

Entrainment of the Human Circadian Clock to the Natural Light-Dark Cycle

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Summary

The electric light is one of the most important human inventions. Sleep and other daily rhythms in physiology and behavior, however, evolved in the natural light-dark cycle [1], and electrical lighting is thought to have disrupted these rhythms. Yet how much the age of electrical lighting has altered the human circadian clock is unknown. Here we show that electrical lighting and the constructed environment is associated with reduced exposure to sunlight during the day, increased light exposure after sunset, and a delayed timing of the circadian clock as compared to a summer natural 14 hr 40 min:9 hr 20 min light-dark cycle camping. Furthermore, we find that after exposure to only natural light, the internal circadian clock synchronizes to solar time such that the beginning of the internal biological night occurs at sunset and the end of the internal biological night occurs before wake time just after sunrise. In addition, we find that later chronotypes show larger circadian advances when exposed to only natural light, making the timing of their internal clocks in relation to the light-dark cycle more similar to earlier chronotypes. These findings have important implications for understanding how modern light exposure patterns contribute to late sleep schedules and may disrupt sleep and circadian clocks.

Results and Discussion

The biological effects of light profoundly influence human physiology and behavior, most notably permitting vision. Light also affects many non-image-forming biological systems in humans and has been shown to increase physiological arousal and enhance cognition, disturb sleep, and permit the synthesis of vitamin D [2–4]. Light is also used medically to treat conditions such as jaundice, skin disorders, and winter depression [2, 5]. A key non-image-forming response to light is entrainment of internal circadian clocks [2, 6–10], which permits organisms to synchronize to environmental time, allowing physiological functions to occur at optimal times of day [1]. Natural selection favored the human circadian clock system to promote energy intake and metabolism, physical activity, and cognition during the light portion of the day and to promote sleep and related functions during darkness at night. Yet, the external lighting environment was dramatically altered in the 1930s when electrical power grids in North America and Europe provided electricity to power electrical

lighting for the masses, permitting humans to spend more time being active in indoor constructed environments. This ability to control our daily exposure to light with the flip of a switch has contributed to an increase in indoor activities and has expanded work and play hours far into the night. In the current study, we quantified how much electrical lighting and the associated reduction in exposure to sunlight in the constructed environment has altered the timing of the human circadian clock by comparing the effects of exposure to electrical plus natural light (referred to henceforth as electrical lighting-constructed environment) to that of exposure to only natural light.

Eight participants (two females) aged 30.3 ± 8.5 years (mean $\pm$ SD) completed a 2-week-long protocol during July in the Rocky Mountains of Colorado, United States, at a latitude of $\sim 40^\circ\text{N}$ and a longitude between 105°W and 106°W . We first examined the internal circadian timing of participants after 1 week of maintaining daily routines of work, school, social activities, self-selected sleep schedules, and exposure to the electrical-lighting constructed environment. This was compared to the effects of exposure to 1 week of outdoor camping in tents and exposure to only natural light (i.e., sunlight and camp fires; no flashlights, no personal electronic devices, etc.) and self-selected sleep schedules (Figure 1).

Participants were exposed to an average of 979 ± 352 lux ($\pm$ SD) during waking hours of the week of electrical-lighting constructed environment (Figure 2). This illuminance level is greater than typically reported [11, 12] (Supplemental Information available online) and likely reflects the outdoor lifestyle of participants and sunny climate of the mountain-desert region of Colorado. Nonetheless, participants' average light exposure increased by more than 4-fold (4487 ± 552 lux; $p < 0.0001$, two tailed) during the week of natural lighting. We also examined light exposure in the first 2 hr after awakening, when the human circadian clock is most sensitive to the phase advancing effects of light [13, 14] or to the compression of internal cycle length [15]. We found that during the first 2 hr awake, participants were exposed to a significantly higher average light level during natural (3074 ± 1035 lux) versus electrical-lighting constructed environment (934 ± 867 lux; $p < 0.001$, two tailed). In addition, the percentage and hours of the waking day spent above light thresholds of 50, 100, 550, and 1000 lux were all greater during natural lighting (Table 1). The only time of day when participants were exposed to more light during electrical versus natural lighting was between sunset and sleep start time (average 21 ± 6 versus 8 ± 2 lux, respectively; $p = 0.001$, two tailed), when the human circadian clock is most sensitive to light-induced phase delays [13, 14].

