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Entrainment to gradual vs. immediate 8-hour phase advance shifts with and without short-wavelength enriched polychromatic green light

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ABSTRACT

Objectives: For optimal health and well-being the sleep episode and the circadian timing system should be properly aligned. We evaluated the effectiveness of different dynamic light and sleep/wake shift schedules for rapid circadian entrainment following an 8-hour advance of sleep.
Methods: Forty-three healthy participants completed an 8-day inpatient protocol in which the 8-hour sleep episode was advanced by 8 hours. Participants were assigned to one of five conditions: (1) dim ambient WHITE light and GRADUAL shift in which the sleep episode was incrementally advanced over 5 days; (2) dim GREEN, short-wavelength (~504 nm) polychromatic light and GRADUAL shift; (3) dim WHITE light and SLAM shift, including an abrupt 8-hour advance on day 3 following an extended 32-hour wake episode; (4) GREEN light and SLAM shift; or (5) COMBINED (higher illuminance WHITE plus GREEN) light and modified SLAM shift with 2 short naps scheduled on the day prior to the abrupt advance. Phase shifts of the plasma dim light melatonin onset and sleep measures were compared to examine effects of protocol condition.
Results: After 5 days, the COMBINED light/modified SLAM shift condition showed larger phase advances of dim light melatonin onset (4.02 ± 1.13 hours) compared to the other 4 conditions (range 1.50 ± 0.96-2.83 ± 2.23 hours; $p < .05$) and resulted in increased REM sleep duration and fewer sleep disruptions.
Conclusions: Consideration of the type of shift and the illuminance and wavelength of light may assist in designing lighting countermeasures to sleep and circadian disruption, which has implications for jetlag, shiftwork, and circadian rhythm sleep disorders.

Introduction

Modern life often causes sleep and work schedules to conflict with the endogenous 24-hour circadian timing system. Optimal sleep can only occur in a limited window of circadian time, and sleeping outside this window compromises the quantity and quality of sleep.[1] Several scenarios exist in which the sleep schedule becomes misaligned from the endogenous circadian drive for sleep, such as shift work or travel across multiple time zones (jetlag), resulting in reduced sleep quantity, quality[2-6,] and health.[7]

Nonvisual photic responses, including circadian phase resetting, are predominantly mediated by intrinsically photosensitive retinal ganglion cells containing the blue-light sensitive pigment melanopsin (λ_{max} 480 nm).[8-14] Short-wavelength light in the blue range has been shown to induce circadian phase shifting efficiently.[15-20] More recently, blue-enriched white light was used to re-entrain endogenous circadian rhythms to either 8-hour advances or 8-hour delays of the sleep/wake schedule over 5 days.[21] This study also included two shift schedules, a gradual and an immediate ("slam") shift, in the 8-hour advance protocols. Results showed no differences in phase advances of melatonin between the gradual and slam shift conditions, but significantly larger phase delays induced by the

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blue-enriched light compared to the white light condition. There was no white light comparison condition for phase advances in that study, however, we recently reported that monochromatic 507 nm blue-green light was more effective than monochromatic 480 nm blue light at both suppressing melatonin secretion and delay resetting circadian phase.[18]

Several studies have examined the role of light wavelength on phase advance shifts over a shorter timeframe,[22-24] and while they generally report greater sensitivity to short-wavelength light (456-470 nm), the results were often only marginally different from longer wavelength green light (eg, 497-548 nm). It is unclear whether the lack of clear wavelength-dependent differences was due to fewer advancing cycles, overall irradiance levels reaching a ceiling, how lights were equated (ie, by irradiance rather than photons[23]), or unknown photoreceptor mechanisms.

To learn more about the spectral sensitivity of phase advance shifts, we, therefore, proposed to test the efficacy of exposure to short-wavelength green light for phase advance shifts, with the goal of designing a protocol that would most rapidly re-entrain the circadian timing system after an 8-hour phase advance of the sleep/wake schedule. To this end, we originally designed a study of four light/shift conditions: WHITE light GRADUAL shift, GREEN light GRADUAL shift, WHITE light SLAM shift, and GREEN light SLAM shift, to compare green vs. white light and gradual vs. slam shift and hypothesized that both green light and gradual shift conditions would produce the largest phase advances of the melatonin rhythms with the least disruption to sleep. Preliminary results in n = 23, suggested no differences between green light and dim white light conditions, but potentially larger phase advances in the slam shift protocols compared to the gradual shift. Therefore, we added a fifth condition that combined a higher illuminance white light with green light in a modified slam shift (COMS) and hypothesized that there would be larger phase shifts of melatonin in the COMS condition compared to the other light and shift conditions.

Methods

Ethical approval

Forty-three participants (24.0 ± 5.1 years; 20 F) completed an 8-day inpatient protocol at the Intensive Physiological Monitoring Unit of the Center for Clinical Investigation at the Brigham and Women's Hospital. All participants gave written informed consent prior to enrollment and were compensated for their participation. Study procedures were approved by the Partners Human Research Committee (IRB protocol #2007P002526) and conformed to standards set forth in the Declaration of Helsinki.

