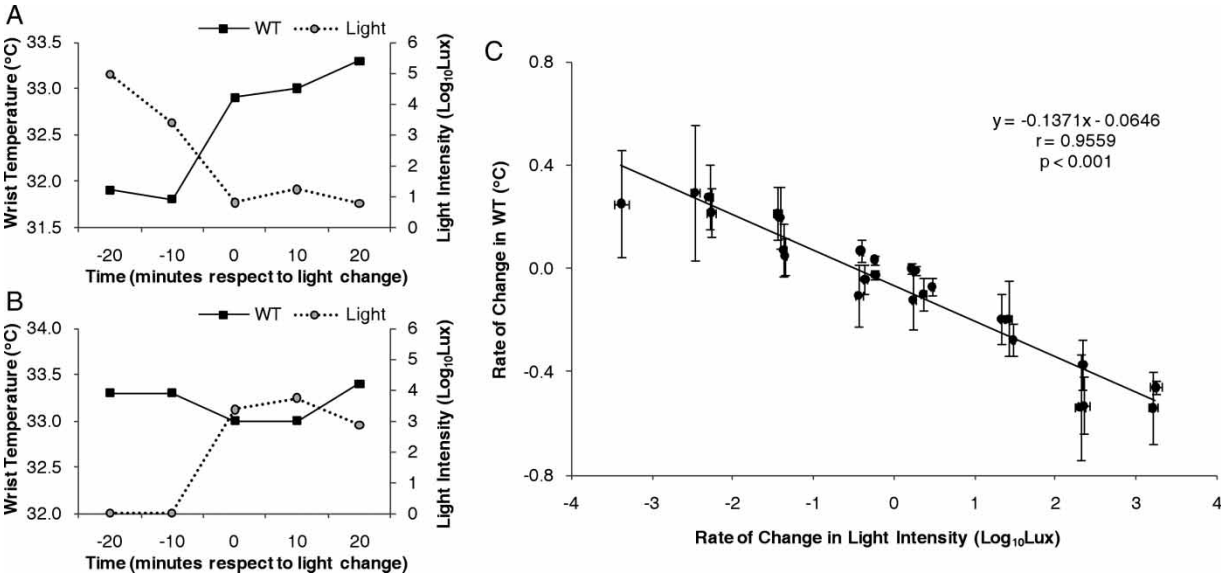

FIGURE 4. Acute effects of light on wrist temperature. Two examples of wrist temperature changes produced by negative (A) and positive (B) changes in light exposure. The rate of change for wrist temperature in response to changes in light exposure (in logarithmic units) is shown in C. This graph shows the average of all WT changes for any given light-intensity change and subject (in this case, only 6 men and 6 women were studied). The values are expressed as mean ± SEM.

TABLE 2. Duration and intensity of light exposure

	Day	Night	*p*
<10 lux	2:46 ± 0:07[a]	8:26 ± 0:08[a]	0.01
10–500 lux	5:10 ± 0:07[b]	4:55 ± 0:08[b]	n.s.
500–1000 lux	0:35 ± 0:02[c]	0:24 ± 0:02[c]	0.01
>1000 lux	1:18 ± 0:04[d]	0:26 ± 0:04[d]	0.01

Duration and intensity of light exposure during the photophase and scotophase for all the subjects (n = 88). Duration is expressed as mean ± SEM (h:min). Different letters in the same column indicate significant differences ($p < .05$). The last column indicates the *p* value when comparing day and night.

TABLE 3. Relationship between light exposure and sleep

		Sleep				
		IS	IV	RA	CFI	Midpoint
Light exposure	IS	0.484**	−0.164	0.297*	0.502**	−0.495**
	IV	−0.313*	0.227	−0.113	−0.319*	0.151
	RA	0.559*	−0.286*	0.292*	0.577**	−0.341*
	MI	0.343*	−0.069	0.085	0.330*	−0.425**
	Morning	0.437**	−0.108	0.204	0.439**	−0.651**
	Evening	0.304*	−0.136	0.106	0.303*	−0.287*
	Night	−0.206	0.265	−0.310*	−0.262	0.241
	LQI	0.420**	−0.201	0.229	0.435**	−0.571**