After the week of exposure to the electrical-lighting constructed environment, characteristic circadian and sleep patterns for adults were observed. Specifically, average melatonin onset occurred ~ 2 hr prior to sleep start time (Figures 3 and S1A), sleep start time was around 12:30 a.m., melatonin midpoint occurred in the second half of the solar night, and melatonin offset occurred after wake time around 8:00 a.m. [19–21]. After the week of exposure to natural lighting, all measured markers of internal circadian time were ~ 2 hr

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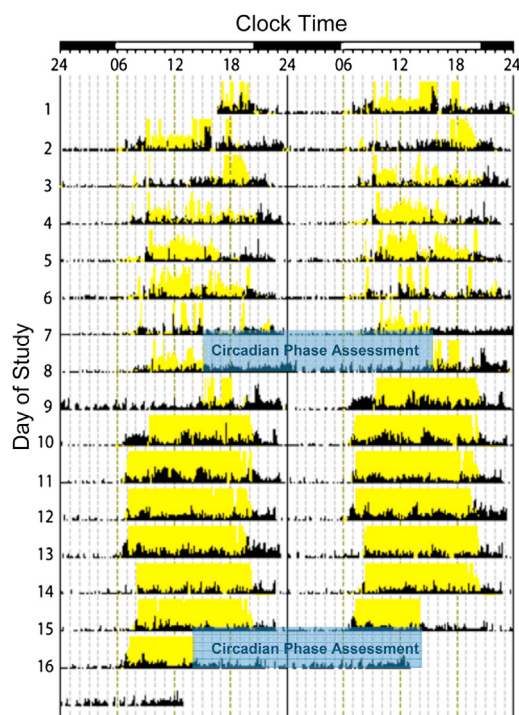


Figure 1. Experimental Protocol from One Participant

Data represent recordings from the Actiwatch-L recorder, with activity denoted by black ticks and light exposure above $\sim 1,000$ lux threshold denoted in yellow. Data are double plotted, with successive days plotted both next to and beneath each other; clock hour is indicated on the abscissa. Light-dark cycle (open and closed bars) on the top abscissa denotes approximate sunrise and sunset times. Sleep episodes are characterized by low activity levels. Exposure to electrical and natural lighting and sleep timing while the participant continued to live in their work-home-social constructed environment are shown on days 1–7. The initial assessment of internal circadian phase occurred on days 8–9 in the laboratory (denoted by blue shading). After one night of sleep at home, exposure to the natural light-dark cycle while camping and associated sleep times occurred on days 10–16. On the last day of camping (day 16), subjects were driven directly to the laboratory for follow-up assessment of internal circadian phase on days 16–17. Conditions were sequential so that sunrise and sunset times would be as similar as possible between conditions.

earlier (Figure 3, all $p < 0.01$; Bonferroni correction required $p < 0.0167$, one tailed), and, remarkably, melatonin onset occurred on average near sunset, the melatonin midpoint occurred in the middle of the solar night, and melatonin offset occurred before wake time just after sunrise. Sleep timing was related to circadian timing after electrical lighting-constructed conditions and less so after exposure to only natural light (Table S1 and Figure S2). The advance in timing of melatonin onset was significantly larger than changes in sleep start and wake times, which changed by ~ 1.2 hr (Figure 3, both $p < 0.02$; Bonferroni correction required $p < 0.025$, two tailed). Weekly sleep duration (6.7 ± 0.9 hr electrical versus 6.8 ± 0.7 hr natural lighting; $p = 0.268$, two tailed) and sleep efficiency ($87.6\% \pm 5.6\%$ electrical versus $87.0\% \pm 4.6\%$ natural lighting; $p = 0.49$, two tailed) did not significantly change, indicating that a change in sleep amount or efficiency did not contribute to the current findings. We did find, however, that the circadian advance in melatonin onset was significantly correlated with the change in sleep timing (Pearson correlation: DLMO_{25%} versus sleep start time $r = 0.85$, $p < 0.005$; DLMO_{25%} versus wake time $r = 0.87$, $p < 0.005$; DLMO_{25%}

