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Dynamic lighting schedules to facilitate circadian adaptation to shifted timing of sleep and wake

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Abstract

Circadian adaptation to shifted sleep/wake schedules may be facilitated by optimizing the timing, intensity and spectral characteristics of light exposure, which is the principal time cue for mammalian circadian pacemaker, and possibly by strategically timing non-photic time cues such as exercise. Therefore, circadian phase resetting by light and exercise was assessed in 44 healthy participants [22 females, mean age (±SD) 36.2 ± 9.2 years] who completed 8-day inpatient experiments simulating night shiftwork, which included either an 8-h advance or 8-h delay in sleep/wake schedules. In the advance protocol (n=18), schedules were shifted either gradually (1.6 h/day across 5 days) or abruptly (slam shift, 8 h in one day and maintained across 5 days). Both advance protocols included a Dynamic Lighting Schedule (DLS) with 6.5-h exposure of blue-enriched white light [704 melanopic Equivalent Daylight Illuminance (melEDI) lux] during the day and dimmer blue-depleted light (26 melEDI lux) for 2 h immediately before sleep on the shifted schedule. In the delay protocol (n=26), schedules were only abruptly delayed but included four different lighting conditions: (1) 8-h continuous room-light control; (2) 8-h continuous blue-enriched light; (3) intermittent (7 × 15-min pulses/8 hours) blue-enriched light; (4) 8-h continuous blue-enriched light plus moderate intensity exercise. In the room-light control participants received dimmer white light for 30 min before bedtime whereas in the other 3 delay protocols participants received dimmer blue-depleted light for 30 mins before bedtime. Both the slam and gradual advance protocols induced similar shifts in circadian phase (3.28 h ± 0.37 vs. 2.88 h ± 0.31, respectively, p=0.43) estimated by the change in the timing of timing of dim light melatonin onset (DLMO). In the delay protocol, the continuous 8-h blue-enriched exposure induced significantly larger shifts than the room light control (−6.59 h ± 0.43 vs. −4.74 h ± 0.62, respectively, p=0.02). The intermittent exposure induced ~60% of the shift (−3.90 h ± 0.62) compared to 8-h blue-enriched continuous light with only 25% of the exposure duration. The addition of exercise to the 8-h continuous blue-enriched light did not result in significantly larger phase shifts (−6.59 h ± 0.43 vs. −6.41 h ± 0.69, p=0.80). Collectively our results demonstrate that, when attempting to adapt to an 8-h overnight work shift, delay shifts are more successful, particularly when accompanied by a DLS with high melanopic irradiance light stimulus during wake.

Introduction

Many physiological processes are under circadian regulation (as reviewed in [1–6]). Disruption of circadian rhythms are associated with impaired neurobehavioral performance (e.g., [7–9]), adverse health outcomes (e.g., [10–12]) and increased risk of errors and accidents (e.g., [13–16]). Light exposure is the most robust environmental time cue for resetting the central circadian clock in humans [17, 18]. The magnitude of these resetting effects depend on the intensity [19], timing [20, 21], spectral composition [22], duration [23, 24], pattern [25–27] and history of light exposure [28]. The circadian system of shiftworkers rarely adapts to the changes in sleep-wake and light/dark cycles associated with working night shifts and therefore circadian disruption and sleep loss are common, and likely contribute to adverse health and safety outcomes [29–33].

Improved lighting schedules remain the most promising countermeasure to facilitate circadian adaptation to shiftwork (e.g., [34–38]). Specifically tuning the lighting characteristics may optimize lighting countermeasures for circadian phase resetting (e.g., [34–44]). Both duration and irradiance of light exposure follow a non-linear relationship with circadian phase resetting such that short-duration (i.e., several minutes) and indoor illuminance (~100 lux) exposures induce robust phase resetting that is approximately half of the maximal response that can be attained with long duration (~6 h) and very bright (10,000 lux) exposures [19, 23, 24]. Intermittent light exposures also induce responses that are non-linear with respect to light duration; for example, six 15-minute pulses of 10,000 lux light delivered over 6.5 hours induce ~75% of the phase resetting induced by a single 6.5-hour continuous bright light pulse, despite having only 23% of the duration [26, 27]. The timing of light is also crucial: light exposure in the early part of the night in normally entrained individuals induces phase delays whereas exposure in the morning shortly after the circadian nadir of the core-body temperature rhythm (approximately 7 to 8 hours after the onset of melatonin secretion) induces phase-advance shifts, and therefore, light needs to be appropriately timed to induce the desired shift [20, 45]. Finally, the spectrum of light used is also an important consideration. The principal photoreceptors that mediate circadian phase resetting are the intrinsically photosensitive retinal ganglion cells (ipRGCs), which express the photopigment melanopsin that is preferentially sensitive to short-wavelength (λ_{max} ~480 nm) blue light [46–51]. Therefore, light enriched with short-wavelengths induces more robust phase resetting [45], whereas light depleted in the short-wavelength range induces less phase resetting and stimulant effects [52–54]. Manipulating these properties, including varying them over time to create dynamic lighting schedules, can improve and possibly optimize circadian phase resetting and promote circadian adaptation to shifted sleep-wake schedules.

Non-photic cues such as the timing of daily exercise have also been shown to induce modest shifts in the timing of the central pacemaker [55–61]. Several studies have reported significant phase delays of the central pacemaker in humans induced by high- to moderate-intensity exercise conducted overnight [55, 56, 61], although some studies examining the interaction between bright light exposure and exercise have failed to observe an additive response [58, 62].