Correlation coefficients and level of significance (*$p < .01$, **$p < .001$) for the correlation analysis between light exposure and sleep variables: interdaily stability (IS), intradaily variability (IV), relative amplitude (RA), and circadian function index (CFI). Midpoint indicates middle of the night sleep. MI indicates mean intensity throughout the 24-h period; Morning, Evening, and Night indicate the mean light exposure between 08:00 and 15:50 h, 16:00 and 23:50 h, and 00:00 and 07:50 h, respectively. LQI expresses the values obtained for the light quality index.

(Figure 7D), greater day-night contrast was associated with higher values for IS (0.52 ± 0.02 vs. 0.35 ± 0.03, $p < .001$), RA (0.03 ± 0.00 vs. 0.02 ± 0.00, $p < .05$), and CFI (0.62 ± 0.03 vs. 0.52 ± 0.02, $p < .01$).

The final characteristic of light exposure that may be important for WT and sleep is the light quality index (LQI). High LQI represents daylight exposure during the environmental daytime, whereas low LQI is a sign

TABLE 4. Relationship between wrist temperature and sleep

		Temperature				
		IS	IV	RA	CFI	TM5
Sleep	IS	0.394**	-0.057	0.140	0.243	-0.368**
	IV	-0.127	0.301*	-0.189	-0.194	0.048
	RA	0.093	-0.141	0.093	0.107	-0.097
	CFI	0.380**	-0.098	0.157	0.252	-0.351*
	Midpoint	-0.427**	0.116	-0.144	-0.266	0.421**

Correlation coefficients and level of significance (*$p < .01$, **$p < .001$) between sleep and wrist temperature variables: interdaily stability (IS), intradaily variability (IV), relative amplitude (RA), circadian function index (CFI), and midpoint of the 5 h of maximum values (TM5). Midpoint indicates middle of night sleep.

