

ORIGINAL ARTICLE

The evening light environment in hospitals can be designed to produce less disruptive effects on the circadian system and improve sleep

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Abstract

Study Objectives: Blue-depleted lighting reduces the disruptive effects of evening artificial light on the circadian system in laboratory experiments, but this has not yet been shown in naturalistic settings. The aim of the current study was to test the effects of residing in an evening blue-depleted light environment on melatonin levels, sleep, neurocognitive arousal, sleepiness, and potential side effects.

Methods: The study was undertaken in a new psychiatric hospital unit where dynamic light sources were installed. All light sources in all rooms were blue-depleted in one half of the unit between 06:30 pm and 07:00 am (melanopic lux range: 7–21, melanopic equivalent daylight illuminance [M-EDI] range: 6–19, photopic lux range: 55–124), whereas the other had standard lighting (melanopic lux range: 30–70, M-EDI range: 27–63, photopic lux range: 64–136), but was otherwise identical. A total of 12 healthy adults resided for 5 days in each light environment (LE) in a randomized cross-over trial.

Results: Melatonin levels were less suppressed in the blue-depleted LE (15%) compared with the normal LE (45%; $p = 0.011$). Dim light melatonin onset was phase-advanced more (1:20 h) after residing in the blue-depleted LE than after the normal LE (0:46 h; $p = 0.008$). Total sleep time was 8.1 min longer ($p = 0.032$), rapid eye movement sleep 13.9 min longer ($p < 0.001$), and neurocognitive arousal was lower ($p = 0.042$) in the blue-depleted LE. There were no significant differences in subjective sleepiness ($p = 0.16$) or side effects ($p = 0.09$).

Conclusions: It is possible to create an evening LE that has an impact on the circadian system and sleep without serious side effects. This demonstrates the feasibility and potential benefits of designing buildings or hospital units according to chronobiological principles and provide a basis for studies in both nonclinical and clinical populations.

Statement of Significance

Evening and night exposure to blue light exert particularly disruptive effects on the circadian system, but tunable LED-systems allow for blue-depleted evening lighting more adapted to human circadian biology. We demonstrate that when a blue-depleted light environment is integrated into a large-scale building complex, this has quantifiable effects on the circadian system and sleep. Our study was performed in a new acute psychiatric hospital unit where healthy participants resided for 5 days, a similar duration as patient admissions. This shows that it is possible to use the evening light environment to target circadian disruption and sleep in such a setting and it may have additional applications in a range of settings where control over incident and ambient light is feasible.

Key words: circadian rhythms; lighting; sleep; arousal; hospitals

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Introduction

Light is the most important time-giver for the human circadian system [1–3]. Throughout evolution, this system has continuously adapted to the signal created by the cyclic shifts in nature from daylight to nighttime darkness. The advent of electric lighting transformed visual perception in evening environments, increasing the number of hours available for both productivity and recreation. However, exposure to artificial light during normal dark periods exerts additional effects because of the nonvisual effects of light, such as delaying the circadian phase, suppressing melatonin production, delaying sleep onset, changing sleep architecture, and increasing alertness [4–6]. Furthermore, circadian disruption can have negative effects on both mental and somatic health and can contribute to depression, insomnia, metabolic abnormalities, obesity, immune impairment, poor cognitive performance, and a greater risk of cancer [7]. These substantial changes in timing, color, and intensity of evening light have occurred at a rapid pace with regard to the evolutionary perspective and likely have widespread and ongoing implications for health and sleep at a societal level [8]. In contrast, residing in natural darkness at night has been shown to phase-advance circadian rhythms and sleep timing [5, 9]. It remains unknown whether it is possible to create a scalable and usable indoor light environment (LE) that mitigates the negative effects of artificial evening light on circadian rhythms, sleep, and arousal.

The effects of light on the circadian system are primarily mediated by the intrinsically photosensitive retinal ganglion cells (ipRGCs) [10–12], which project to the circadian pacemaker in the suprachiasmatic nucleus of the hypothalamus. ipRGCs are primarily sensitive to short-wavelength, blue light ($\lambda_{\text{max}} \sim 480 \text{ nm}$) [10], suggesting the potential to mitigate the negative effects of evening artificial light by modifying the spectral composition of the indoor LE [8]. It has previously been shown that selectively filtering out short-wavelength, blue light in the evening or night reduces melatonin suppression and alertness [13–18], indicative of impeded ipRGC signaling. However, these effects were established under laboratory conditions, whereas a naturalistic setting introduces large variability in irradiance and illuminance resulting from general movement, changes in direction of gaze, light emitting screens, and ambient light. Therefore, it remains to be determined whether meaningful physiological effects can be achieved when such lighting modifications are applied in general housing or institutional settings.

The application of evening blue-depleted lighting may extend to many situations where it is feasible to exert a high level of control over all light sources. It may, however, hold potential in hospitals in which sleep–wake disruptions are ubiquitous and light levels at times may exceed those in household settings. It is known that patients with critical illnesses often have disrupted circadian rhythms [19], a phenomenon that is associated with a subsequent increase in morbidity and mortality [20, 21]. Moreover, disrupted circadian rhythms and sleep–wake cycles are equally, if not more apparent, in severe mental disorders compared with physical illnesses [22], highlighting the need for non-pharmacological interventions that can be used to target sleep–wake disruption and arousal in clinical psychiatry. Notably, the application of extended darkness in the evening and night [23–25], or filtering out short-frequency, blue light using blue-blocking glasses [26] has been shown to reduce

manic symptoms in patients acutely admitted with mania [27]. Given the potential benefits to this population, we decided to examine the potential application of an evening blue-depleted LE as implemented in a large-scale, multiroom complex such as a hospital by integrating such a lighting system in a new psychiatric unit.

The new hospital unit contains two wards that have identical, mirror-image layouts, and similar levels of photopic lux, albeit different light spectrum compositions in the evening: evening blue-depleted or standard hospital LE. Prior to opening of the unit for patient admissions, we undertook a proof-of-concept study to evaluate the effects of the evening blue-depleted LE on healthy subjects. In a randomized cross-over trial, healthy, young adult volunteers resided for alternating periods of 5 consecutive days in each ward. Our main aims were to test whether residing in the evening blue-depleted LE influenced the timing of dim light melatonin onset (DLMO), melatonin suppression, and polysomnographic sleep variables as compared with the effects of exposure to standard LE. Secondary aims were to determine whether differences in neurocognitive arousal and subjective levels of sleepiness could be identified and whether any side effects might be associated with residing in the blue-depleted LE.