Screening procedures

Study participants completed extensive screening procedures to determine eligibility prior to admission to the inpatient protocol, including medical history and physical examination with ECG, laboratory tests of blood and urine samples, eye examination, questionnaires, and interview with psychologist to confirm good medical/psychological health. Participants were asked to refrain from using medications, caffeine, and nicotine during the 3-week screening interval, which was verified with toxicological lab testing. They were also asked to maintain a self-selected, stable, 8-hour/night sleep schedule, which was verified with daily call-ins to a time-stamped voicemail at each bedtime and wake time, and with wrist actigraphy in the final week prior to admission. Individuals with a current or prior history of medical or psychological/psychiatric conditions, current or prior use of specific medications, or determination of eye abnormality/condition were excluded. Nightshift work within 3 years prior to the study and travel across more than 1 time zone in the 3 months prior to admission was also exclusionary.

Experimental design and protocol groups

Participants were studied in an environment free of time cues during the 8-day study. The study protocol (Fig. 1) consisted of a baseline day with 8:16 hours sleep/wake schedule, which was set according to participants' at-home sleep patterns during the week prior to admission. This was followed by 5 days with shifted sleep/wake schedules and a 30-hour constant routine (CR) procedure (days 7-8) under conditions of dim light, wakefulness, constant temperature, semirecumbent posture, and hourly isocaloric snacks (150 mEq Na+/100 mEq K+ [±20%]) and 2500 mL fluids/24 hours. Following the CR, participants were allowed an 8-hour recovery sleep and then discharged.

Participants were assigned to one of five protocol arms, which differed by light condition and shift schedule (Fig. 1). During the 8-day study, sleep/wake schedules were advanced by 8 hours using 3 distinct schedule protocol designs: (1) a gradual shift in which the sleep episode was advanced by 1.6 hours each day for 5 days until an 8-hour advance was achieved; (2) a "slam" shift in which the sleep episode was abruptly advanced by 8 hours after an extended 32-hour wake episode, and then maintained at this advanced time for 4 days; and (3) a modified slam shift in which the extended wake interval prior to the 8-hour advance of sleep and included two nap opportunities. One nap was scheduled for 2 hours during the afternoon, and the second nap for 4 hours beginning at the habitual bedtime. For both gradual and slam shift conditions, two different ambient lighting conditions, designated WHITE or GREEN, were employed during wake on days 3-6. In the modified slam shift condition, ambient room light was COMBINED (WHITE+GREEN) during wake on days 3-6. Thus, the five protocol conditions were: WHITE GRADUAL (WG), GREEN GRADUAL (GG), WHITE SLAM (WS), GREEN SLAM (GS), and COMBINED modified SLAM (COMS).

Lighting conditions

Lighting was provided by ceiling-mounted fluorescent lamps with digital ballasts (Lutron Electronics Co, Inc, PA) and transmitted through a UV-stable filter (Lextran 9030 with prismatic lens; GE Plastics, MA).

In the WHITE light conditions (WG and WS), the ambient room light was generated by 4100 K fluorescent lamps (melanopic Daylight Equivalent Ratio [melDER] ~0.61[25]) (F96T12/41U/HO/EW, 95 W; F32T8/ADV841/A, 32 W; F25T8/TL841, 25 W; Philips Lighting, the Netherlands). Maximum ambient light during scheduled wake was ~184 lux (~112 melanopic Equivalent Daylight Illuminance [melEDI] lux) when measured in the horizontal plane at a height of 187 cm, and ~90 lux (~55 melEDI lux) when measured in the vertical plane at the cornea (137 cm) during wake on days 2-6 (Supplementary Table 1, Supplementary Fig. 1).

In the GREEN light conditions (GG and GS) the ambient room light was generated by ceiling-mounted green, fluorescent lamps (melDER 2.07) (Sunnex Biotechnologies, Winnipeg, MB Canada [U.S. patent # 5447,527, CDN patent # 1334,399]). Maximum ambient light during scheduled wake was ~207 lux (~428 melEDI lux) when measured in the horizontal plane at a height of 187 cm, and ~90 lux (~186 melEDI lux) when measured in the vertical plane at the cornea (137 cm) (Supplementary Table 1, Supplementary Fig. 1). The ambient light appeared green and resulted in an altered color perception of items in the room. In the GG condition, the green light occurred during wake episodes on days 2-6; and in the GS condition, the green light was scheduled for the second half of the extended wake episode (day 3) and subsequent wake episodes until day 6 (Fig. 1).