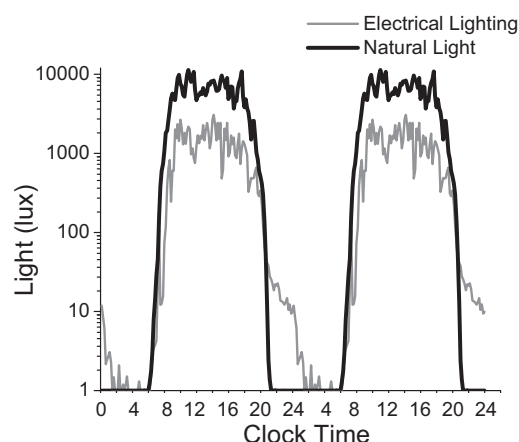


Figure 2. Light Exposure

Average light exposure (lux) plotted on a log scale during the week of exposure to electrical lighting in the constructed environment and exposure to the natural light-dark cycle while camping. Data are double plotted so that light levels across midnight (24 hr local clock time) can be more easily observed. For reference, 1 lux is equivalent to the light exposure received by the eye when gazing at a candle 1 m away, moonlight is ~ 0.1 lux, typical indoor lighting is ~ 200 lux, sunrise or sunset is $\sim 10,000$ lux, and a bright blue midday sky is $>100,000$ lux. See also Figure S3 and Table S1.

versus sleep start time $r = 0.48$, $p = 0.11$; nonsignificant trend for DLMO_{25%} versus wake time $r = 0.77$, $p < 0.0133$; Bonferroni correction required $p < 0.0125$; two tailed).

Our findings demonstrate a fundamental physiological principle of human circadian timing—internal biological time under natural light-dark conditions tightly synchronizes to environmental time, and in this regard, humans are comparable to other animals [22–24]. Our findings also speak to a paradox in our understanding of the neurobiology of brain arousal. Specifically, the circadian low point in brain arousal, as defined by cognitive performance level or physiological markers of sleepiness, occurs approximately 2 hr after habitual wake time [25, 26], near to the timing of the melatonin offset. This paradox, that we are most sleepy from a circadian perspective after habitual wake time, may be a consequence of the change in the circadian timing of wake time in the electrical-lighting constructed environment (Figure 3). After exposure to natural light, we found the timing of the circadian clock to be ~ 2 hr earlier and melatonin offset to occur more than 50 min prior to wake time, suggesting that if human circadian and sleep timing was in synchrony with the natural light-dark cycle, the circadian low point in brain arousal would move to before the end of the sleep episode, making it easier to awaken in the morning. Related, the earlier timing of the melatonin onset after exposure to natural light would promote earlier bedtimes, whereas the later evening timing of melatonin onset and light exposure in the electrical light-constructed environment would promote brain arousal and could contribute to later bedtimes and disturbed sleep.