Methods

Study design

Participants completed a comprehensive screening procedure, 7-day pre-randomization monitoring, and the 13-day study protocol. Prospective participants were eligible for inclusion in the research if their habitual sleep–wake patterns were within normal parameters (defined for the purposes of the study as weekday bedtime between 10:30 pm and 12:00 am and weekday rise time between 06:30 am and 08:00 am), with small intraindividual variations (<2 h) between weekdays and weekends and they tested negative for color blindness on the Ishihara plate test.

Exclusion criteria were evidence of any current medical or psychological conditions, current use of prescription medication(s), family history of severe mental illness, current sleep disorders, night shift work in the preceding 2 years, trans-meridian travel in the preceding 2 months exceeding one time-zone, and/or current use of nonprescription drugs or illicit substances (not including alcohol or nicotine).

During the 7-day pre-randomization monitoring, all participants were asked to maintain a fixed sleep–wake schedule (bedtime: 11:00 pm–12:00 am, rise time: 07:00 am–08:00 am) and wear an actiwatch. Participants were asked to refrain from the ingestion of alcohol and/or caffeine after 12:00 pm for the duration of the project.

A randomized cross-over design (see [Figure 1](#) and [Supplementary Figure S1](#)) was chosen for this study as within-participant variation was expected to be lower for our main outcomes compared with between-participant variation, thus allowing for a smaller number of participants. Participants resided for a total of 10 days (2 conditions of 5 days each) in late September 2017 in a new 40-bedded acute psychiatric unit at St. Olavs Hospital in Trondheim, Norway. Individuals were randomized to first reside 5 days in one of two wards followed by an intermission day and then to reside the next

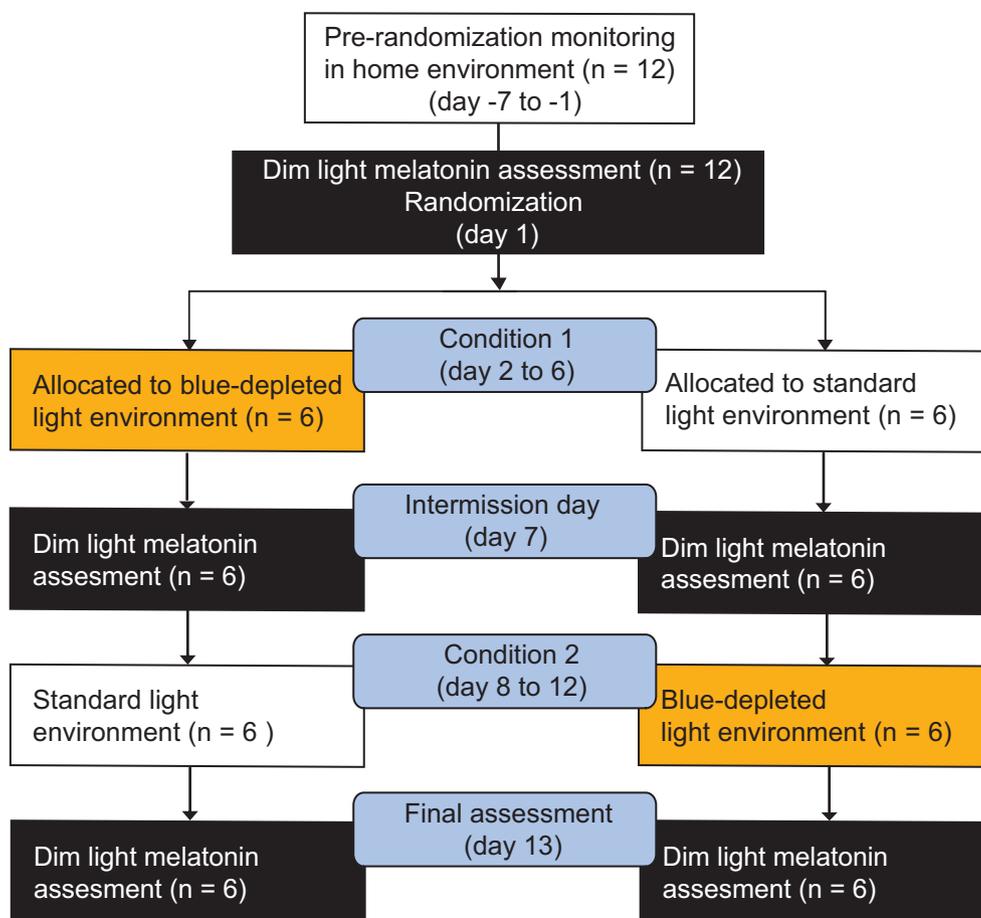


Figure 1. Overview of the study design. Flowchart of the randomized cross-over design describing the location of the participant at each key time point in the trial along with information regarding the nomenclature for the different phases in the study.

5 days in the other ward. The only difference between the two wards was the light spectrum to which residents were exposed during the evening and night (see [Supplementary Figure S2](#) for an overview of the unit). One ward provided a blue-depleted LE in the bedrooms, bathrooms, hallways, and common areas from 06:30 pm until 06:50 am and standard hospital lighting throughout the day, whereas the other ward utilized standard LE at all times. In addition, participants in the blue-depleted LE were asked to use blue-blocking filters (lowbluelights.com) on their electronic media devices in the evenings. Each ward consisted of 20 bedrooms with common areas for socializing and dining.

Participants were given a timetable at the beginning of each 5-day condition that detailed the type and timing of assessments. Hospital staff members were present to maintain safety and assist in the day-to-day running of the wards (e.g. delivery of meals).

During residency at the hospital unit, all participants were awoken by 07:00 am and expected to leave the unit by 08:00 am and return by 05:00 pm. Between 05:00 pm and 06:00 pm, participants had dinner in a common dining room (with standard hospital lighting). At 06:00 pm, participants returned to the LE they were currently allocated to and were free to spend their time in their rooms or the common areas. Participants were requested to retire to their bedrooms for sleep by 11:00 pm and turned the lights off during the sleep opportunity.