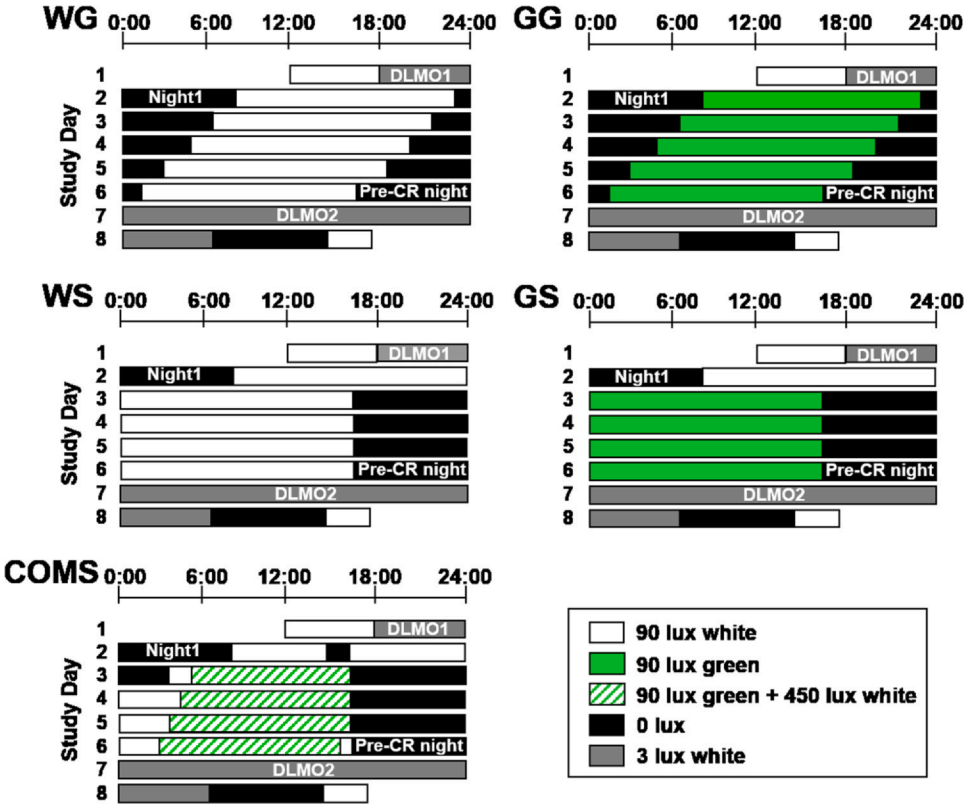

Fig. 1. Representative raster plots of 5 different protocols conditions of the 8-day study. Study participants were randomized to 1 of 5 conditions: WHITE GRADUAL (WG), GREEN GRADUAL (GG), WHITE SLAM (WS), GREEN SLAM (GS), and COMBINED SLAM (COMS), which included 2 nap opportunities on days 2 and 3. All protocol conditions included 6 hours of dim light (gray bars) prior to the first sleep episode (Night1) during which the phase of the dim light melatonin onset (DLMO1) was assessed. The 8-hour sleep episodes (black bars) were advanced using various shift/light protocols until an 8-hour advance was reached on day 6 (Pre-CR night). All participants completed a 30-hour constant routine (CR) beginning at wake time on day 7 during which DLMO2 was assessed

In the COMBINED light condition (COMS) the ambient room light was 90-lux fluorescent white light (4100 K, as described above) during wake on day 2 and during early portions (~1-4 hours) of wake on days 3-6. For the remainder of the wake episodes on days 3-6, the ambient room light consisted of a combination of 4100 K white light (nominally ~450 lux at the cornea) and the 90-lux green light setting (as described above). The maximum light of the combined lighting was ~1414 lux (~1158 melEDI lux) when measured in the horizontal plane at a height of 187 cm (Supplementary Table 1, Supplementary Fig. 1). During the design of the COMS condition, increasingly higher illuminances of white light (beginning at 90 lux) were combined with the 90-lux green light until visual color acuity was restored as assessed by a Farnsworth-Munsell color vision test.[26] The resulting white light used was the level at which the green light no longer caused altered color perception. The combination green and white light was scheduled for 10-12 hours in an advancing manner (see Fig. 1) to target the advance region of the human phase response curve (PRC).[27-31]

For 6 hours prior to bedtime on day 1 and during the 30-hour CR on days 7 and 8, the ambient room light was ~3.3 lux (~2 melEDI lux) at 137 cm from the floor in the vertical plane and had a maximum of ~15 lux (~9 melEDI lux^2) at 187 cm from the floor in the horizontal plane in all protocol conditions for the assessment of melatonin phase. Participants remained in darkness (< 0.02 lux) during scheduled sleep/nap episodes.

Assessment of circadian phase and phase shifts

Phase shifts of melatonin were calculated using the time of dim light melatonin onset (DLMO) on the first day (DLMO1) and during the CR (DLMO2). Hourly blood samples were collected throughout the study via an indwelling intravenous catheter placed in the forearm, maintained briefly (< 1 hour) on ice before centrifugation (2200-2800 rpm, 2°C) followed by frozen storage (−80°C) for subsequent assay. Plasma melatonin samples were assayed using the BÜHLMANN Melatonin Radioimmunoassay (ALPCO Diagnostics, Salem, NH), had a functional sensitivity of 0.9 pg/mL and analytical sensitivity of 0.3 pg/mL, intra-assay precision of 7.9%-8.2%, and interassay precision of 11.7% (SolidPhase Inc, Portland, ME). DLMO was determined as the time at which plasma melatonin levels crossed 10 pg/mL by linear interpolation, and net phase shifts were calculated as the difference in clock time between DLMO2 and DLMO1.

The timing of the sleep/wake and light/dark schedule in all laboratory protocols were based on participants' preinpatient sleep patterns and therefore, differed between individuals. The phase of DLMO1 relative to bedtime (phase angle of entrainment) on night 1 was calculated for each person and included in models to examine whether phase angle predicted the degree of DLMO phase shift among the protocol conditions.