In the current study, we examined multiple approaches to resetting the circadian clock to facilitate adaption to a typical overnight shift experienced by shiftworkers. First, we compared two interventions designed to phase advance the clock by implementing a dynamic lighting schedule with blue-enriched (high melanopic) white-appearing light during most of the wake episode and blue-depleted (low melanopic) white-appearing light shortly before sleep in concert with either a gradual (over 5 days) or an immediate ('slam') 8-hour advance of the sleep-wake schedule. Immediate (slam) shifts are commonly applied in various shift work settings, even outside of spaceflight. Second, we compared multiple dynamic lighting interventions designed to facilitate an 8-hour immediate phase delay of the sleep-wake schedule, including a continuous 8-hour blue-enriched white light exposure with and without intermittent exercise, an intermittent blue-enriched light exposure, and a continuous background lighting control. We hypothesized that the gradual condition would be most effective in the advance group and that the continuous blue-enriched light alone would be most effective in the delay group.

Methods

Participants

We studied 44 healthy individuals (22 females, mean age (±SD) 36.2 ± 9.2 years; Table 1) in an 8-day inpatient protocol in the Intensive Physiology Monitoring Unit in the Center for Clinical Investigation at Brigham and Women's Hospital. All participants had comprehensive physical, psychological and ophthalmologic exams, including a negative Ishihara color blindness test, with nonremarkable results. Before entering the study, participants were instructed to maintain a regular, self-selected sleep schedule (8 h time in bed) and report to a time- and date-stamped voicemail at bedtime and waketime for three weeks. Compliance was confirmed with actigraphy (Actiwatch-L, Minimitter, Inc., NY) for at least seven days prior to admission. Participants were instructed to refrain from use of any prescription, non-prescription and illicit drugs, including caffeine, nicotine and alcohol. Compliance was confirmed by urine and blood toxicology during screening and upon admission. The study was approved by the Partners Human Research Committee (IRB# 2007P002526 and 2013P001288) and all participants provided written informed consent.

Study protocol

Participants were studied in an environment free of time cues (no access to windows, clocks, watches, live television, radio, internet, telephones and newspapers and continually monitored by study staff trained not to reveal time-of-day information). The 8-day study schedule consisted of a baseline day with 8:16 h sleep:wake schedule followed by 5 days with shifted sleep/wake schedules followed by a 30-h constant routine (CR) protocol (detailed below), an 8-h recovery sleep and then discharge (Figure 1A to F).

Sleep was shifted either 8 h earlier (advance protocols) or later (delay protocols) relative to each participant's centered average self-selected bedtime maintained in the week prior to the inpatient protocol. There were two types of advance protocols; either a gradual shift of scheduled sleep by 1.6 h each day over 5 days for a total of 8 h advance [Gradual condition (GR); n=9; 5F] or an abrupt shift of scheduled sleep by 8 h ['slam' condition (SL); n=9; 4F]

(Figure 1). Both advance protocols included a Dynamic Lighting Schedule (DLS) with 6.5-h exposure of blue-enriched white light during the day and dimmer blue-depleted light for 2 h immediately before sleep during the first four days on the shifted schedule.

In the delay protocols, scheduled sleep was shifted 8 h later abruptly ('slam') also starting on the second day of the protocol. There were four types of delay 'slam' protocols, all with an immediate shift of scheduled sleep by 8 h but varying lighting conditions and physical exercise on the first days with the shifted schedule. The four protocols consisted of: (1) 8 h of blue-enriched white light (LE n=7; 4F), (2) 8 h of blue-enriched white light with the addition of intermittent moderate-intensity exercise (LE-EX, n=7; 3F), (3) intermittent (IM) exposure to 7 cycles of 15-min pulses of blue-enriched lighting over the same 8 hours as the 8-h continuous blue-enriched exposure condition (n=6; 3F), and (4) a room-lighting (RM) control condition with 8 h of continuous indoor-intensity white light exposure over the same 8 hours as the 8-h continuous exposure condition (n=6; 3F). All participants except those in the RM condition were exposed to 2 hours (advance) or 30 minutes (delay) of dimmer blue-depleted light prior to bedtime (Figure 1). Participants in the RM condition received dimmer white light for 30 min before bedtime. Whenever participants were awake and not under waketime or pre-bedtime experimental light exposure conditions, they were exposed to ambient lighting. All lighting conditions are detailed below.

During the 30-h CR participants remained awake in constant semi-recumbent posture in dim light with daily nutrition intake divided into hourly portions (150 mEq Na+/100 mEq K+ (± 20%) controlled nutrient, isocaloric [basal energy expenditure x 1.3] diet, 2,500 mL fluids/24h).

Lighting Conditions

Ambient lighting: The light intensity was approximately 23 μW/cm^2 (~55 melEDI lux†, ~89 lux) at 137 cm from the floor in the vertical plane and had a maximum of 48 μW/cm^2 (~93 melEDI lux, ~150 lux) at 187 cm from the floor in the horizontal plane anywhere in the room. On the first day, beginning 6 hours immediately prior to sleep, and during the 30-h CR, maximum ambient light was decreased to approximately 0.87 μW/cm^2 (~2 melEDI lux, ~3.3 lux) at 137 cm from the floor in the vertical plane and had a maximum of 4.8 μW/cm^2 (~9 melEDI lux, ~15 lux) at 187 cm from the floor in the horizontal plane anywhere in the room. Additional radiometric and photometric information are provided in Table 2. Ambient room lighting was generated using ceiling-mounted 4100 K fluorescent lamps (melDER ~0.6[1]) (F96T12/41U/HO/EW, 95W; F32T8/ADV841/A, 32W; F25T8/TL841, 25W; Philips Lighting, The Netherlands) with digital ballasts (Hi-Lume 1% and Eco-10 ballasts, Lutron