Ethics

The protocol was approved by the Regional Ethical Committee in Trondheim (Central Norway; REK: 2017/916) and is registered on the ISRCTN website (Reference: 12419665). Written informed consent was obtained from all participants and the study was undertaken in accordance with the Revised Declaration of Geneva.

Overview of each hospital LE

The lighting fixtures and fittings in each ward were identical and included round downlights, recessed square lights, and built-in reading lights by the desk in the bedrooms (Glamox AS, Oslo, Norway).

Blue-depleted LE (experimental condition)

The blue-depleted LE was created using a LED lighting system that emits both colored and white light. The LED modules inside the light fittings contained a mix of red, green-white, and blue diodes that can be programmed individually to emit different light intensities at different times of the day. To create the evening blue-depleted LE, only the green-white and red diodes emitted light, whereas the blue diode was switched off. The green-white diode emitted a small amount of blue light as it is a blue-chip covered with yellow phosphorus. Blue-blocking

window filters were also deployed in the evening and all televisions had permanent blue-blocking filters (Supplementary Figure S3 shows an example of the bedrooms).

From 07:00 am to 06:00 pm, the light was comprised of standard hospital light (3,000 K). From 06:00 pm to 06:30 pm, there was a transition period from normal to blue-depleted lighting. All light sources were blue-depleted from 06:30 pm to 06:50 am. From 06:50 am to 07:00 am, the lighting underwent a further transition returning it to standard hospital lighting.

Normal LE (control condition)

In this ward, the light spectrum remained constant throughout the 24 h cycle (3,000 K).

Light measurements

Prior to commencing the trial, the light spectrum was assessed using a Mavospec Base light meter (Gossen Foto- Und Lichtmesstechnik GmbH, Nürnberg, Germany). The light measurements demonstrated that the LE in the two wards had similar levels of photopic lux but the levels of melanopic lux were lower in the blue-depleted LE than in the standard LE (see Table 1 for details) [28]. Light exposure will vary with the direction of gaze. However, for the purposes of this study, light measurements were performed horizontally at eye level at standardized locations and times in both units. These locations were patient rooms (1 m into the room, facing windows, standing, with measurement performed horizontally at eye level [160 cm]); bathrooms (standing in front of mirror, with measurement performed horizontally at eye level [160 cm]); common areas such as the TV room (seated in a sofa, facing TV-screen, with measurement performed horizontally at eye level [100 cm]); and hallway (standing beneath a hallway luminaire: the brightest lit area in the hallway).

Assessments

Melatonin

Saliva samples were collected hourly between 07:00 pm and 11:00 pm on study days 1, 6, 7, 12, and 13 using Salivette Cortisol Code blue (Sarstedt AG & Co, Nümbrecht, Germany). Immediately

following sample collection, the samples were centrifuged at 2,200g for 10 min and frozen at -18°C overnight, before they were moved into storage at -80°C the following day. Samples were analyzed using enzyme-linked immunosorbent assay (Direct Saliva Melatonin, EK-DSM, Bühlmann, Schönenbuch, Switzerland).

Melatonin assessment in dim light Participants were exposed to dim light (<3 lux) from 06:00 pm until 11:00 pm on three separate occasions (days 1, 7, and 13). The clock time at which melatonin levels were >4 pg/mL was defined as the DLMO.

Melatonin assessment in blue-depleted and standard LE Evening melatonin concentrations were assessed on study days 6 and 12 (i.e. when participants had been exposed to the different LEs for 5 consecutive days).

Sleep

Participants underwent polysomnography (PSG) on study days 5, 6, 11, and 12. Electrodes were applied to the scalp according to the 20/20 system for electroencephalography recording (F3, F4, C3, C4, O1, O2); electrooculogram, submental electromyogram, electrocardiogram, peripheral pulse oximetry, and electrodes on the legs were also measured. The PSG data were collected using SOMNO HD (SOMNOmedics GmbH, Randersacker, Germany). Signals were sampled at 256 or 128 Hz, low-pass filtered, and stored at 128 Hz. Evaluation of sleep stages (according to the American Academy of Sleep Medicine criteria version 2.4) [29] was undertaken by a clinical neurophysiologist with >10 years of experience with PSG who was blinded to key participant details (such as current LE or order of LE exposure). Time spent in each sleep stage, sleep onset latency, time awake after sleep onset, rapid eye movement (REM) sleep onset latency, and sleep efficiency (percentage of time in bed spent asleep) were estimated.

Subjective sleepiness

Participants rated their subjective sleepiness on the Karolinska Sleepiness Scale (KSS), a 9-point Likert scale (from 1 = "extremely

Table 1. Light measurements in the two LEs

Light measurements	Photopic		Cyanopic		Melanopic		Rhodopic		Chloropic		Erythroptic		Irradiance ($\mu\text{W}/\text{cm}^2$)	Log photon flux	Log photon flux	peak irradiance (nm)
	Lux	Lux	EDI	Lux	EDI	Lux	EDI	Lux	EDI	Lux	EDI					
Standard LE																
Patient room	93	34	34	49	44	58	52	78	75	92	94	28.3	8.28E+13	13.9	605	
Patient bathroom	64	17	17	30	27	37	33	53	51	64	65	18.9	5.58E+13	13.8	610	
Common area, TV room	86	30	30	46	41	54	48	72	69	86	87	26.5	7.75E+13	13.9	610	
Common area, hallway	136	48	48	70	63	83	74	113	109	135	138	42.3	1.24E+14	14.1	610	
Blue-depleted LE																
Patient room	87	1	1	16	15	24	21	52	47	97	97	28.3	8.66E+13	13.9	625	
Patient bathroom	49	2	2	7	6	11	10	29	26	54	55	14.8	4.49E+13	13.7	620	
Common area, TV room	55	0	1	9	8	14	12	32	28	61	61	17.5	5.35E+13	13.7	620	
Common area, hallway	124	1	2	21	19	33	28	74	66	139	139	39.7	1.21E+14	14.1	620	

Light measurements taken inside the hospital in both the blue-depleted and the standard LE. α -opic illuminance (lux) levels for each of the five photopigments are given in concordance with Lucas et al [28], whereas the α -opic equivalent daylight illuminance (EDI) are reported according to the CIE S026:2018 standard [71].

alert” to 9 = “extremely sleepy—fighting sleep”), at 06:00 pm, 08:00 pm, and 10:00 pm on each night spent in the unit, and again at 07:00 am, the following morning [30].