We also observed that exposure to natural light reduced individual differences in the timing of the melatonin rhythm and sleep (Figure 3) and reduced individual differences in the timing between melatonin onset and sunset (Figures 3, 4A, and 4B), resulting in larger circadian advances for those with later chronotypes (Figure 4C). Thus, the clocks of more evening types appear to become even later than those of

Table 1. Light Exposure

Light Exposure above Circadian- Derived Thresholds	Exposure to Electrical Plus Natural Light in the Work-Home-Social Constructed Environment ($\pm$ SD)	Exposure to Only Natural Light while Camping ($\pm$ SD)	p Value, Two Tailed
Percent of Waking Day Spent Above			
1,000 lux	23 $\pm$ 6	71 $\pm$ 2	<0.0000001
550 lux	31 $\pm$ 10	76 $\pm$ 2	<0.00001
100 lux	62 $\pm$ 14	82 $\pm$ 1	0.005
50 lux	70 $\pm$ 13	84 $\pm$ 1	0.023
Hours of Waking Day Spent Above			
1,000 lux	3.8 $\pm$ 1.0	11.4 $\pm$ 0.2	<0.0000001
550 lux	5.1 $\pm$ 1.5	12.2 $\pm$ 0.3	<0.00001
100 lux	10.1 $\pm$ 2.2	13.2 $\pm$ 0.2	0.005
50 lux	11.4 $\pm$ 2.0	13.4 $\pm$ 0.3	0.023

Average exposure of participants to light intensities during waking hours for light levels with characterized circadian properties in accordance with intensity and phase response curves to light [13, 14, 16] are provided. Exposure to above 1,000 lux is commonly used to represent exposure to outdoor light (Supplemental Information). Findings from laboratory phase-shifting studies that exclude natural light show that exposure to 550 lux induces a saturating phase delay shift when comparing a range of light intensities from 3 to ~9,100 lux [16]; exposure to 100 lux induces half of the maximal circadian phase delay achieved by exposure to ~9,100 lux, whereas exposure to 50 lux or less produces smaller phase delay shifts [16]. The table shows that exposure to electrical lighting and constructed indoor work-home-social environments is associated with reduced exposure to sunlight as compared to only natural light while camping.

earlier chronotypes when exposed to less sunlight and electrical lighting in the constructed environment, which may exacerbate sleep and circadian problems such as delayed sleep phase [30] and social jetlag [29]. Social behaviors, removal of electrical lighting, and increased physical activity (Figure S3) during camping may also have contributed to the earlier sleep timing.

Multiple photoreceptors in the retina send environmental lighting information via intrinsically photosensitive retinal ganglion cells directly to the master circadian clock located in the suprachiasmatic nucleus (SCN) of the mammalian brain [31–34]. This light information is processed by the SCN, resulting in photic entrainment to the light-dark cycle. In the current study, we did not determine how many days of exposure to the natural light-dark cycle are needed to entrain the circadian clock to solar time, but such knowledge could aid in developing multicomponent treatments for circadian sleep disorders. For example, exposure to the natural light-dark cycle may help to obtain a desired earlier timing of the circadian clock and sleep for patients with delayed sleep phase. In addition, increased exposure to sunlight combined with a fixed earlier sleep schedule [35] may help adolescents and young adults who need to awaken early for school and work to maintain earlier sleep and wake timings [36, 37]. We have previously shown that exposure to only electrical lighting in the laboratory [9] or to sunlight and electrical lighting in the laboratory under conditions of insufficient sleep [38] delays the circadian clock even later than electrical lighting in the home, work, school, and social constructed environment. That suggests electrical lighting can result in even later sleep timing than observed here.

As our study was conducted in a small number of adult participants under midsummer sunlight conditions in Colorado, United States, additional research is necessary to address