Sleep recordings

Polysomnography (PSG) was recorded throughout all sleep episodes (8 hours) using a Vitaport-3 recording system (TEMEC Instruments, B.V. Kerkrade, The Netherlands). Recordings included the electroencephalogram (EEG; derivations C3, C4, O1, and O2, referenced to contralateral mastoids), right and left electrooculogram, electromyogram, and electrocardiogram. Electrode impedances were < 10 kΩ prior to beginning each recording. EEG signals were filtered (high-pass EEG filter 0.23 Hz; low-pass EEG filter 70.1 Hz; 24 dB/octave, sampling rate 256 Hz) and scored in 30-second epochs according to conventional criteria.[32] Total sleep time (time spent in N1,

N2, N3, and REM sleep); sleep efficiency (% total sleep time of the 8-hour sleep episode [lights off to lights on]); sleep onset latency (SOL, interval between lights off and first 3 consecutive sleep epochs); duration of stages N1, N2, N3, REM sleep, and wakefulness; wake after sleep onset (WASO); wake after final awakening (WAFA; duration of an early final awakening); and number of awakenings longer than 30 seconds were included in analyses to compare differences between sleep just prior to the CR (day 6) while adjusting for sleep on the first night (day 1) among the five protocols.

Data management and statistical analysis

Of the total 43 study participants who completed the 8-day inpatient study, 1 individual from the GG group [2937V0T3] was excluded from all analyses due to technical issues with the melatonin assay and because of significant missing PSG data from the first night. An additional 2 participants were excluded from analysis of melatonin phase shift (1 each from the GS [30F8V] and WS [3119V] groups) because of too many missing blood samples to accurately assess DLMO. For the sleep analysis 5 individuals were excluded: 1 each from the GS [3059V] and COMS [30G9V] groups due to a significant amount of undefined artifact in the PSG recording during the pre-CR sleep episode; and 2 from the WS [28M7V and 28N6V] group, and 1 from the GS [3043V] group because of missing PSG data during the first sleep episode.

All statistical analyses used SAS 9.4 (SAS Institute, Cary, NC). Phase shifts of the melatonin rhythm and sleep measures were compared among the 5 protocol conditions using analysis of variance (ANOVA) to assess the main effect of condition. First, conditions were compared individually using an omnibus test. Next, the COMS condition was compared to the other protocols combined into a single group. Effect sizes for significant findings are reported as unstandardized regression estimates. The starting phase angle of entrainment was included as a covariate when examining phase shift. Comparisons of residualized change in pre-CR sleep measures accounted for the first night sleep. Secondary analyses comparing effects of light condition (green vs. white) and shift condition (gradual vs. slam) on phase shift and sleep measures (excluding the COMS condition) were conducted and results are shown in Supplementary Materials. Additional secondary analyses comparing the COMS condition to the slam shift conditions (WS and GS) and to the gradual shift conditions (WG and GG) are also shown in Supplementary Materials. p values < .05 were considered significant and values > .05 but less than .1 were considered marginal results.

Results

Melatonin phase shifts

Average advance phase shifts of the melatonin rhythm are shown for each protocol condition in Table 1. Individual phase shifts are shown in Fig. 2 and mean melatonin profiles are plotted by protocol condition in Supplementary Fig. 2. There was a main effect of protocol condition on the magnitude of the melatonin phase advance shift (ANOVA; $F(5,34) = 2.96$ $p = .025$). Individual comparisons showed that the COMS condition had larger phase shifts (4.02 ± 1.13 hours; see Table 1) than each of the other conditions by 1.22-2.82 hours (WG: 1.98 ± 0.82 hours, $p = .022$; GG: 2.82 ± 0.91 hours, $p = .004$; WS: 1.60 ± 0.67 hours, $p = .022$; GS: 1.22 ± 0.67 hours, $p = .076$). The GG condition appeared to have the smallest phase shift (1.50 ± 0.96 hours), which was significantly smaller than the COMS condition (shown above) but only trended toward a significant difference compared to the GS condition (−1.60 ± 0.92 hours, $p = .090$). Compared to the other protocols combined into a single group, the phase shift in the COMS condition was 1.70 ± 0.54 hours greater ($p = .003$). Individual phase shifts and phase angle of entrainment from night 1 are listed in Supplementary Table 2. Comparisons of the light conditions (green vs. white) and the shift types (gradual vs. slam) excluding the COMS condition are shown in Supplementary Table 3. Results of the secondary analyses comparing the COMS condition with the gradual and the slam conditions are shown in Supplementary Table 4. There was not a main effect of initial phase angle on DLMO shift.

Sleep measures

PSG measures of sleep recorded during the 8-hour sleep episode prior to the CR were compared among protocol conditions, while

Table 1
Summary of sample characteristics, phase shift of melatonin, phase angle of entrainment between melatonin and sleep on night 1, and polysomnographic (PSG) sleep measures from the final sleep episode after adaptation by protocol condition