Neurocognitive arousal

As a neurocognitive measure of arousal, participants completed the Connors Continuous Performance Test-3 (C-CPT-3) [31] between 09:00 pm and 10:00 pm on study days 4 and 10. In brief, the C-CPT-3 is a computerized test in which the letters A–Z are presented consecutively on a monitor (physical blue-blocking filters were used in front of monitors in both LEs). The test consists of 360 trials and lasts for 14 min. The participants are asked to press a response button each time a letter (targets, 80% of trials) was presented but to withhold their response when the letter was X (nontargets, 20% of trials). The participants were asked to respond as quickly and accurately as possible. Outcomes are reported on four commonly derived measures of response speed, consistency throughout testing, and accuracy; that is, reaction time, standard deviation of the reaction times, omissions (failure to respond to targets), and commissions (response to nontargets) [32, 33].

Actigraphy

Participants wore an actiwatch on their nondominant wrist (Actiwatch Spectrum, Philips Respironics Inc., Murrysville, PA), for both the 7 days of pre-randomization monitoring and throughout the 13-day study period. Sleep–wake data (divided into 30-s epochs) were used to estimate the sleep regularity index (SRI). The SRI indicates the percentage of epochs in each 24-h in which sleep–wake states are similar to the corresponding epoch in the previous 24 h [34]. Rise times were generated automatically from actigraphy recordings using an actigraphy software program (Actiware version 5.70.1, Philips Respironics Inc., Murrysville, PA). For bedtimes, participants indicated time they went to bed using an event-marker press on the actiwatch. If this information was missing, we used the reported bedtime recorded in the sleep diary.

Side effects

Subjective side effects Participants completed the Committee of Clinical Investigations (UKU) side effect rating scale on days 7 and 13. Although generally used in the evaluation of new psychotropic drugs, this scale was selected for the present trial as it assesses potential side effects across several important domains (i.e. psychiatric, neurological, autonomic, and other) [35]. The scale has 40 core items in addition to some sex-specific ratings (3 for males and 5 for females). The total score ranges from 0 to 129 for men and 0 to 135 for women, with higher scores indicating the presence of more side effects. However, as increased sleepiness and longer/deeper sleep duration represent desired benefits rather than side effects of exposure to blue-depleted LE, these items were excluded from our analysis.

Color perception Ability to discriminate colors was assessed using the Farnsworth–Munsell 100 Hue Color Vision Test (FM-100) on two occasions (day 2 or 3 and day 8 or 9). The FM-100 measures the amount of errors an individual makes in a color-hue sorting task. Superior color discrimination ability is defined as an error score <20, average ability as a score of 20–100, and low ability by a score >100 [36].

Sample size

A previous study reported that 3 days in a natural light–dark environment (without artificial lighting at night) advanced melatonin onset by 1.4 h and 6 nights advanced DLMO by 2.6 h (without artificial lighting at night) [5]. Other studies had reported that blue-blocking glasses at night had the same effect as darkness on melatonin secretion [15, 37]. As such, we assumed a priori that melatonin onset could be advanced by approximately 1.5 h following 5-day exposure to a blue-depleted LE with an estimated standard deviation of 45 min (a SD similar to that reported for melatonin onset in healthy controls [38] and the above-mentioned studies [5, 15, 37]). We estimated that a sample size of eight individuals would give a 90% chance of detecting these differences with a significance level of 0.05 (two-sided testing). As dropouts from the cross-over design were difficult to predict reliably, we determined we should recruit 12 participants (to allow for 30% attrition).

Randomization

The random allocation sequence was generated by the Unit of Applied Clinical Research (Department of Medicine and Health Sciences, NTNU). The members of the research group could not influence the process in any way.

Statistics

All statistical analyses were performed using R statistical package (version 3.5.2., R Core Team, Vienna, Austria, <https://www.R-project.org/>) and all figures were generated using GraphPad Prism (version 8.1.2, GraphPad Software, San Diego, California, www.graphpad.com/). A statistical significance level of $p < 0.05$ was chosen for all analyses. A within-subject approach was used in the main analyses to estimate the effects between the two LEs. The analyses were performed by a statistician who was blinded to participant allocation.

Melatonin

The effect of LE on concentrations of salivary melatonin was assessed using a linear mixed model. The combination of study day (day of melatonin assessment), LE, and hour was taken as the fixed effect. The combination of participant ID number and LE were taken as random effects. The assumption of normality was met using a logarithmic scale for the outcome variable. This model estimates the concentrations of melatonin for each of the 5 h included in the melatonin assessments undertaken in the different LEs and dim light. This method implicitly accounts for missing values. The modeled values were in turn used to calculate melatonin suppression and DLMO phase-shifts. As the interaction between LE and study day was specified in the model, any differences in the effects of LE for the order of exposure to each LE could be estimated. Individual levels of melatonin suppression and phase-shifts were calculated from the observed melatonin concentration values.

Melatonin suppression Melatonin suppression is reported as a percentage, which represents the level of melatonin in the two different LEs relative to the level of melatonin the following night in dim light. It was calculated using the area under the

curve (AUC) from 07:00 pm to 11:00 pm on days 6 and 12 divided by the AUC from 07:00 pm to 11:00 pm on days 7 and 13.

Phase shift of DLMO Phase shift was taken as the difference between timing of DLMO after residing in an LE for 5 days (days 7 or 13) and timing of DLMO at baseline (day 1). Linear interpolation was utilized to find the timing of DLMO.

Sleep

Similar linear mixed models were specified to test overall differences in PSG variables between the LEs and by condition order, and to test differences in bedtime, rise time, and SRI between pre-randomization monitoring, condition 1, and condition 2.

Subjective sleepiness, arousal, and side effects

For mean subjective sleepiness (KSS) in the evening and morning, intraindividual differences were calculated and tested for significance using one-sample Student's *t*-tests. The same approach was used for the color perception test (FM-100). As some measures from the C-CPT-3 and scores on the UKU side effects rating scale were not normally distributed, we used a Wilcoxon signed-rank test to examine intraindividual differences between the two LEs for these outcomes.