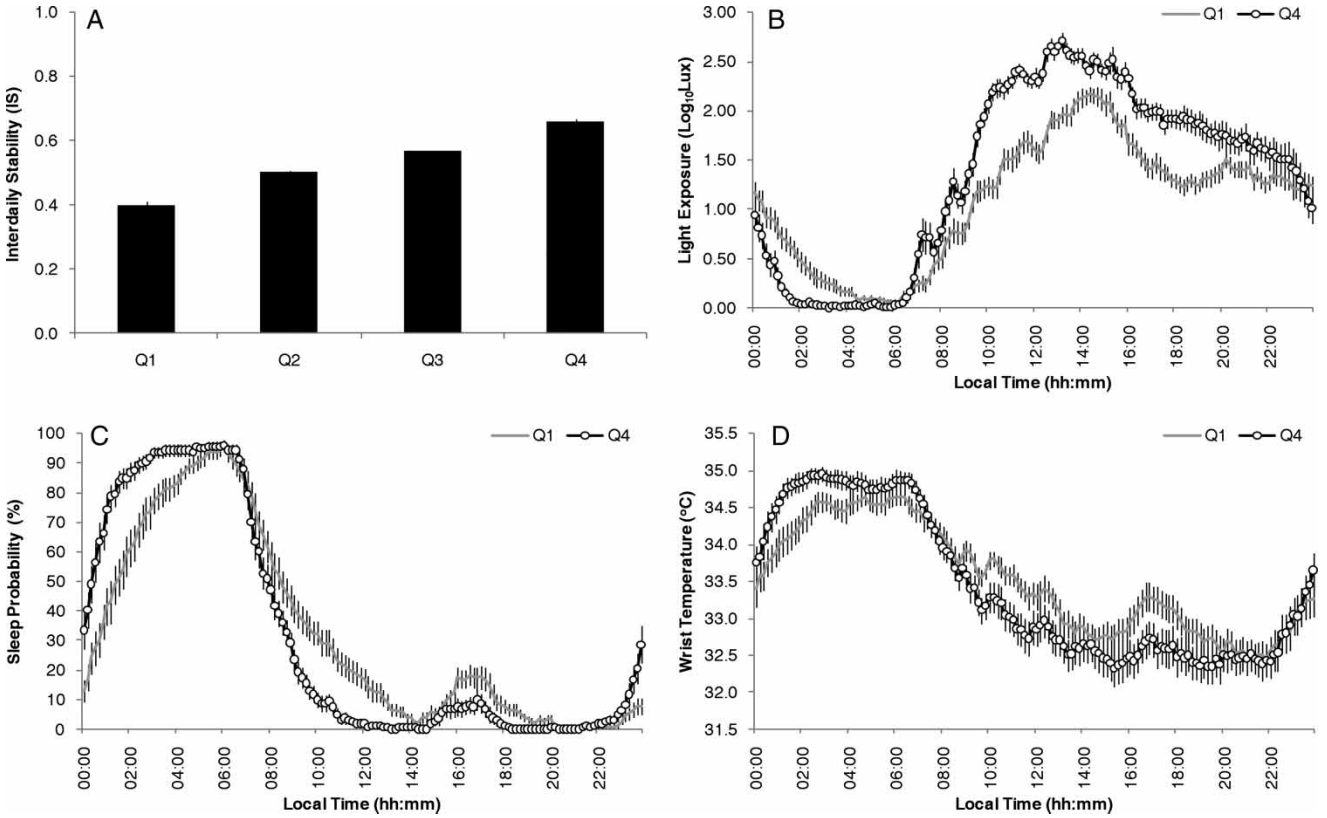

FIGURE 5. Quartile distribution according to the interdaily stability of light exposure. (A) Subjects distribution into quartiles using the interdaily stability of light exposure as the main classifying criterion (n = 88). Values are expressed as mean ± SEM. (B) Mean light-exposure patterns for quartile 1 (Q1, grey line) and 4 (Q4, black line with white circles) subjects. Their corresponding sleep and wrist temperature rhythms are shown in C and D, respectively.

of nighttime light exposure during the environmental daytime. LQI scores for the different quartiles are shown in Figure 8A, with the corresponding light exposure for quartiles 1 and 4 in Figure 8B. High LQI values were associated with higher values for sleep IS (0.75 ± 0.02 vs. 0.64 ± 0.03, $p < .01$), RA (1.00 ± 0.00 vs. 0.98 ± 0.01, $p < .01$), and CFI (0.90 ± 0.01 vs. 0.86 ± 0.01, $p < .01$) (Figure 8C), as well as phase advance measured in terms of sleep midpoint (04:23 ± 00:10 h vs. 05:40 ± 00:13 h, $p < .001$). Similarly, a high LQI is associated with a higher IS (0.49 ± 0.03 vs. 0.40 ± 0.03, $p < .05$) and phase advance, measured as M5 time (03:53 ± 00:12 h vs. 04:57 ± 00:22 h, $p < .05$), in the WT rhythm (Figure 8D).

When only considering the Q1 and Q4 quartiles of WT characteristics (IS, IV, RA, and CFI), no statistical differences were observed between them in their light-exposure pattern. However, when subjects were sorted by phase marker (TM5), higher mean light intensity during the morning (1.95 ± 0.07 vs. 1.72 ± 0.06, $p < .05$) was observed in those subjects presenting more phase advance.