	WHITE GRADUAL	GREEN GRADUAL	WHITE SLAM	GREEN SLAM	COMBINED SLAM
	Mean (SD)/#	Mean (SD)/#	Mean (SD)/#	Mean (SD)/#	Mean (SD)/#
Age, y	24.20 (5.76)	25.20 (3.49)	24.40 (5.74)	22.55 (4.27)	23.82 (5.91)
Gender, F/M	2/3	2/3	5/6	5/6	6/5
n-DLMO shift	5	4	10	10	11
DLMO shift[1], h	2.01 (0.97)	1.50 (0.96)	2.33 (1.53)	2.83 (2.23)	4.02 (1.13)
Baseline phase angle[2], h	2.05 (0.95)	3.08 (1.42)	1.89 (1.13)	2.26 (1.50)	2.15 (1.23)
n-PSG measures	5	4	9	9	10
TST[3], min	345.60 (92.84)	382.00 (93.80)	419.06 (65.77)	403.39 (52.92)	414.80 (54.73)
SOL[4], min	15.80 (10.37)	8.75 (6.98)	8.50 (4.20)	20.61 (21.12)	19.80 (18.27)
SE[5], %	71.74 (19.44)	79.50 (19.52)	87.26 (13.68)	83.95 (11.01)	86.33 (11.39)
N1, min	22.30 (12.87)	19.88 (7.28)	24.17 (14.82)	18.94 (11.78)	11.35 (5.15)
N2, min	182.30 (44.72)	172.75 (75.79)	209.17 (46.07)	195.56 (43.65)	203.50 (42.35)
N3, min	80.80 (20.61)	103.63 (41.57)	84.33 (16.78)	95.11 (17.96)	91.60 (28.02)
REM, min	61.20 (29.10)	85.88 (14.24)	101.44 (32.83)	93.94 (21.63)	108.35 (19.15)
Wake, min	133.70 (94.37)	97.75 (93.50)	59.72 (66.15)	75.28 (52.77)	63.25 (55.14)
WASO, min	119.60 (89.12)	89.13 (94.12)	51.39 (63.96)	54.83 (56.21)	43.45 (59.24)
WAFA, min	64.50 (93.51)	0.75 (0.65)	11.44 (32.47)	14.56 (41.99)	0.05 (0.16)
# Awakenings	15.20 (5.4)	19.00 (6.16)	12.22 (10.06)	10.67 (7.55)	4.30 (2.63)

[1] Phase shift of the dim-light melatonin onset (DLMO) was calculated as DLMO2-DLMO1.
[2] Phase angle of entrainment was defined as the number of hours DLMO1 occurred before lights out (bedtime). Sleep measures include total sleep time (TST); sleep onset latency (SOL); sleep efficiency (SE); duration of stage N1, N2, N3, REM, and wake; wake after sleep onset (WASO); wake after final awakening (WAFA); and the number of awakenings > 30 seconds.
[3] TST was calculated as the sum of N1, N2, N3, and REM sleep durations.
[4] SOL was calculated as the time from lights off to the first 3 consecutive 30-second epochs of scored sleep.
[5] SE was defined as the % TST of the sleep period (480 minutes).