Missing values were pairwise deleted in the calculation of individual mean scores for the UKU side effects scale and the KSS. One individual was missing all KSS-scores in the blue-depleted LE and was thus excluded from those analyses. There were no missing values on the C-CPT-3 or the FM-100.

Results

Subjects and study design

As shown in [Figure 1](#), 12 healthy young adults (mean age \pm SD: 23.0 \pm 3.1 years, 7 women) completed the eligibility screening and pre-randomization monitoring and participated in the 13-day trial protocol. Complete data were obtained for the main outcome assessments of melatonin and PSG. Prior to undertaking the analyses, we checked data distributions, etc.,

for outliers. This resulted in the exclusion of one melatonin concentration value associated with one participant to avoid over-estimating the difference in melatonin suppression between conditions (at 11:00 pm when residing in the blue-depleted LE this participant had an extreme concentration of melatonin which was considered most likely to be a measurement error). All but one of the secondary outcome assessments had complete data (one individual did not complete the KSS evaluations).

Melatonin levels and DLMO phase shift

Melatonin suppression was significantly lower when participants resided in the blue-depleted compared with the standard LE (mean difference = 27%, 95% confidence interval (CI): 4% to 51%, $p = 0.020$). Melatonin suppression was 18% (95% CI: -3% to 34%, $p = 0.09$) in the blue-depleted LE and 45% (95% CI: 29% to 57%, $p < 0.001$) in the standard LE. From observed values, 10 out of 11 individuals with complete suppression data exhibited lower levels of melatonin suppression in the blue-depleted LE (see [Supplementary Figure S4](#) for details). DLMO occurred 0:34 h (95% CI: 0:10 to 0:54 h) earlier following residence in the blue-depleted compared with the standard LE ($p = 0.008$). Compared with DLMO at baseline, DLMO was phase-advanced by 1:20 h (95% CI: 1:00 to 1:38 h, $p < 0.001$) following residence in the blue-depleted LE, and by 0:46 h (95% CI: 0:25 to 1:09 h, $p < 0.001$) after residing in the standard LE ([Figure 2](#)). From observed values, 11 of 12 individuals presented greater phase advancement of DLMO after residing in the blue-depleted LE ([Supplementary Figure S5](#)).

Changes in total sleep time and REM sleep

Total sleep time (TST) was 8.1 min longer in the blue-depleted compared with the standard LE ($p = 0.032$). Furthermore, participants exhibited 13.9 min more REM sleep when residing in the blue-depleted compared with the standard LE ($p < 0.001$). As shown in [Table 2](#), no significant differences were observed between LEs with regard to the variables sleep onset latency, REM sleep onset latency, wake after sleep onset, sleep efficiency, or time in non-REM sleep stages 1–3.

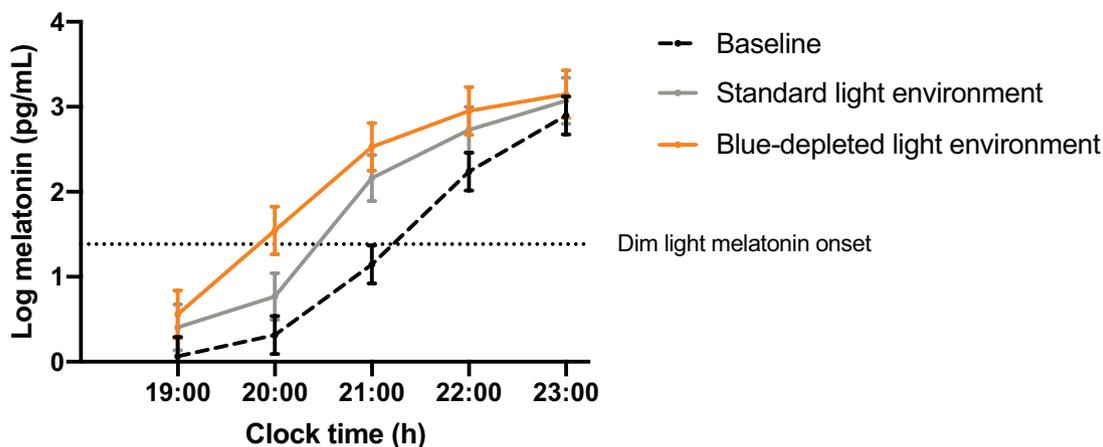


Figure 2. Melatonin concentration by hour and condition. Estimated mean dim light melatonin log concentrations hourly between 07:00 pm and 11:00 pm at baseline and after residing 5 nights in the blue-depleted and the standard LE. Error bars indicate the estimate \pm standard error of the mean. The dotted line indicates the 4 pg/mL threshold for DLMO. Melatonin concentrations between 07:00 pm and 11:00 pm differed significantly when individuals resided in the blue-depleted LE compared with the standard LE.

Table 2. Sleep as measured by polysomnography

Sleep variables (min)	Blue-depleted LE		Standard LE		Difference		P
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	
Total sleep time	440.2	432.6 to 447.8	432.1	424.5 to 439.7	8.1	0.7 to 15.5	0.03
Time in REM	89.7	80.8 to 98.6	75.8	66.9 to 84.7	13.9	6.0 to 21.7	0.001
Time in N1	30.8	26.6 to 35.1	33.5	29.3 to 37.8	-2.7	-7.9 to 2.4	0.30
Time in N2	225.6	213.7 to 237.6	224.8	212.8 to 236.7	0.9	-8.3 to 10.1	0.85
Time in N3	94.8	84.3 to 105.4	98.7	88.1 to 109.3	-3.9	-10.9 to 3.0	0.27
Sleep onset latency	10.3	7.6 to 12.9	11.9	9.3 to 14.6	-1.7	-5.1 to 1.7	0.34
REM onset latency	128.0	110.7 to 145.3	125.2	107.9 to 142.5	2.8	-21.0 to 26.6	0.82
Wake after sleep onset	23.0	16.8 to 29.3	22.6	16.3 to 28.8	0.5	-5.8 to 6.7	0.89
Sleep efficiency*	93.0	91.6 to 94.5	92.6	91.2 to 94.1	0.4	-1.0 to 1.8	0.59

Estimates of means in PSG-measured sleep-variables during the last 2 nights residing in the evening blue-depleted LE or the standard LE, and the estimated mean differences between LEs. Estimates, 95% confidence intervals and p-values were calculated from a mixed model with $n = 12$ participants. REM, rapid eye movement; N1, non-REM sleep stage 1; N2, non-REM sleep stage 2; N3, non-REM sleep stage 3.