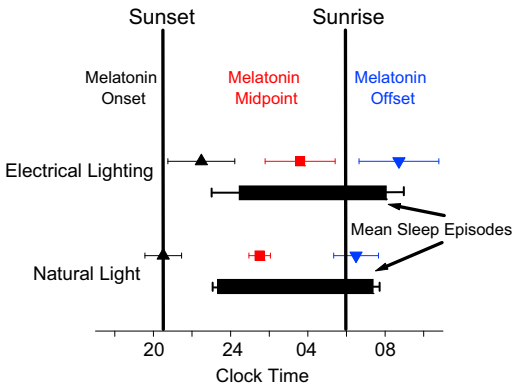


Figure 3. Circadian and Sleep Timing

Timing of the average melatonin onset (black upward triangles), melatonin midpoint (red squares), and melatonin offset (blue downward triangles) after a week of exposure to electrical lighting in the constructed environment versus exposure to the natural light-dark cycle while camping. Average sunrise and sunset times are provided for the ~2-week study. Average sunrise time occurred 11 min later and sunset 4 min earlier during the week of camping as compared to the week of electrical lighting. Sleep start and wake times are presented as average times during each week. Error bars represent $\pm$ SD. We did not observe a change in the duration of the melatonin rhythm defined by the time between melatonin onset and offset ($p = 0.66$, two tailed). Exposure to longer dark episodes, as occur naturally at latitudes away from the equator during winter, is likely necessary to expand the duration of the melatonin rhythm [17, 18]. Larger differences in circadian timing during exposures to the electrical-lighting constructed environment versus natural light than that observed in our midsummer study may also be expected during winter. See also Figures S1–S3 and Table S1.

study limitations by testing a larger number of subjects of different ages and cultures and by examining effects of different latitudes and seasons to more fully explore the influence of natural light on human circadian physiology. More research designed to explore the contribution, effects and potential benefits of increased exposure to natural or simulated daytime sunlight and reduced exposure to electrical light in the constructed environment on human circadian physiology is also warranted.

In summary, our findings clearly demonstrate that reduced exposure to sunlight and the widespread use of electrical lighting in the constructed environment has altered human circadian physiology leading to a major change in the timing of our sleep and wakefulness. Natural sunlight is a stronger environmental zeitgeber or time cue for the internal circadian clock than is electrical lighting in the constructed environment. Our findings show that individual differences in the timing of internal circadian clocks are more likely to be expressed under the weaker environmental time cue of constructed environments, reduced exposure to sunlight, and exposure to electrical lighting. Exposure to only sunlight while living outdoors reduced individual differences in circadian timing as predicted by entrainment theory for circadian clocks in the presence of strong zeitgebers [39]. Increased exposure to sunlight may help to reduce the physiological, cognitive and health consequences of circadian disruption.

Experimental Procedures

Chronotype was determined once using the Morningness-Eveningness Questionnaire (MEQ) [27] and the Munich Chronotype Questionnaire (MCTQ) [28, 29] for each participant's habitual diurnal preference/behavior. According to the MEQ, one subject was definitely an evening type, one a

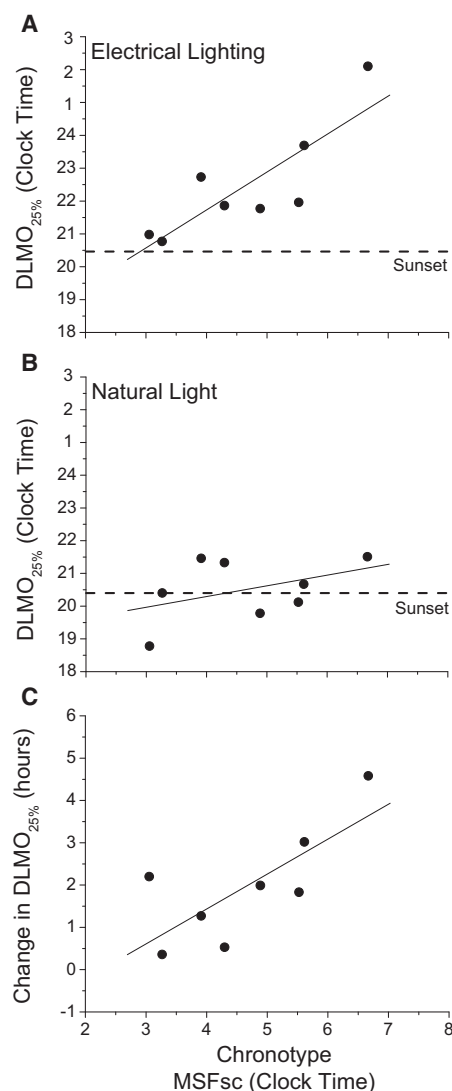


Figure 4. Association between Chronotype and Circadian Timing and the Change in Circadian Timing