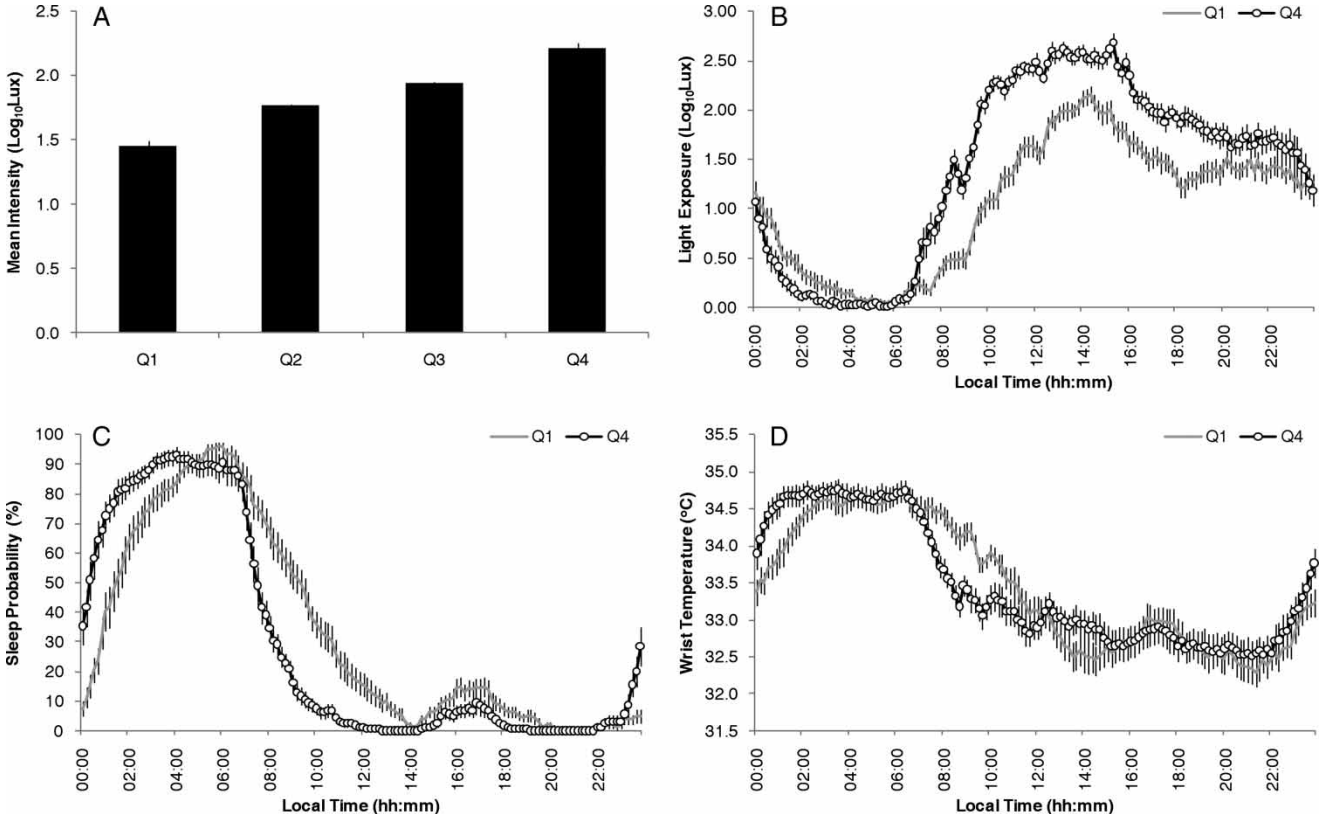

FIGURE 6. Quartile distribution according to the mean intensity of light exposure during the morning. (A) Subjects distribution into quartiles using the mean intensity of light exposure during the morning (08:00–16:00 h) as the main classifying criterion (n = 88). Values are expressed as mean ± SEM. (B) Mean light-exposure patterns for quartile 1 (Q1, grey line) and 4 (Q4, black line with white circles) subjects. Their corresponding sleep and wrist temperature rhythms are shown in C and D.

DISCUSSION

To our knowledge, the present study is the first attempt to simultaneously measure during an extended span of time (1 wk) an input (light exposure) and two circadian outputs (WT and sleep) in young, healthy subjects under normal-living conditions. We, therefore, propose the use of a temperature/light data logger to measure light exposure by means of a noninvasive, inexpensive, and nondisruptive method. Acute changes in light intensity exhibit an inverse relationship with WT, whereas regularity, light exposure timing, day-night light-exposure contrast, and the newly proposed LQI are the main parameters associated with significant changes in WT and sleep rhythms.