†As the 'non-visual' responses to light peak at approximately 480 nm, standard photopic illumination measures such as lux or footcandles, which are calibrated for the human color vision (photopic) system (which peaks at 555 nm), do not accurately express the 'strength' of the light stimulus for non-visual responses. While Correlated Color Temperature (CCT, K) has been used as a shorthand to predict the non-visual effects of light (as higher CCT light sources tend to have more short-wavelength light), CCT is also not sufficiently accurate to quantify 'non-visual' light. New standard international (SI) units have therefore been provided by the Commission Internationale de l'Eclairage (CIE, International Commission on Illumination, Austria) to define light for these purposes (CIE, 2018)63. L'eclairage, C.I.D. Cie system for metrology of optical radiation for iprgc-influenced responses to light. Cie s 026/e:2018. In, Vienna (Austria), 2018. and these units are also provided herein, including melanopic Equivalent Daylight (D65) Illuminance (EDI), an estimate of how much light stimulates melanopsin, and the melanopic Daylight Equivalent Ratio (DER), which expresses melanopic EDI as a function of photopic illuminance (lux), and is a useful shorthand for expressing relative differences in light spectra; higher melanopic DER values denote light with more melanopsin stimulation.

Electronics Co., Inc., Coopersburg, PA) transmitted through a UV-stable filter (Lexan 9030 with prismatic lens, GE Plastics, Pittsfield, MA). Regular illuminance and irradiance measures were recorded using an IL1400 radiometer/photometer with an SEL-033/Y/W or SEL-033/F/W detector, respectively (International Light, Inc., Newburyport, MA).

Optimization of light timing using model simulations: Timing of all light exposures, as described below, was informed by simulations of our mathematical model of the effects of light on the circadian system [64, 65]. Model simulations were initialized based on DLMO timing (described below) from 11 participants studied previously using the same baseline procedure [66]. Simulations were performed to test the timing and duration of light exposure that would maximize the phase shift magnitude for each protocol type across all 11 simulated participants. For the advance protocol, light exposure durations from 0 to 6.5 hours and light exposure timing from 0 to 6.4 hours after habitual wake were tested; the final selected timing and duration maximized phase advances (target: 8-hour advance) and minimized the occurrence of a phase shift in the delay direction across all 11 participants. For the delay protocol, a similar approach was used in which initial DLMO was varied over a range from 4 hours prior to habitual bedtime to 1 hour after habitual bedtime in 0.5-hour increments and endogenous circadian period (τ) was varied from 23.5 h to 24.8 h in 0.1-h increments. We did not have preliminary phase delay shift data to test against the model as we did for the advance protocol; therefore, light exposure durations from 4 to 8 hours and light exposure timing from 10 hours before habitual wake to 6 hours before habitual wake were tested; the final selected timing and duration maximized phase delays (target: 8-hour phase delay) and minimized the occurrence of a phase shift in the advance direction across all DLMO/τ combinations. The light input to the model (in photopic lux) and its effect on the circadian system was calibrated based on the phase resetting in response to ceiling-mounted 4100 K fluorescent lamps and does not account for the differential sensitivity of the circadian system to short-wavelength blue light; we estimated 1500 lux as light input to the model during scheduled light exposures was the best approximation for the anticipated effect of ~750 melEDI lux of blue-enriched white LED light.

Experimental lighting for advance protocols: All participants in the phase advance protocols were exposed to high intensity blue-enriched white LED light (~704 melEDI lux, ~260 μW/cm^2, ~750 lux, 0.94 melDER, ~6500 K; measured at the eye 137 cm from the ground and 61 cm away from the source in a seated position at a desk with the lighting modules directly in front of the participant; Table 2); for 6.5 hours beginning on day 2, starting 1.6 h before scheduled wake-time on baseline day 1 and then 1.6 hours earlier each day thereafter until the CR for both the gradual and slam shift. Participants were exposed to dimmer blue-depleted white LED light (~26 melEDI lux, ~18 μW/cm^2, ~52 lux, 0.51 melDER, ~2700 K; measured at the eye 137 cm from the ground and 152 cm away from the source in a semi-recumbent position in bed with the lighting modules directly in front of the participant) for 2 h before bedtime (Table 2).

Experimental lighting for delay protocols: Participants in the delay protocols were exposed to experimental light for 8 hours beginning on day 2, starting 1.6 h before scheduled bedtime on baseline day 1. Seven participants received high intensity blue-enriched light

(as described above for the advance conditions) and six received room-intensity ambient white LED light (~65 melEDI lux, ~29 μW/cm^2, ~94 lux, 0.69 melDER, ~4500 K; measured at 137 cm from the ground and 61 cm from the light source) (Table 2). Participants in the optimized light condition were exposed to dimmer blue-depleted light (as described above) for 0.5 h before bedtime, whereas participants in the standard lighting condition were exposed to dimmer ambient white LED light (~35 melEDI lux, ~16 μW/cm^2, ~52 lux, 0.69 melDER ~4500 K; measured at 137 cm from the ground and 152 cm from the source; Table 2). In the intermittent light exposure protocol, the start and end of the lighting intervention were identical to the continuous light protocol but participants received 7 cycles of 15-min pulses of high intensity blue-enriched white LED light (~704 melEDI lux, ~260 μW/cm^2, ~750 lux, 0.94 melDER, ~6500 K; measured at the eye 137 cm from the ground and 61 cm away from the source in a seated position at a desk with the lighting modules directly in front of the participant; Table 2) every 63 to 64 min over 8 hours. In between the pulses, participants were exposed to the room-intensity ambient white LED light (~65 melEDI lux, ~29 μW/cm^2, ~90 lux, 0.69 melDER, ~4500 K; measured at the eye 137 cm from the ground and 61 cm away from the source in a seated position at a desk with the lighting modules directly in front of the participant).