Chronotypes derived from the Morningness-Eveningness Questionnaire (MEQ) [27] and the Munich Chronotype Questionnaire (MCTQ) [28, 29] were significantly correlated ($r = -0.96$, $p < 0.001$, two tailed). Associations between chronotype scores and circadian phase were similar regardless of the chronotype measure used; therefore, we present data from the MCTQ using the timing of midsleep on free days corrected (MSFsc) [28]. After exposure to electrical lighting, we found a strong association between chronotype and the timing of the DLMO_{25%} (A; $r = 0.83$, $p = 0.01$, two tailed). After exposure to natural light, however, no significant association between chronotype and circadian timing was observed (B; $r = 0.42$, $p = 0.28$, two tailed), likely due to a reduction in variance of the clock hour of the DLMO_{25%} in the stronger zeitgeber of the natural light-dark cycle. Chronotype was significantly correlated with the change in DLMO_{25%} (C; $r = 0.75$, $p = 0.031$, two tailed), such that participants with later chronotypes, denoted by later clock times of the MSFsc, showed larger advances in the timing of their DLMO_{25%}. On average, for every hour of MSFsc chronotype under electrical-lighting conditions, DLMO_{25%} moved 0.83 hr earlier after exposure to natural light. Symbols represent individual subjects and positive values indicate advances in the DLMO_{25%} in hours. The solid line represents a linear fit of the data and the dashed line represents sunset.

moderate evening type, four were intermediate types, and two were moderate morning types. Wrist activity monitors, with photodiodes that measure lux, were used to determine average weekly activity levels, sleep start

time, wake time, sleep duration, sleep efficiency—percent time spent asleep during the sleep episode using the medium sensitivity threshold—and light exposure levels for each participant (Actiwatch-L, Minimitter Respironics; Supplemental Experimental Procedures and Figure S3). Sunrise and sunset times were obtained from the United States National Oceanic and Atmospheric Association. After each lighting condition, we assessed internal circadian time of participants in the laboratory under dim lighting, ~ 1.9 lux (~ 0.6 watts/m²) in the angle of gaze, and seated or supine posture conditions to control for factors that influence markers of the circadian clock. Napping was permitted overnight between saliva samples to reduce influences of sleep deprivation on subsequent behavior the next day. Circadian timing was determined by the timing of the dim light salivary onset, midpoint and offset of the circadian melatonin rhythm (LDN Melatonin Direct RIA; Rocky Mountain Diagnostics) as these measures are the most commonly used and precise markers of the circadian clock in humans [40]. Moreover, melatonin onset and offset represent the beginning and end of the internal biological night, respectively [17, 18, 41]. So that individual differences in melatonin amplitude could be controlled for, melatonin onset (DLMO_{25%}) and melatonin offset (DLMO_{off25%}) were defined as the linear interpolated point in time at which melatonin levels reached 25% of the fitted peak-to-trough amplitude of each individual's data as determined by a three-harmonics least-squares regression analysis [9, 10]. The melatonin midpoint (MP_{25%}) was calculated as the midpoint between onset and offset. Unless noted, data were analyzed with mixed-effects ANOVAs using condition as a fixed factor and participant as a random factor. One-tailed tests were used for directional hypotheses, and Bonferroni corrections were used for multiple comparisons. Data are presented as mean $\pm$ SD.

Supplemental Information

Supplemental Information includes Supplemental Experimental Procedures, four figures, and one table and can be found with this article online at <http://dx.doi.org/10.1016/j.cub.2013.06.039>.

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