The classical conception of light as a mere input to the circadian system should be questioned in humans, considering the fact that contemporary humans spend most of their time indoors, with very low levels of natural light and with artificial light sources providing illumination both day and night. As a result, light exposure is voluntarily and also unconsciously manipulated to match rest-activity rhythms, as well as working and leisure activities. The rhythm of light exposure should, therefore, be considered simultaneously as an input, and, in some aspects, a result of the circadian system function, which in turn provides feedback to the suprachiasmatic nuclei (SCN). Unlike our ancestors, who lived in natural environments, the last five generations of people residing in developed countries have been able to self-select their light-dark cycle. The main differences between these two lifestyles with regard to light exposure are an overall decrease in light intensity and regularity; a modification in light timing, with delayed and reduced exposure during the day, and increased light at night; alterations in the rate of change over time of light exposure; and shift in the light spectrum towards artificial light sources. These changes in light input are, in part, the reason why it is hypothesized that a large proportion of people suffer from some degree of circadian rhythm disruption (or chronodisruption) in modern society (Erren et al., 2009; Francis et al., 2008; Mottram et al., 2010; Reiter et al., 2007). There is currently a growing body of scientific evidence that links chronodisruption to increased risk of developing certain diseases, and to worsening of preexisting medical conditions, such as cancer, metabolic syndrome, insomnia, affective disorders, cognitive impairment, and cardiovascular diseases, as well as premature aging (Erren et al., 2009; Garaulet & Madrid, 2010; Reiter et al., 2007; Turner et al., 2010).

Wrist skin temperature, recorded under ambulatory conditions with minimal discomfort by means of an iButton sensor, has previously been proposed by our