Experimental light was generated by custom designed four-channel (red, green, blue, white) LED fixtures (Bionetics, VA, USA). Spectrophotometry recordings were made using a PR-650 SpectraScan Colorimeter (CR-650, PhotoResearch Inc., Chatsworth, CA, USA). The spectral power distribution plots for each of the four Correlated Color Temperature (CCT) conditions that comprised the ambient and experimental lighting conditions are presented in Figure 1 G–J. These spectral recordings were used to calculate retinal photopigment weighted illuminances using the Commission Internationale de l'Eclairage (CIE, International Commission on Illumination, Austria) S 026 Toolbox (CIE S 026/E:2018) at 4 nm increments [63]. Results are presented in Table 2.

Exercise protocol

Participants (n=7) in the exercise protocol had all events identical to the continuous blue-enriched light protocol but during the 8-hour LE, each participant completed 3 bouts of exercise, each lasting for 45 minutes, separated by 60 minutes of rest in between. Exercise was completed on all four days of light exposure. The first exercise bout started 3 hours and 10 minutes after the beginning of the light exposure, which corresponded to 10 hours and 10 minutes after wake (18 hours and 10 minutes from habitual wake on baseline days). During each exercise bout, participants were required to pedal at 65–70 revolutions per minute (RPM) on a bicycle ergometer (Cybex model 700R, Cybex, International Inc., Medway, MA), to maintain an intensity of 65–75% of their age-predicted maximal heart rate (208 – 0.7 x age), considered a moderate level of exercise. Each participant wore a heart rate monitor during exercise and was monitored in real-time by a trained research technician to ensure compliance with the exercise intensity (Polar H7 sensor and Polar M450 monitor, Polar Electro, Bethpage, NY).

Circadian phase assessment

Blood samples were collected hourly beginning 6 hours before bedtime on the first day of the inpatient study for 26 hours, and again from the beginning of the CR until the wake time following recovery sleep after the 30-h CR. Saliva samples were collected hourly for the first 6 hours preceding bedtime on the first day of the inpatient study and throughout the 30-h CR. Blood samples were assayed for melatonin; saliva samples were assayed for melatonin in 2 participants [3467V5T1 (RM condition) and 3543V (IM condition)] because of missed blood samples due to IV failure. Blood and saliva samples were not assayed in the same individual. Melatonin concentration was determined using RIA (Kennaway G280 antiserum; Specialty Assay Research Core Laboratory, Brigham and Women's Hospital, Boston, MA). Intra- and inter-assay coefficients of variation (%CV) were 10% at 1.9 pg/mL and 7.2% at 21.9 pg/mL, and 12.65% at 3.06 pg/mL and 12.12% at 22.36 pg/mL, respectively. Circadian phase was determined from the dim light melatonin onset (DLMO), defined as the time at which melatonin levels crossed a 10 pg/mL threshold for plasma or a 4 pg/mL threshold for saliva (time of crossing determined by linear interpolation [67]).

Data analysis

Data are presented as mean ± SE unless stated otherwise. Circadian phase shifts were calculated as the difference in clock time between initial and final DLMO such that advances were positive and delays were negative per convention. Data were analyzed using General Linear Models with lighting condition, age category (age was dichotomized as <40 versus ≥40 years) or sex as main effects, as appropriate. Normal distribution of the primary outcome measure of phase shifts and residuals in regression models was confirmed using the Shapiro-Wilkinson test and visual inspection of QQ-plots, respectively. All statistical analyses were carried out using SAS 9.4 (SAS, Cary, NC).

Results

A subset of the phase resetting data were published previously as part of a secondary analysis comparing phase resetting of central and peripheral metabolic rhythms [68].

Timing of light exposure and relative alignment between circadian phase and sleep

Post-hoc analysis showed that the timing of light onset relative to DLMO on the first day of the experiment was appropriate [45] for advancing or delaying the circadian pacemaker (Figure 2A and B) in all but one individual: the timing of light in one participant in the slam advance protocol (3414V) was mistimed such that the first cycle of light exposure began 6.2 hours after DLMO (~1 hour prior to estimated CBT min, Figure 2A), which is expected to induce phase delays instead of advances. The shift estimated at the completion of 4-cycle light-exposure intervention was −6.7 h phase delay in this individual. Additionally, an initial DLMO could not be calculated in one participant (28E6V2T3) due to missing blood samples due to IV failure during the first scheduled sleep episode, which also precluded determining a DLMO estimate from salivary melatonin as saliva samples were not collected during sleep. Therefore, data from these two individuals were removed from all analyses. On average, light exposure onset occurred 9.11 h ± 0.22 after DLMO in the advance protocols and 1.32 h ± 0.24 after DLMO in the delay protocols.

As an additional indicator of group-level homogeneity in circadian alignment between the study conditions, the initial DLMO phase relative to start of scheduled bedtime (phase angle difference, PAD) was not significantly different among all protocols (Figure 2C), which was on average −2.47 h ± 0.17 before bedtime (range −4.92 – 0.43 h). In contrast, the final PAD was significantly different between advance (2.20 h ± 0.25) and delay protocols (−4.82 ± 0.41, $p<0.0001$, Figure 2D).

Timing of exercise relative to circadian phase and exercise characteristics

Post-hoc analysis showed that the timing of the first bout of exercise relative to DLMO on the first day of the experiment was, on average, 4.88 h ± 0.45 after DLMO (range 3.77 – 7.09 h). When averaged across all exercise bouts, the mean intensity achieved was 68.82% ± 0.85 of age-adjusted maximum heart rate, and light exposure at the level of the eye during the exercise was 750.17 ± 19.88 lux (~704 melEDI lux).