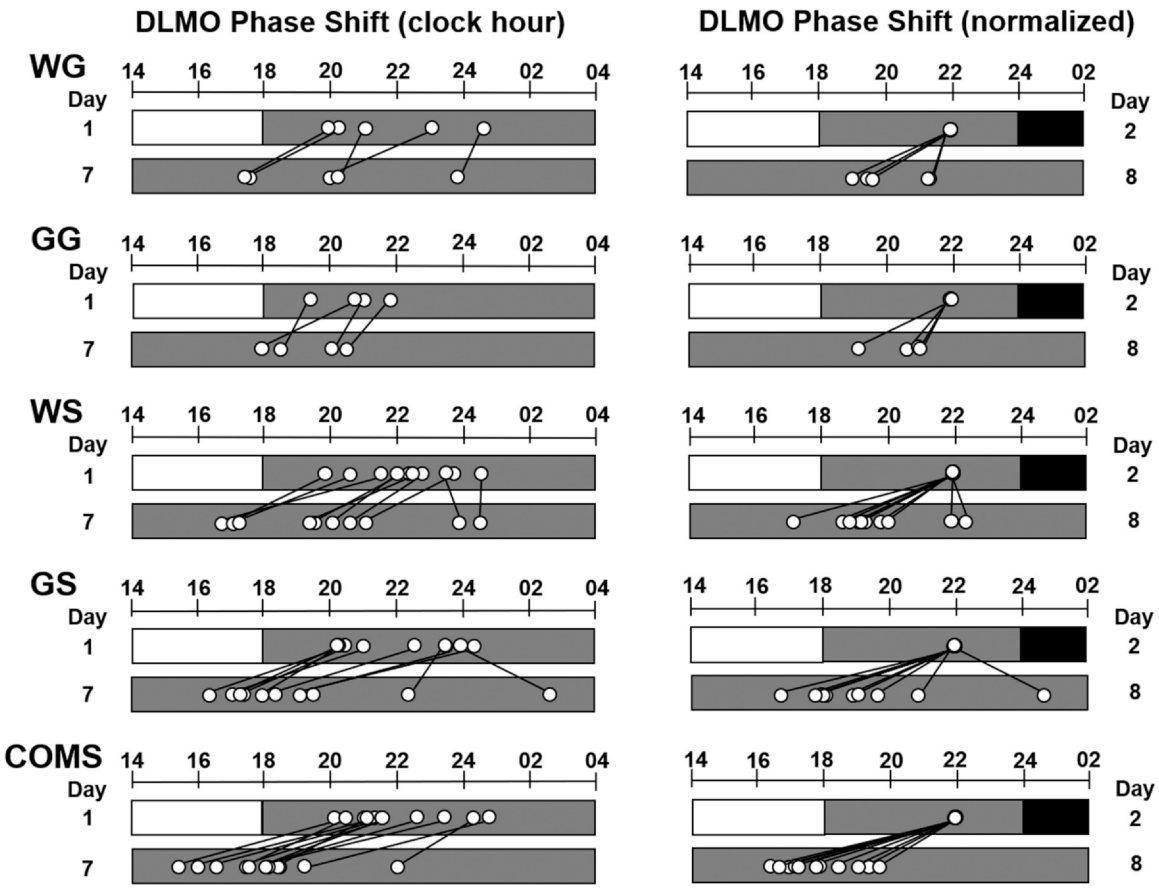

Fig. 2. Phase shifts of the dim light melatonin onset (DLMO) following an 8-hour advance of the sleep schedule. Individual phase shifts were calculated as the difference between DLMO1 (open symbols on day 1/2) and DLMO2 (open circles on day 7/8) for each protocol condition: WHITE GRADUAL (WG), GREEN GRADUAL (GG), WHITE SLAM (WS), GREEN SLAM (GS), and COMBINED SLAM (COMS). Phase shifts are plotted in clock time (left panels) and normalized relative to DLMO1, which was set to the mean DLMO1 (21:57) and sleep onset defined as 24:00 for the entire sample (right panels).

controlling for the 8-hour sleep episode night 1. Results showed significant differences for SOL, the duration of REM sleep, WAFA, and the number of awakenings greater than 30 seconds (Table 1). The COMS group had longer SOL than WS (13.64 ± 6.06 minutes; $p = .03$), obtained more REM sleep than WG (42.57 ± 14.00 minutes; $p = .005$), spent less time awake after final awakening than WG (−62.40 ± 23.72 minutes; $p = .01$), and woke fewer times than GG (−6.92 ± 2.46 times; $p = .008$). Compared to the other protocol conditions combined into a single group, sleep among those in the COMS group was not significantly different.

Discussion

The COMS protocol condition, consisting of the combination of ~90 lux polychromatic short-wavelength green light with ~450 lux white light and a modified slam shift schedule that included 2 nap opportunities, showed the most rapid partial circadian entrainment to an 8-hour advance of the sleep episode. This supported our hypothesis that combining the dim green light (90 lux) with higher illuminance white light (450 lux), would induce greater phase shifts than the 90-lux green or 90-lux white light alone. It cannot be determined, however, if the larger phase advances were due to the brighter white light (450 lux), the gradual schedule of light exposure within the slam shift protocol (see Fig. 1) that attempted to limit the combined light to nondelaying times, the two scheduled naps (with accompanying dark pulses)[33] during days 2-3 of the study, other unidentified factors, or any combination of these.

Of note, although the largest phase shifts were seen in the COMS condition, by 1.70 hours larger than the other conditions combined, none of the conditions induced complete phase-resetting required by the 8-hour advance of the sleep schedule. This was most evident by the largest mean DLMO phase shift (4.02 ± 1.13 hours) of the COMS condition after 5 days being half of the required shift and even at an individual level, the larger phase shifts in the COMS group were less than 6 hours (Fig. 2). One possible reason for the incomplete re-entrainment, particularly in the WG, GG, WS, and GS conditions, is that the dim ambient light level used (~90 lux) was not sufficient to induce larger phase shifts and indeed, there was no difference in advances of DLMO among these groups. If the larger phase shifts in the COMS group were due to a higher illuminance, the results suggest that ambient room light, even when short-wavelength enriched, may need to be at a higher illuminance than 450 lux to achieve this re-entrainment. This conclusion is supported by the lack of difference between phase advances in the dim green or dim white light conditions (in Supplementary Materials) and by prior studies using multiple consecutive days of exposure to white light to advance the endogenous circadian phase. For example, in a protocol involving a 5-hour 180-lux light exposure on 3 consecutive days showed an average 1.26 ± 0.65 hours phase advance of the plasma melatonin midpoint.[34] An earlier study using a similar protocol but with higher illuminance (~1260 lux) showed an average 2.77 ± 0.59 hours phase advance of the core body temperature rhythm after 3 days.[35] That study also repeated the 3 days of light exposure with a CR procedure before and after each series and the average phase advance of the second 3 days of light exposure was larger (3.05 ± 0.54 hours). More recently, in a similar comparison of a gradual vs. a slam advance phase shift over 5 days,[21] we showed that exposure to 6.5 hours of blue-enriched white light (750 lux, 704

melEDI lux) shifted the melatonin rhythm by about 3 hours (slam: 3.28 hours, gradual 2.88 hours). As in the current study, the shift schedule patterns were not significantly different when the same light source was used. Of interest, however, is the observation that the COMS condition, which had a lower lux and melanopic EDI lux, appeared to be more efficient than the shorter, blue-enriched light exposure.[21] Collectively, these findings reveal that exposure to short-wavelength enriched white light at illuminances typically observed indoors can produce significant phase advances of the circadian clock, but are insufficient to reset the circadian phase to an 8-hour advance in 5 days.