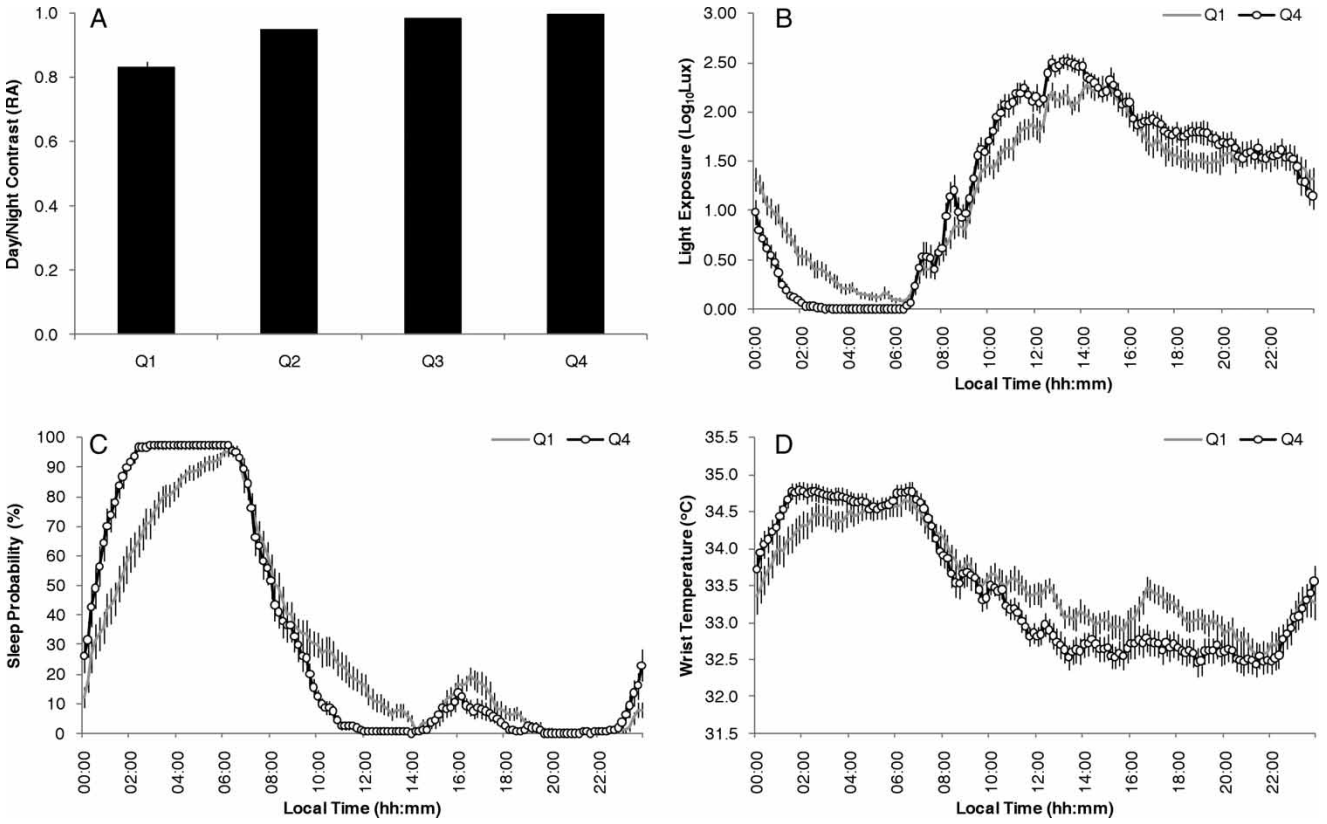

FIGURE 7. Quartile distribution according to the relative amplitude of light exposure. (A) Subjects distribution in quartiles using the relative amplitude of light exposure as the main classifying criterion (n = 88). Values are expressed as mean ± SEM. (B) Mean light-exposure patterns for quartile 1 (Q1, grey line) and 4 (Q4, black line with white circles) subjects. Their corresponding sleep and wrist temperature rhythms are shown in C and D.

group as an index of circadian system function (Ortiz-Tudela et al., 2010; Sarabia et al., 2008). To complement this information with the most important environmental zeitgeber, the light-dark cycle, we propose to use a small lux meter for the ambulatory monitoring of light exposure. The use of a lanyard to place the light sensor close to the eyes, as previously described by Smith and Eastman in 2009, provides more representative data for light irradiance received by the eyes than a wristband, as has been proposed previously (Cole et al., 1995; Emens et al., 2009; Francis et al., 2008; Goulet et al., 2007; Mottram et al., 2011; Okudaira et al., 1983).

When subjects are indoors, most light intensities are <500 lux, as occurs in those subjects working in an Antarctic station during winter (Francis et al., 2008; Mottram et al., 2010), and values between 50 and 200 lux were quite frequent in our recordings. These intensities are close to the circadian threshold (Duffy & Wright, 2005). In contrast, sunlight, even on very overcast days, is >2000 lux. Thus, we can consider 1000 lux as a reliable level to differentiate between artificial and natural light. It was surprising that our young subjects were only exposed to light brighter than 1000 lux for 1 h 18 min during the day, and 20 min during the natural night. These values are in the range of light exposure values for young adults in industrialized countries, most of whom typically receive only 20–120 min of daily light exposure >1000 lux (Espiritu et al., 1994; Hebert et al., 1998; Mishima et al., 2001; Savides et al., 1986).

The 24-h pattern of light exposure was similar to that previously described (Emens et al., 2009; Goulet et al., 2007; Hebert et al., 1998; Savides et al., 1986), with maximum light exposure occurring at midday, which coincides with a break at work, as has previously observed by other authors (Heil & Mathis, 2002; Okudaira et al., 1983). WT shows a circadian rhythm with higher values during sleep and lower values during waking hours, as has also already been described (Ortiz-Tudela et al., 2010; Sarabia et al., 2008). In fact, WT is known to oscillate in parallel to sleep probability (Sarabia et al., 2008). However, simultaneous recording of all three variables showed that light exposure displays a daily pattern with an approximately inverse relationship to that observed for WT and sleep probability.