*Sleep efficiency is given in percent.

Table 3. Neurocognitive test outcomes

C-CPT3 test variables (ms)	Blue-depleted LE		Standard LE		Estimated difference	
	Mean	SD	Mean	SD	Z	P
Hit reaction time	356.7	27.1	369.9	60.2	-0.18	0.85
Hit reaction time SD	73.0	13.0	65.3	16.2	-2.03	0.04
Commissions*	32.4	17.1	27.3	16.0	-0.98	0.32
Omissions*	0.3	0.3	0.3	0.5	-0.09	0.93

Mean scores with standard deviations (SD) on Connor's Continuous Performance Test-3 variables in both LEs and the estimated differences between the LEs (Wilcoxon signed-rank test with $n = 12$ participants).

*Commissions and omissions are reported in percent of targets.

Subjective levels of sleepiness and neurocognitive arousal

No significant difference (mean difference = 0.18, 95% CI: -0.09 to 0.47, $p = 0.16$) was detected between mean evening subjective sleepiness scores for the 11 individuals residing in the blue-depleted (4.98 ± 2.05) compared with the standard LE (4.79 ± 1.85). The mean morning subjective sleepiness also did not significantly differ (mean difference = 0.02, 95% CI: -0.82 to 0.86, $p = 0.96$) between the 11 individuals with complete data for subjective sleepiness residing in the evening blue-depleted versus standard LE (5.91 ± 2.24 vs. 6.04 ± 2.24 , respectively). [Supplementary Figure S6](#) details the mean subjective sleepiness scores as measured at different times of the day. Participants exhibited higher variability in their response times (standard deviations of hit reaction times) throughout the C-CPT-3 computerized response test in the blue-depleted compared with the standard LE ($p = 0.042$). No statistically significant differences were detected between the two lighting conditions in mean hit reaction time or number of omission or commission errors (see [Table 3](#) for details).

Side effects and color perception

Participants reported very few side effects on the UKU rating scale in either the blue-depleted (0.17 ± 0.42) or standard LE (0.12 ± 0.39), with no significant difference between the LEs ($Z = -1.69$, $p = 0.091$). Tiredness/fatigue represented the side effect most frequently reported in the blue-depleted LE (7 reports compared with 2 in the standard LE). Participants made

152 more errors (95% CI: 128 to 177, $p < 0.001$) on the FM-100 color-hue sorting task when residing in the blue-depleted (192 ± 33.4) compared with the standard LE (39.3 ± 23.1). Mean number of errors in the blue-depleted and normal LE were categorized as evincing low and average ability, respectively.

Post hoc analyses of melatonin-data by condition order

For participants who first resided in the blue-depleted LE and then resided in the standard LE, melatonin suppression was respectively, 18% (95% CI: -16% to 41%, $p = 0.26$) in the first condition and 62% (95% CI: 47% to 73%, $p < 0.001$) in the second condition (mean difference: 44%, 95% CI: 16% to 79%, $p = 0.002$).

For participants who first resided in the standard LE and then resided in the blue-depleted LE, melatonin suppression was respectively 34% (95% CI: 8% to 53%, $p = 0.013$) in the first condition and 18% (95% CI: -10% to 39%, $p = 0.19$) in the second condition (mean difference: 16%, 95% CI: -17% to 50%, $p = 0.33$). There was no statistically significant effect of order on the difference between conditions (mean difference: 28%, 95% CI: -19 to 73, $p = 0.23$).

For participants who first resided in the blue-depleted LE, DLMO was phased advanced by 0:55 h (95% CI: 0:30 to 1:20, $p < 0.001$) compared with baseline. After residing in the standard LE as the second condition, there was no significant change in DLMO (mean difference: -0:19 h [delay], 95% CI: -0:49 to 0:14, $p = 0.19$) compared with DLMO after residing in the blue-depleted LE.

For participants who first resided in the standard LE, DLMO was phase advanced by 0:55 h am (95% CI 0:30 to 1:33, $p < 0.001$) compared with baseline. After residing in the blue-depleted LE as the second condition, DLMO was further phase advanced by another 0:50 h (95% CI: 0:11 to 1:15, $p = 0.01$) compared with DLMO after residing in the standard LE. There was an effect of order in that the effect of the blue-depleted LE was larger in condition 2 (mean difference: 1:10 h, 95% CI: 0:20 to 2:01, $p = 0.009$). Findings for melatonin concentrations by the condition are shown in [Supplementary Figure S7, D and E](#).

Post hoc analyses of PSG by condition order

For participants first residing in the blue-depleted LE, there were no statistically significant differences between LE in PSG variables. For participants first residing in the standard LE, REM sleep was 19.6 min longer ($p < 0.001$) and TST was 11.9 min longer ($p = 0.02$) in the blue-depleted LE compared with in the standard LE. There was a significant order effect for one PSG variable in that the blue-depleted LE had a larger effect on reducing sleep onset latency in condition 1 (mean difference: 8.5 min, 95% CI: -16.7 to -0.2, $p = 0.04$).

Post hoc analyses of sleep times across study phases

These post hoc exploratory analyses are reported as they provide insights regarding potential effects on individuals of residing in a regularized environment (e.g. inpatient unit with fixed rise times, meal times, or bedtimes) during the two study conditions representing time spent in the unit compared with their usual living environment.

Participants went to bed 0:35 h (95% CI: 17 to 0:52, $p < 0.001$) earlier in condition 1 compared with the pre-randomization period (when the participants resided at home). There were no significant differences in bedtimes between condition 1 and condition 2 (mean difference: 0:10 h, 95% CI -0:09 to 0:30, $p = 0.31$). Furthermore, participants rose 1:26 h (95% CI: 1:09 to 1:44 h) earlier in condition 1 than in the pre-randomization period ($p < 0.001$); no significant differences in rise times were found between condition 1 and condition 2 ($p = 0.92$). There was statistically significant correlation between phase-shifts in bedtime and phase-shifts in DLMO for the pre-randomization period to condition 1 ($r = 0.66$, 95% CI: 0.13 to 0.89, $p = 0.02$), but no statistically significant correlation for condition 1 to condition 2 ($r = 0.26$, 95% CI: -0.36 to 0.73, $p = 0.40$). The SRI increased significantly from 85% (95% CI: 83% to 88%) in the pre-randomization period to 95% (95% CI: 93% to 98%) in study condition 1 ($p < 0.001$). However, there was no statistically significant difference in the SRI from condition 1 to condition 2 ($p = 0.14$). Details are provided in [Supplementary Figure S7, A–C](#).