Another factor that could potentially affect the magnitude of the observed phase shifts is the circadian timing of the light exposure. On average, there was no difference in the initial phase angle among protocol conditions, although it is possible on an individual level that the initial light exposures occurred at different circadian times according to the PRC and potentially reduced the overall effect. Designing a common lighting regime that resets all individuals equally is not possible given the 5-hour range in entrained circadian phases observed within study populations, as is apparent here (Fig. 2) and in many prior laboratory studies,[36-38] and likely underestimates circadian variation under real-world conditions.[39,40] In a group environment, a "one-size-fits-all" lighting solution inevitably cannot expose people to light at the same circadian phase, potentially attenuating the overall mean shift. Nonetheless, the superiority of the COMS slam-shift condition over both gradual lighting conditions (GW and GG) and the two slam-shift conditions that used dimmer light (SW and SG; see Supplementary Table 4) was largely due to the absence in the COMS group of individuals who exhibited a delay rather than an advance shift in response to the stimulus (Fig. 2). This has important implications for the design of schedules that require all individuals on a team or group to be exposed to the same ambient lighting conditions during a substantial phase advance shift (as occurs during Eastward travel across multiple time zones). We specifically attempted to schedule the COMS condition in a more appropriate phase for advancing the circadian pattern, which may explain the observed results. Furthermore, given that light is detected continually by the circadian system, the use of ambient room light throughout the 16-hour wake episodes, rather than specific light exposures of a shorter duration, inevitably distributes light across both phase advance and delay regions of the PRC, and therefore may have contributed to smaller overall phase advances in all conditions. Prior light history may also reduce the impact of the experimental exposures,[41-43] but is difficult to predict given that systematic quantification of the role of light history irradiance, spectrum, and time course is in its infancy.

It is unclear whether potential phase delays may have contributed to the partial re-entrainment because masking/suppression of the melatonin profile by light, particularly in the slam conditions (WS and GS, Supplementary Fig. 2), prevents the ability to accurately determine circadian phase on days 2-6. Suppression of melatonin levels was also evident in the COMS condition but appeared to be less than in the other slam protocols due to the inclusion of 2 nap opportunities (ie, "dark pulses") during the extended wake episode, particularly the 4-hour "dark pulse" scheduled to begin at the participants' habitual bedtime, and limiting the combined 90-lux green and 450-lux white light to a portion of the wake episode in an advancing pattern each day. Night shift work involving circadian desynchrony has been recognized as a probable human carcinogen (IARC Monograph[44]), and repeated melatonin suppression by light that commonly occurs during night shift work is believed to contribute to increased cancer risk. Possible mechanisms point to the various anticancer properties of melatonin[45] and/or potential antioxidant effects of melatonin to rescue flies and mice from lethal effects of sleep deprivation related to cancer[46] although other factors involved in night shift work (eg, circadian disruption, sleep loss) have also been shown to independently increase risk.[47,48] Dark episodes in the COMS condition, which may have reduced melatonin suppression, coupled with greater phase shifts suggest that the COMS condition was more efficient for rapid re-entrainment to a large advance of the sleep episode and may have greater health implications from better alignment of circadian phase with the sleep/wake cycle.

The effects of protocol condition on postshift sleep measures were also examined as an additional marker of circadian re-entrainment. Results were consistent with the melatonin phase-shifts showing better postshift sleep in the COMS condition for more REM, less WAFA, and fewer number of awakenings relative to other specific protocol groups. Based on the larger phase shifts in the COMS condition, we might have expected greater REM duration given that REM is highly circadian regulated.[49] Improved sleep quality, indicated by less time awake after final awakening and fewer awakenings during the sleep episode, may also be a sign of faster re-entrainment. Surprisingly, participants in the COMS group also showed greater SOL, although only in comparison to the WS group and still within the normal range for SOL (10-20 minutes). While it is unclear why it took longer to fall asleep in the COMS group or if the result was related to the light condition, this may reflect lower sleep pressure from better sleep during preceding nights whereas in the WS group, mean SOL below the normative range (8.5 minutes) is a marker of high sleep pressure indicative of poor sleep on previous nights. Greater alerting effects of presleep light in the COMS group may also account for the longer SOL.[50,51] Additionally, analyses included preshift (night 1) sleep measures to account for potential group differences independent of light/shift protocol or phase shifts and this resulted in a small sample size decrease, which may have impacted findings. On a related note, the small sample size of the light and shift groups, particularly the gradual shift conditions (WG and GG, n = 5 each) was a limitation and may have contributed to the results. Specifically, there might have been a significant difference in amount of phase shift and/or sleep measures between the gradual and slam shift protocols in a larger sample.

Comparing the results from this study with others using short-wavelength light to induce phase advances, the COMS conditions showed favorably in terms of producing the largest phase shifts. Two studies developed a PRC to short-wavelength light using different protocols, light irradiance, and exposure duration and timing.[15,16] The first used a short light duration (90 minutes) of three 30-minute intermittent pulses of blue LED light (~450-500 nm, ~185 lux) once a day for 3 consecutive days.[15] Circadian phase of DLMO was assessed using a 3-day ultradian light/dark cycle, forced desynchrony protocol before and after the light exposure, and results showed average phase advances of less than an hour. Use of a single, longer duration exposure (6.5 hours) of monochromatic blue light (480 nm) in a protocol, which included 32-55 hours CR procedures before and after the light exposure, showed a maximum fitted phase advance of 1.3 hours.[16]

Finally, given the effectiveness of monochromatic blue-green light (507 nm) at both suppressing melatonin secretion and delay resetting circadian phase[18] and our earlier finding that dim monochromatic 555 nm green light may be more effective than dim blue light at inducing circadian phase resetting,[52] these findings with green-enriched polychromatic light challenge the oversimplification that blue light is always more effective than green light in inducing circadian resetting responses in humans. The relative contribution of different photoreceptors to nonvisual responses is dynamic and changes over time, and with the irradiance of light exposure,[18,53] demonstrating a more complex system than a melanopsin-only model in fully explaining circadian resetting responses in humans. This complexity has important implications for the establishment of indoor lighting standards, and for the design of lighting environments to facilitate circadian health.