A common characteristic of natural light exposure is the high variability of its intensity, which contrasts with the more constant values observed under laboratory conditions or artificial lighting. Acute changes in light exposure are associated with transient changes in WT in the opposite direction. Thus, positive changes in light intensity diminish WT, and consequently sleepiness, and vice versa. This inverse relationship could be explained by the alerting properties of light through sympathetic activation inducing blood-vessel constriction

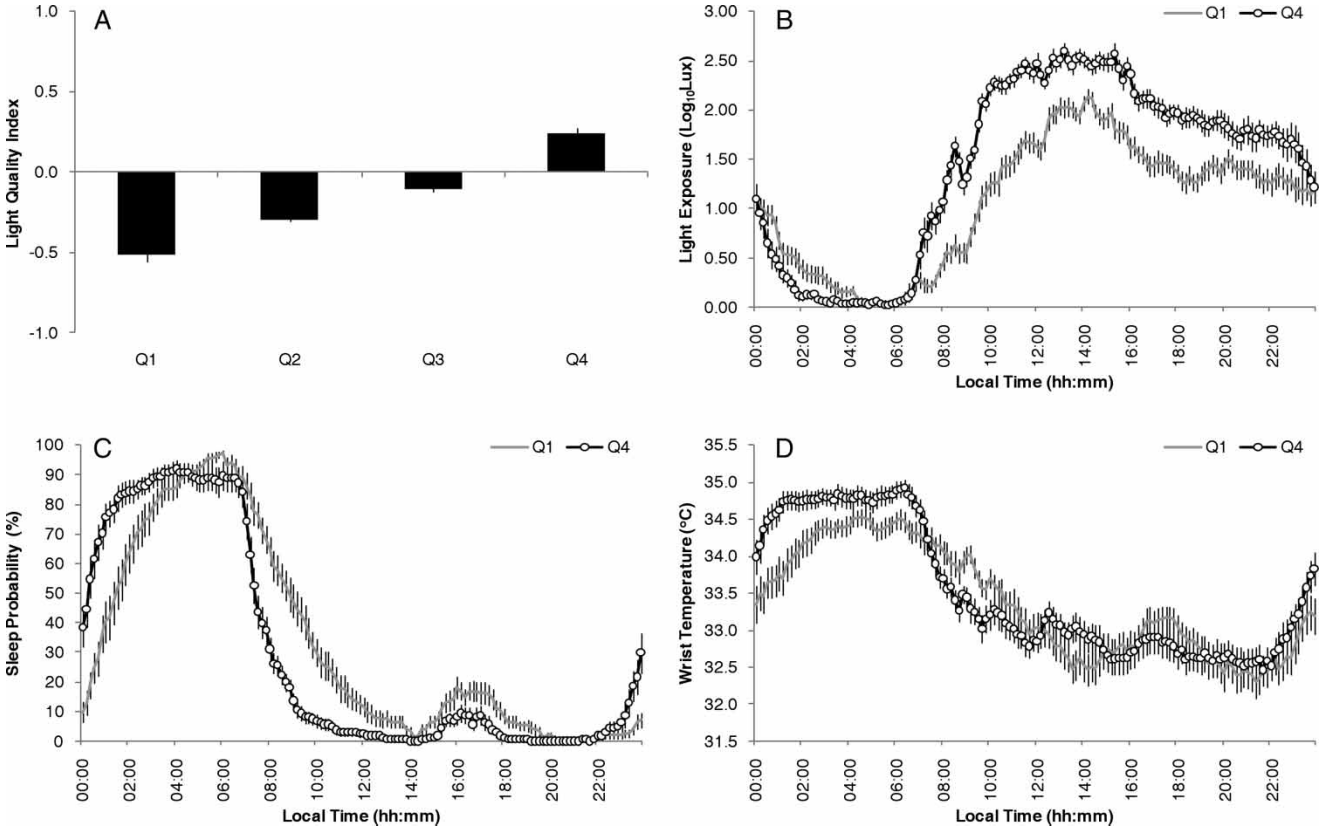

FIGURE 8. Quartile distribution according to the light quality index. (A) Subjects distribution into quartiles using the light quality index as the main classifying criterion (n = 88). Values are expressed as mean ± SEM. (B) Mean light-exposure patterns for quartile 1 (Q1, grey line) and 4 (Q4, black line with white circles) subjects. Their corresponding sleep and wrist temperature rhythms are shown in C and D.

and, in turn, reduction in skin temperature (Buijs et al., 2003). Other authors have demonstrated the short-term effect of bright-light exposure on reducing melatonin and sleepiness and on increasing alertness, heart rate, and core temperature (Cajochen et al., 2005; Ishibashi et al., 2010; Phipps-Nelson et al., 2009). Laboratory studies have suggested that short, intermittent periods of exposure to bright light, such as those characteristic of our modern lifestyle, may have a much greater impact on circadian entrainment than has previously been recognized (Hebert et al., 1998; Okudaira et al., 1983; Savides et al., 1986).