Discussion

In this study, we demonstrated that it is possible to create an evening LE in a large, multiroom complex such as a hospital that had a meaningful effect on objective measures of circadian rhythms, sleep, and arousal, albeit little or no influence on subjective assessments of sleepiness or side effects. Specifically, we found that when healthy adults reside for 5 consecutive days in an evening blue-depleted LE, they exhibit substantially reduced

suppression of melatonin production and phase-advancement of endogenous circadian rhythms compared with when residing for a similar period in standard LE conditions. Moreover, melatonin levels in the blue-depleted LE did not differ from those in a dim LE (<3 lux), suggesting that it is possible to design a well-tolerated LE that is similar to near-darkness; that is, “virtual darkness” [27], with regard to its effect on melatonin production. Furthermore, residence in the blue-depleted LE also increased TST and time in REM sleep. We suggest that not only may these effects be relevant for general housing and the healthy population, but the potential therapeutic effect of these adaptations may be even more pronounced in hospital settings.

In particular, sleep disturbances are virtually ubiquitous in critically ill inpatients admitted to hospital units [39–42]. In inpatient psychiatry, sleep disturbances receive particular attention as they constitute trans-diagnostic symptoms of most major mental disorders [22, 43, 44]. These have primarily been treated with medication; however, although chronotherapeutic treatments of these symptoms have been tested [27], their use to date has been limited owing to low feasibility in the clinic as they require acutely ill individuals to adhere to strict treatment regimens. In addition, whereas several hospital units and nursing homes have been built with variations of circadian lighting [8], most have focused on altering indoor daylight properties rather than exerting rigorous control over evening ambient and electric light. To the best of our knowledge, this is the first demonstration that creating such an evening blue-depleted LE is possible in a multiroom complex and the first evaluation of the effects of residing in such an environment using a randomized cross-over trial including objective markers of circadian rhythms, sleep, and arousal. Furthermore, the minimal individual input required by participants together with the failure to detect serious side effects suggests that this design could be applicable in numerous inpatient settings, allowing for effective dissemination of a non-pharmacological intervention targeting circadian rhythms and sleep in hospitals, and in psychiatry in particular. Thus, these findings with healthy adults in a hospital environment constitute an important step toward the implementation of chronotherapeutic interventions in the hospital setting.

In the current study, the two units had identical but mirrored layouts and similar levels of photopic lux and irradiance, whereas levels of melanopic, cyanopic, and rhodopic lux were lower in the blue-depleted LE [28]. A challenge in hospital settings is to create an LE that has meaningful physiological effects without major side effects but is also sufficiently bright to allow hospital staff to perform necessary tasks. Based on previously published work regarding the dose–response relationship between melanopic illuminance and melatonin suppression, we decided to maintain melanopic lux below approximately 20 in the blue-depleted LE [10, 17, 45, 46]. Consistent with this, our findings regarding melatonin suppression are in line with previous work, although one recent study found that suppression can occur at lower levels of melanopic lux under optimal laboratory conditions [47]. Recent research has also shown that large differences exist between individuals with regard to the response of the circadian system to light [48]. Individual differences were also observed in our data on individual participants; however, 11 out of 12 participants exhibited larger circadian effects in the blue-depleted than in the normal LE (see [Supplementary Figures S1 and S2](#)). It

has also been shown that certain patient groups, such as those with bipolar disorders [27], seasonal affective disorder [49], and circadian rhythm disorders [50, 51] display greater circadian responses to light than nonpatient groups. Additionally, some of the most widely used medications in psychiatric disorders, selective serotonin reuptake inhibitors, appear to increase the sensitivity of the circadian system to light [52, 53], and some evidence exists of decreased retinal sensitivity in individuals with depressive disorder [54]. Thus, it is likely that a blue-depleted LE may exert differential effects on melatonin suppression in particular patient groups or those taking certain medications compared with healthy control populations, highlighting the need to evaluate how different patient groups will respond to changes in the LE in clinical trials [55].

Notably, a longer TST was observed following residence in the blue-depleted LE. In particular, the 8 min difference was similar to that reported in a meta-analysis of PSG data from treatment trials of cognitive-behavioral therapy for insomnia, which is considered the gold standard of insomnia treatment [56]. This suggests the potential of more pronounced effects in psychiatric inpatient populations, among whom levels of disrupted sleep are higher [43, 44, 57], in turn implying that the blue-depleted LE may be sufficient to meaningfully improve sleep for inpatients. Furthermore, we also observed increased duration of REM sleep. REM sleep propensity has been shown to be influenced by circadian rhythms [58] and reductions in REM sleep have been observed in the first sleep cycle following blue-light exposure concomitant with phase-delay of circadian rhythms [6, 59]. These findings are complimented by REM sleep increases in the first sleep cycle following administration of melatonin [60]. REM sleep has also been implicated in emotional brain processing [61], which may be relevant in mental illness. However, findings from clinical samples are ambiguous and REM dysregulation has been observed in affective disorders [62, 63]. Thus, the effect of a blue-depleted LE on REM sleep may have clinical implications that need to be addressed in future trials.

Nevertheless, although we observed an effect on objective markers of circadian rhythms and sleep, no differences were detected in subjective sleepiness between conditions in the evening or morning. This is similar to prior reports indicating a lack of differences in subjective sleepiness following exposure to blue-depleted light in the evening [13]. This finding may be important for hospital staff working evening or night shifts in a blue-depleted LE. However, we did observe that participants in the blue-depleted LE exhibited higher variability in response-times during the continuous performance of a neurocognitive test, indicating that levels of neurocognitive arousal were lower in the blue-depleted LE. Interestingly, this discrepancy between subjective sleepiness and objective arousal was also observed in the above-cited study of blue-depleted lighting [13]. The decreased arousal may be explained in part by a lower circadian drive for alertness resulting from circadian phase-advancement in the blue-depleted LE [64] but also from a reduction in the direct alerting effects of short-wavelength light [65, 66]. Notably, decreased pre-sleep arousal may be beneficial for agitated inpatients in a psychiatric unit and may also facilitate sleep onset.