Conclusion and public health relevance

Taken together, results suggest that the COMS protocol condition facilitated more rapid circadian re-entrainment as evidenced by greater phase advance shifts, more REM sleep, and fewer sleep disruptions following advance of the sleep schedule. Compared to other studies designed to entrain the circadian clock to a phase advance of sleep, our protocol involved use of a lower illuminance (~450 lux) delivered in an unobtrusive manner (rather than maintaining fixed gaze, sitting in front of a light box, using a Ganzfeld dome). This has broader public health implications for use of similar countermeasures in different populations and environments such that the moderate level of illuminance would likely lead to reduced complaints of headaches, eye strain, or glare on computer screens and result in improved compliance with procedures allowing for greater freedom for the individual. The combination of white light with the green light also prevents the altered color-perception experienced in the green light condition alone and would therefore enable implementation of this technology to ensure circadian synchronization in any number of settings. Importantly, this may provide a lighting countermeasure to sleep and circadian disruption for use more broadly such as in the case of rotating shiftwork, jetlag, and circadian rhythm sleep disorders.

Dr. Czeisler's contributions to this work

This original article reports on findings from one of Dr. Czeisler's numerous research studies investigating the use of light to alter the circadian timing system, align the human biological clock with the external environment and optimize sleep and health. This work builds on a rich literature of previous studies (many from Dr. Czeisler's group) understanding the role of light timing, duration, intensity, pattern, history, and wavelength circadian resetting and is motivated by the goal of designing ways to improve circadian rhythms and sleep, particularly for those most vulnerable to misalignment.

Author contributions

Anne-Marie Chang: Methodology, Investigation, Data curation, Visualization, Writing – original draft. Clare Anderson: Conceptualization, Investigation, Data curation, Writing – review & editing. Sean W. Cain: Conceptualization, Investigation, Writing – review & editing. David A. Reichenberger: Methodology, Formal analysis, Writing – review & editing. Joseph M. Ronda: Software, Resources, Data curation. Steven W. Lockley: Resources, Formal analysis, Visualization, Writing – review & editing. Charles A. Czeisler: Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

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Declaration of conflicts of interest

A-MC has no conflicts of interest to disclose for this work. Outside of the work presented here, A-MC has received a grant to the Pennsylvania State University from Kunasan, Inc., and honoraria/travel support for lectures from the University of Miami.

CA has no conflicts of interest for this work, but in the interest of full disclosure: CA has received a research award/prize from Sanofi-Aventis; contract research support from VicRoads, Rio Tinto Coal Australia, National Transport Commission, Tontine/Pacific Brands, and AAA Foundation; industry funding through ARC Linkage scheme with Seeing Machines and Cogstate Ltd; and lecturing fees from Brown Medical School/Rhode Island Hospital, Ausmed, Healthmed and TEVA Pharmaceuticals; and reimbursements for conference travel expenses from Philips Healthcare. In addition, she has served as a consultant to the Rail, Bus and Tram Union, the Transport Accident Commission (TAC), the National Transportation Committee (NTC), VicRoads, and Melius Consulting. She has also served as an expert witness and/or consultant in relation to fatigue and drowsy driving, and was a Theme Leader in the Cooperative Research Centre for Alertness, Safety and Productivity.

SWC has received research funds from Versalux and Delos, and consulted for Beacon Lighting, Versalux, and Dyson.

DAR has no conflicts of interest to disclose.

JMR has no conflicts of interest to disclose.

SWL reports commercial interests from the last 3 years (2020-2023). His interests are reviewed and managed by Brigham and Women's Hospital and Partners HealthCare in accordance with their conflict-of-interest policies. SWL has received consulting fees from Hintsa Performance AG, Stantec and View Inc, and has consulting contracts with Absolute Rest, Akili Interactive, Apex 2100 Ltd, Ashurst Risk Advisory, Consumer Sleep Solutions, KBR Wyle Services, Light Cognitive; Lighting Science Group Corporation/HealthE; Mental Workout/Timeshifter. He has received honoraria and travel or accommodation expenses from Bloxhub, Clifton College, Danish Centre for Lighting, and University of Toronto; and travel or accommodation expenses (no honoraria) from Wiley; and royalties from Oxford University Press and Monash University. He holds equity in iSleep pty. He has received an unrestricted equipment gift and investigator-initiated grant from F. Lux Software LLC, and a Clinical Research Support Agreement and Clinical Trial Agreement with Vanda Pharmaceuticals Inc. He is an unpaid Board Member of the Midwest Lighting Institute (non-profit). He is part-time adjunct professor at the University of Surrey, UK. He holds several pending (US20190366032; US20210162164 US20220151552) and one awarded (USD943612) patents. He has served as a paid expert in legal proceedings related to light, sleep and health.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.sleh.2023.09.007.

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