What can be considered as a healthy circadian pattern is very difficult to define, and is still a matter of discussion, although most authors agree with regard to which parameters can characterize a healthy circadian rhythm. They include circadian pattern regularity across different days (high interdaily stability), reduced fragmentation (or low intradaily variability), high amplitude, a period close to 24 h, and a circadian phase correctly aligned with environmental cues (Myers & Badia, 1995; Van Someren et al., 1999). Recently, in order to classify individuals according to their circadian system functionality, we proposed a scoring index (Ortiz-Tudela et al., 2010) that we call the circadian function index (CFI), which combines three nonparametric indices, stability, fragmentation, and amplitude, as previously proposed by Van Someren and coworkers (1999).

In the present work, we have found the best circadian rhythms for WT and sleep are associated with high regularity in the light-dark cycle, high RA, and high LQI, whereas high fragmentation and nocturnal light exposure are associated with the worst circadian sleep patterns. From these results, it seems that it may be possible to modify specific characteristics of the light-dark exposure in order to improve the organization of the circadian system. For example, improvement in the CFI for WT can be achieved by an increase in light regularity. But if the objective is to induce a phase change, morning light is associated with a phase advance.

It has been reported that environmental illumination is inversely correlated with insomnia (Hood et al., 2004; Mishima et al., 2001). According to our results, some cyclic parameters of light exposure are associated with the sleep-wake 24-h rhythm. Thus, the light-dark pattern stability, day-night contrast, morning light, evening light, and LQI are associated with better sleep-wake characteristics, whereas nocturnal light exposure and fragmentation are related to phase delay and worse sleep-wake pattern characteristics. These results confirm previous observations indicating that natural bright-light exposure improves sleep quality and mood (Dumont & Beaulieu, 2007; Wirz-Justice et al., 1996), as

previously demonstrated in light-controlled studies with blue-enriched white light (Glickman et al., 2006; Viola et al., 2008) and bright-light therapy (Even et al., 2008; Kirisoglu & Guilleminault, 2004). However, our results show that the circadian clock is influenced by the overall pattern of light-dark exposure, and not merely by isolated instances of bright light, as it was thought from laboratory studies. Our results also confirm the importance of prior light history when analyzing subsequent light synchronizing effects, as already suggested (Smith & Eastman, 2009).

Because modern humans spend most of their time indoors with only short, intermittent periods of exposure to natural sunlight, and since artificial light sources have a spectral distribution unlike that of natural light, it would be important to record the spectral composition of light to which the subjects are exposed using ambulatory devices in order to know how it affects the human circadian system, as seems to be the case (Duffy & Wright, 2005).

In summary, we have demonstrated acute changes in light intensity are associated with opposite, transient changes in WT. High values of light intensity plus morning, evening, and day-night contrast were associated with higher scores for rhythmic parameters related to good circadian WT and sleep rhythms, whereas nocturnal light exposure and fragmentation were associated with lower scores. However, the highest CFI scores for WT or sleep-wake rhythms were not necessarily associated with differences in light-dark exposure (data not shown). Accordingly, from our results we can conclude the combined use of a portable lux meter along with skin WT and sleep recordings enables noninvasive ambulatory monitoring of circadian system status and light-dark exposure in subjects under normal living conditions and with minimal discomfort. Naturalistic studies using 24-h ambulatory light monitoring can provide very relevant information on the characteristics of the light-dark cycle, the most important zeitgeber in humans, which is essential for maintaining healthy circadian functions. The corresponding modification of light-exposure patterns may help prevent and/or reverse some health problems generated by circadian disruption.

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