Phase shift

Phase delay shifts were larger than phase advance shifts, for these particular light levels and exposure times, with considerable inter-individual differences within each condition (representative melatonin profiles are shown in Figure 3A–F), although a direct comparison between phase advance and delay shifts could not be made due to differences in protocol including different durations of light exposure. At the end of the 4 days of shifted sleep-wake routine, all light exposure conditions resulted in statistically significant resetting of DLMO relative to initial phase (all, $p<0.002$, Figure 3G), and all shifts were significantly more than a 1 hour (which is what would have been expected if there were only a daily “drift” in phase of 0.2 h per day predicted from average intrinsic period) [69]. The phase shifts were not different between the two phase-advance protocols (GR: 2.88 h ± 0.31, SL: 3.28 h ± 0.37, $p=0.43$) (Figure 3G). In contrast, phase shifts were significantly different among the 4 phase-delay protocols with the largest mean phase-delay shifts observed in the LE condition and the smallest in the IM condition (IM: −3.90 h ± 0.62, RM: −4.74 h ± 0.62, LE-EX: −6.41 h ± 0.69, LE: −6.59 h ± 0.43, $p=0.005$) (Figure 3G). The mean shifts in the IM and RM conditions were not statistically different from each other ($p=0.31$) (Figure 3G). Likewise, the mean shifts in LE-EX and LE conditions were not statistically different from each other ($p=0.80$), although the LE-EX and LE conditions were both associated with significantly larger shifts than the IM and RM conditions ($p<0.05$) (Figure 3G).

Effect of age and sex

Since circadian characteristics including phase and phase angle of entrainment are different between younger and middle-aged groups and between men and women [70–73], we conducted exploratory analyses to evaluate whether age, sex or their interaction were independent predictors of phase resetting in the advance or delay protocols. In the advance protocols, women had larger phase-advance shifts than men (3.52 ± 0.29 and 2.55 ± 0.33 hours, respectively, $p=0.047$, Figure 3H) but age (dichotomized as younger or older than 40) or the interaction between sex and age were not different ($p=0.60$ and 0.15, respectively, Figure 3H and I). In contrast, in the delay protocols, age had a significant effect on phase resetting with younger participants shifting more (5.90 ± 0.38 and 4.26 ± 0.63 hours,

respectively, p=0.035, Figure 3I), but sex or the interaction between sex and age did not differ between groups (p=0.89 and 0.38, respectively Figure 3H and I).

Discussion

In the current study, we examined whether the timing, intensity and spectra of lighting can be optimized to facilitate circadian adaptation to shifted sleep/wake schedules similar to transitions between typical day and overnight shifts. We also assessed whether strategically timed physical exercise along with light exposure may further enhance circadian adaptation to shifted sleep/wake schedules. When optimized in intensity and spectral characteristics and timed strategically to delay the circadian clock (using a mathematical model), light exposure promoted robust circadian adaptation (86% of target 8-hour shift). Intermittent bright light exposure was more efficient per minute than continuous exposure (inducing ~60% of the circadian adaptation with only 25% of the total duration) but was significantly less effective in absolute terms. The addition of intermittent moderate-intensity exercise did not induce any additive circadian adaptation. These results support the use of dynamic lighting schedules that delay the circadian pacemaker to promote adaptation to shifted sleep-wake schedules, as occurs in the transition from day to evening or night shift.

The ‘slam’ phase delay protocols with 8 h of continuous blue-enriched white light achieved nearly the full targeted phase shift; the average shift was −6.6 h with a range from −5.0 to −8.2 h. When exercise was added, there was no additional net shift (average −6.4 h) and the range was similar (−3.8 to −8.9 h). This result was similar to the average phase delay of −7.3 h of the melatonin rhythm in young participants achieved in a 3-day slam shift with 5 h of 5,700 melEDI lux (9,500 lux, 4100K) [74] and with 5 hours of 6,000 melEDI lux (10,000 lux, 4100K) in younger and older participants (−6.6 h and −6.8 h, respectively; [75]).

In contrast, the advance shift protocol was qualitatively less effective (~3 h shift in response to the 8-hour target), regardless of whether there was an abrupt or gradual shift in the sleep/wake light/dark schedule was used. Importantly, however, while we were able to time the light exposure appropriately to induce phase advances or delays, and tried to stimulate maximal shifts, we did not explicitly attempt to time the light exposure relative to the phase response curve (PRC) that would induce equal advance or delay shifts, which likely contributes to the qualitatively less circadian adaptation observed in the advance protocols. Robust phase advances, however, are possible with very bright light. In earlier work, a similar protocol that gradually advanced the sleep-wake cycle by 10 hours (2 hours per day for 5 days), showed that 5–8 hours/day of ~6,000 melEDI lux (10,000 lux, melDER ~0.6, 4100K) shifted central circadian markers by at least 8 hours earlier whereas modest lighting ~90 melEDI lux (150 lux, melDER ~0.6, 4100K) had no significant resetting effects (~1 h; [76]). While differences between the protocols in our study and the previous studies make direct comparisons difficult, the combined data are consistent with a dose-response for the phase advancing effects of gradual-shifts in light exposure [~90, ~450, and ~6,000 melEDI lux (150, 750 and 10,000 lux) exposure once per day over 4 to 5 days with ~1.6 hour shifts in the sleep schedule resulted in ~1 h, 3 h and 8 h net phase advances, respectively]. Our data also are consistent with the intensity-dependent phase advancing effects of light following an 8-hour ‘slam’ shift [74, 77]; our ~3 h shift to 6.5 h of ~704 melEDI lux (750

lux) over 4 days falls on the dose-response generated by 3 days of exposure to 5 hours of 0.02–5,700 melEDI lux (0.03–9,500 lux, 4100K, melDER ~0.6) of light timed to phase advance.