Participants reported very low numbers of side effects in both LEs in the current study. No overall difference was detected in side effect scores between the LEs, suggesting that the blue-depleted LE did not have an obvious adverse impact on participants. The most frequently reported side effect in the

blue-depleted LE compared with the standard LE was increased fatigue/tiredness. Participants were also less adept at discrimination of color hues in the blue-depleted LE, scoring in the low-ability range compared with the normal-ability range in the standard LE. This finding may be of practical consequence when designing hospital units with changes in LE; for example, not using amber colors for signs or markers in medical charts.

As exploratory analyses, we also tested potential order effects in the trial. First, we did not find significant suppression of melatonin in the blue-depleted LE irrespective of the order of exposure. Second, we found an effect of the order on the difference in DLMO phase-shifts between conditions, with the largest effect of the blue-depleted LE when it was received as the second condition. However, there may be an additional effect of going from a home environment to a highly regularized inpatient environment with fixed bedtimes, rise times, and mealtimes, which may also have impacted the results. Participants were going to bed about 35 min earlier, rising on average 1.5 h earlier, and had higher sleep regularity in condition 1 compared with that during the pre-randomization monitoring. They therefore regularly woke and were exposed to light earlier in the morning. Advancing bedtime, rise time, and exposure to daylight in the morning have a strong phase-advancing effect [67]; thus, any additional effect of the evening blue-depleted LE may be masked by these factors. In contrast, rise times and sleep regularity did not differ between condition 1 and condition 2. In support of this, we also found that the change in bedtimes from the pre-randomization period to condition 1 correlated with the change in DLMO, but this was not the case between condition 1 and condition 2. This may indicate that when adjusted to the sleep-wake schedule, the effect of the evening blue-depleted compared with standard LE is more prominent.

Chronotherapeutic interventions that remove all light in the evening or block blue light with orange-tinted glasses [27] have demonstrated efficacy in reducing symptoms of mania in acutely admitted inpatients. These effects may be mediated by circadian or sleep pathways or may be the result of direct pathways influencing mood-centers in the brain, which have recently been identified in rodents [68]. Conversely, a recent exploratory study found no effects of blue-depleted light emitting diode (LED)-lighting on psychiatric symptoms in an inpatient psychiatric unit for affective disorders [69]. However, in this study incident or ambient light sources, such as TVs, mobile phones, or windows, were not controlled; moreover, the experimental light system was only installed in patient rooms, not corridors and common areas, and participants were thus free to enter and exit the experimental condition. This is problematic as the circadian system has recently been shown to be sensitive to very low levels of melanopic lux [47] or brief light exposures at night [17], and because increased sensitivity has been reported in several relevant patient groups [27, 49]. In contrast, the hospital unit in the current study is designed to allow a high level of control over both incident and ambient light. However, some extra effort may be needed from hospital staff to ensure adequate control over light in a psychiatric hospital unit, such as making blue-blocking filters available for mobile devices. In addition, these findings may be relevant across a variety of hospital units and might also possibly extend to other settings where control over ambient and incident light may be feasible such as trains, planes, and hotels.

Several limitations should be considered when interpreting the results from this study. First, an apparent effect was detected from residing in the hospital unit for the first week regardless of LE, suggesting that some degree of stabilization of sleep-wake rhythms could be achieved via a more regular routine. However, we did not design this study to investigate effects by condition order and these analyses, therefore, had limited statistical power. Second, researchers were given permission to access the hospital unit for only a limited time period (before it opened to acute admissions); thus, the study design had to consider such practicalities. Ultimately, as only a one-day washout phase was possible between the LEs, carryover effects cannot be excluded. However, this intermission is similar to that in other studies of the effects of light on evening melatonin and sleep [6, 13]. Third, participants resided in the unit from 05:00 pm until 08:00 am. During the day, they had to leave the unit owing to construction work. Participants in the current study thus may have been exposed to higher levels of light during daytime than the average patient housed in the hospital unit. Given that prior light history may exert protective effects against light exposure at night [70], the effects of a blue-depleted LE may be larger for an inpatient remaining indoors for most of the day. Fourth, 20 out of 48 PSG recordings were stopped at the designated wakeup time at 07:00 am. Therefore, when analyzing the data, the 07:00 am endpoint was applied to all recordings to minimize the influence of these events. Fifth, owing to the color of the light it was impossible to blind participants with regard to the specific LE in which they were residing. However, we did not observe a difference in subjective sleepiness scores, suggesting that expectancy effects were limited. Sixth, as we focused on a group of healthy young adults and the degree of some effects may differ in older adults with psychiatric disorders, some of our findings may not generalize across these populations. Seventh, we did not perform continuous measurements of light exposure at the eye level of the participants. Thus, we cannot control for the light exposure each participant was subjected to. Nevertheless, the current proof-of-concept study offered important insights regarding the effect of the modified hospital lighting system and provided a unique opportunity to apply physiological measurements such as melatonin assays and PSG, which are not always feasible for use with inpatients with severe mental disorders.

In conclusion, we have shown that the evening LE in a naturalistic setting can be modified according to chronobiological principles to have beneficial effects on the circadian system and sleep, without side effects. This offers translational relevance as it could readily be provided as a potential therapeutic intervention to large numbers of hospitalized patients with little increase in staff or patient burden.

Supplementary material

Supplementary material is available at SLEEP online.

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Author contributions

H.K. and K.L. conceived the study idea. D.V., K.L., and H.K. designed the study, with support from T.S., M.E., and A.O. D.V. and H.S.H. performed the data collection. D.V., H.K., and Ø.S. planned and performed the statistical analyses, with support from A.O. M.E. scored the PSG recordings. D.V., J.S., and H.K. wrote the initial draft with critical revisions from K.L., C.L.V., K.K., P.M.F., H.S.H., Ø.S., A.O., G.M., T.S., and M.E.

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