We and others have shown that intermittent light-exposure patterns achieve majority (~60–70%) of the phase resetting as continuous exposure [27]. For example, six 15-min pulses of bright light pulses delivered across a 6.5-h window induces ~70% of the phase resetting response of a 6.5-h continuous exposure administered at the same circadian window in a single night, despite the actual bright light stimulus in the combined intermittent pulses being 23.1% of the continuous 6.5-h exposure [27]. The same protocol using intermittent monochromatic blue (460 nm) light delivered 57% of the shift of continuous exposure [25], consistent with the current study using blue-enriched white light. Intermittent phase advancing light is equally efficient as delays, ranging between ~63% to ~86% on average, depending on the relative duration of the continuous bright light exposure [78].

Exercise in humans has also been reported to influence the central circadian timing system and several studies have assessed the effectiveness of exercise as a circadian phase resetting agent in humans [55–58, 61, 62, 79, 80]. Consistent with our findings, however, studies that have examined the interaction of exercise and bright light on circadian rhythms in humans found that adding exercise to bright light does not appear to induce an additive response [58, 62]. Our exercise protocol was consistent with a prior study [61] that reported significant circadian phase delays of the melatonin rhythm induced by exercise alone administered during the biological night for 7 consecutive days, although the timing of exercise was ~2 hours later relative to initial endogenous circadian phase, which may have contributed to smaller phase shifts due to exercise in our protocol. Whether there is a more optimal timing for the exercise intervention to be combined with light exposure to facilitate circadian adaptation warrants further evaluation in future studies; however, a recently developed phase response curve of circadian resetting by exercise suggests that critical window for exercise to phase delay or advance the central clock may be limited to about three hours for each direction of shift [57]. Therefore, optimally combining exercise with light to facilitate phase resetting may require exquisite timing and may not prove to be feasible in an operational setting. There may be additional benefits of incorporating exercise as a shiftwork countermeasure, however. For example, exercise increases physiological arousal and can help promote alertness in the short-term [60, 81]. Additionally, while we and others have evaluated the role of exercise in resetting the central circadian clock using the timing of the melatonin rhythm as the main outcome measure, additional studies are required to assess whether exercise is a potential non-photic cue for resetting other circadian rhythms, especially metabolic rhythms.

We also observed condition-specific effects of age and sex on circadian phase resetting. The lack of an age-dependent difference in phase advance responses is consistent with the results of a previous study with an 8-hour ‘slam’ advance over 3 days with 5 hours of 6,000 melEDI lux (10,000 lux) white light, which also did not observe an effect of age on phase advance resetting [75]. One possible reason for the differences is that the endogenous period of the human circadian pacemaker is, on average, greater than 24 h (~24.2 hours [69, 71]); this facilitates delay shifts over advances. Our exploratory analysis evaluating sex

differences in phase resetting is consistent with an effect of circadian period; on average, women have a shorter endogenous circadian period (24.09 h) compared to men (24.19 h) [71], and we found that women had larger phase advances than men. Interestingly, we also found that the younger individuals (ages 25–40 years), on average, had significantly larger phase-delay shifts than the older (ages >40–55 years) individuals. Younger individuals do not, on average, however, have longer endogenous periods than older individuals [73], even though they tend to have a later circadian phase and are evening chronotypes [70, 73]. In our study, however, initial circadian phase and phase angle of entrainment prior to intervention were not different between the younger and older age groups. Therefore, it is unlikely that the larger phase delays observed in the younger age group can be attributed solely to baseline differences in circadian characteristics between the two age groups.

A potential difference in the age groups may be differences in lens transmission, with aging leading to reduced transmission of short-wavelength light due to yellowing of the lens, which can in turn lead to attenuated light responses [82, 83]. Although we did not see a similar difference with age in the advance-shift protocols it may have been masked by the overall smaller phase shifts in this protocol compared to the delay-shift protocols. While hypothesis generating, these results need to be interpreted with caution and require further evaluation in future studies as both sex- and age-differences are key considerations in designing effective shiftwork countermeasures. Operationally, shift workers prefer delaying shifts over advancing shifts [84]. Overall, our results are consistent with prior observations and underscore that even with optimized lighting and strict scheduling of the light/dark schedule it may be difficult to achieve circadian adaptation to advancing work schedules. This is an important consideration when designing shift schedules in applied settings where shift workers may require both advances and delays in their schedules with less than optimal control over the their light dark schedules and lighting conditions.

There are several strengths of our study. The light exposure and exercise interventions were carried out under controlled laboratory conditions with monitoring to ensure compliance. Circadian phase assessments were based on quantification of plasma and salivary melatonin, a reliable and accurate marker of central circadian phase in humans. Final phase assessments were assessed under a ~30-h constant routine protocol ensuring that even large phase shifts would not lead to phase estimates being missed. Additionally, both advance and delay shifts were assessed. There are several limitations, however. Our study is based on healthy entrained individuals with no prior history of shiftwork. Future studies need to extend these findings to shift workers of different ages, medical conditions, prescription and non-prescription drug use, and habits (e.g., caffeine use) and under field conditions, although mixed field and laboratory data of simulated shiftwork using 6,000 melEDI lux (10,000 lux of white light, 4100K) are broadly consistent with our findings [85]. Our sample sizes were limited within each experimental condition and further work is necessary with larger sample sizes with adequate statistical power to confirm the exploratory findings related to sex- and age-dependent differences.

Circadian disruption similar to that studied here during simulated shiftwork is also common during space missions. Data from Space Shuttle Missions STS-90 and STS-95 showed that crew members failed to synchronize to an advance shift in their sleep-wake schedule [86].

This may have been mostly due to suboptimal lighting conditions that included dim ambient lighting with intermittent exposure to bright light due to the 90-min orbital solar light-dark cycle. International Space Station (ISS) crewmembers, who are occasionally exposed to rapid shifts in their sleep-wake schedules, spend about 20% of their time sleeping and waking at an adverse circadian phase [87], increasing their potential for accidents and errors. Lighting interventions to facilitate circadian adaptation of crew members prior to launch have been used as a countermeasure since early 1990. Carefully timing bright (10,000 lux) long-duration (~8 hours) light exposure and darkness can facilitate rapid circadian adaptation of ~12 hours in 3 days [35]. These protocols posed practical challenges, however, often associated with the high illuminance used (e.g., ~10,000 lux) which can produce glare, impair visual acuity, and induce headaches, nausea and irritability. Moreover, energy constraints during flight often precludes access to higher irradiance light sources [88, 89].

The current study utilized a prototype of a new, tunable multi-LED lighting source being installed on the ISS that is being operationalized with three settings: i) general illumination: 4500K white light, ~210 lux; ii) phase shifting/alertness: 6500K, ~420 lux; iii) pre-sleep: 2700K, ~90 lux [90]. The recent international standard for measuring light related to circadian, neuroendocrine and neurobehavioral responses permits the conversion of the NASA illuminances to melEDI lux values of ~145, ~395 and ~46, respectively [63]. The study was designed to test various light schedules to facilitate the 8-hour gradual or slam shifts often required in anticipation of upcoming mission tasks such as docking and undocking [86]. Overall, our results suggest that dynamic lighting schedules facilitate circadian adaptation to delay shifts in sleep-wake and work-rest schedules and would be a more appropriate operational approach. While the precise timing will depend on the shift schedule employed, we would reiterate the recommendation of a recent expert review [91], with a minimum of 250 melanopic EDI lux at the eye while awake (including at work) and, once at home, <10 melanopic EDI lux for the 3 hours before bed, or as long as possible before sleep after arriving home after an evening or night shift, if less than 3 hours. There does not appear to be a difference between gradual and abrupt shifts when advancing sleep-wake schedules. Whether delay schedules are differentially affected by gradual or abrupt shifts cannot be determined from our study and should be the focus of future studies, along with further refinement of individual circadian timing, light intensity and light duration to achieve full responses in all individuals.

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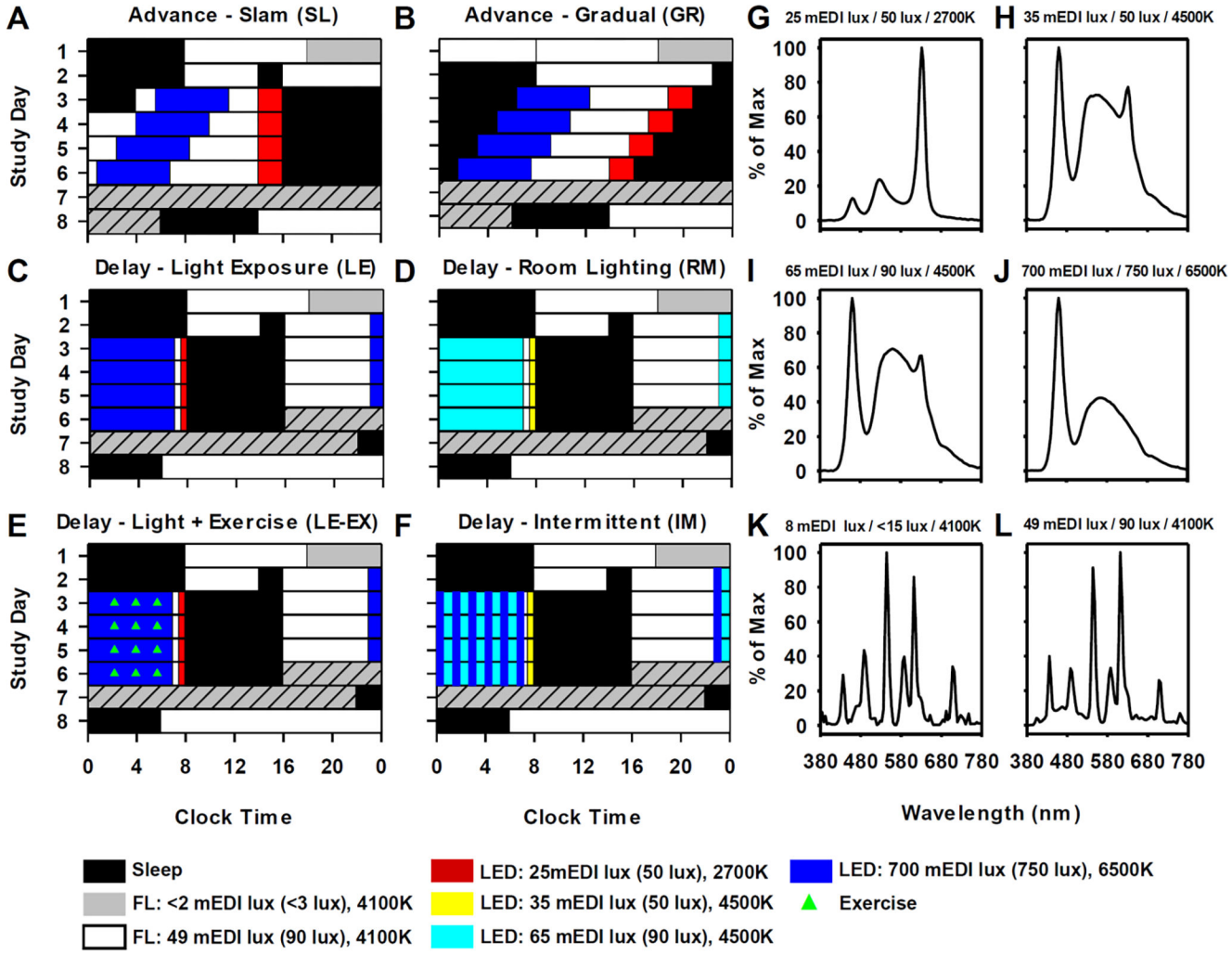

Figure 1. Study protocol and spectral power distribution diagrams.

Representative study protocol rasters (A-F) for participants scaled for a self-selected habitual bedtime of midnight to 8 am. Black represent scheduled sleep episodes. Colored and white bars represent scheduled wake under different lighting conditions. Hashed bars represent the 30-h constant routine interval. Spectral power distributions for all lighting conditions used in the study are shown in G-L. Note that total light irradiance varied within in each of the lighting conditions, but only the highest irradiance used in each light condition is shown for presentation purposes.

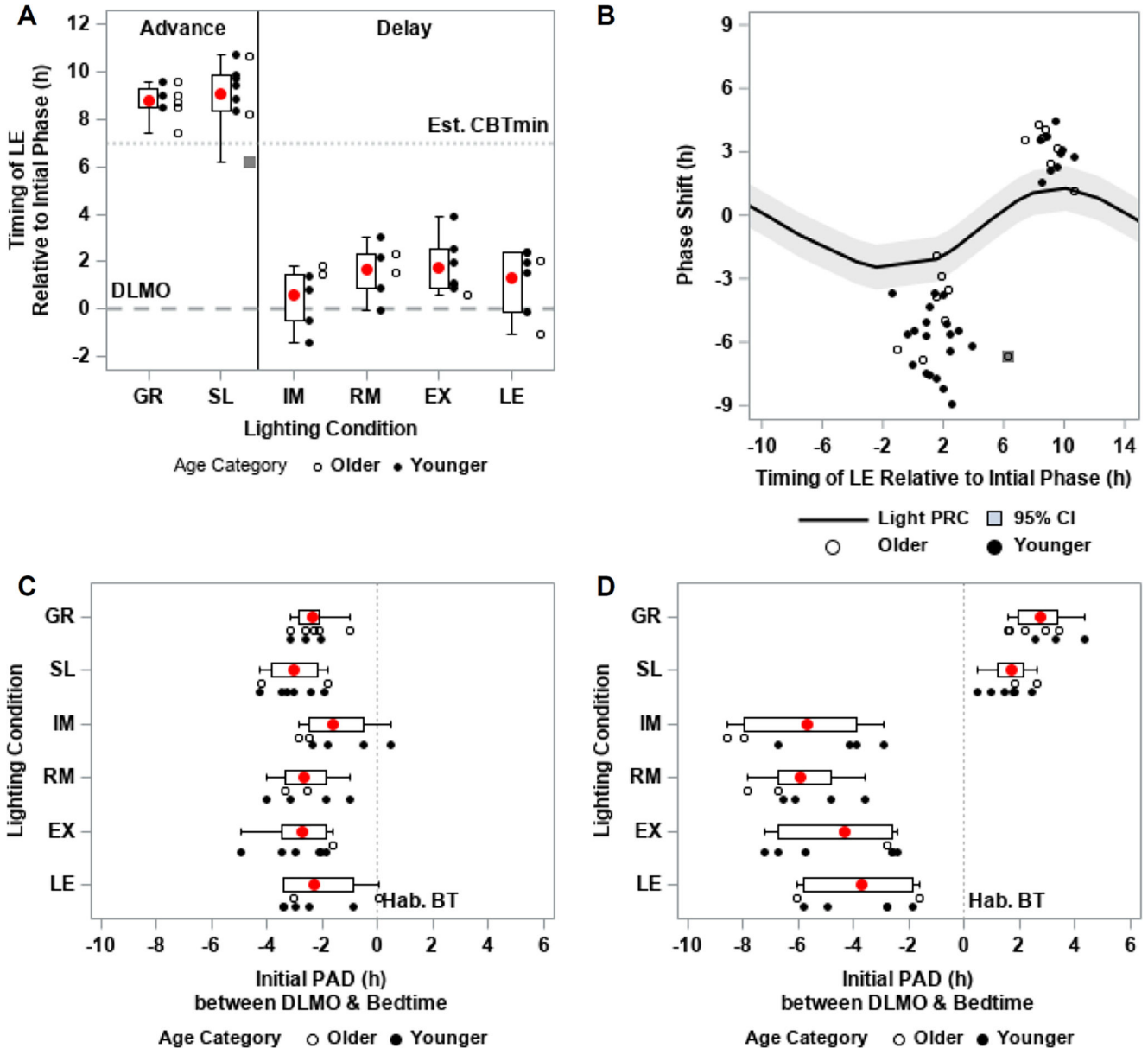

Figure 2. Timing of light exposure and relative alignment between circadian phase and sleep.

The distribution in the onset of the time of the first of four cycles of light exposure (LE) relative to initial circadian phase (DLMO: dim light melatonin onset) for each participant in each of the 6 protocols is shown (A). The box and whisker plots show the mean (symbols within the box), 25th and 75th percentile (box limits), and the 10th and 90th percentiles (whiskers). Dashed horizontal lines indicate circadian phase of 0 (DLMO: dim light melatonin onset), dotted horizontal lines indicate estimated minimum of the core body temperature rhythm (calculated as DLMO + 7 hours) [92, 93]. The starting time of LE relative to initial circadian phase for each participant is also shown with the previously published phase response curve (PRC) [45] for melatonin phase shifts derived from a single 6.5-hour exposure to 480-nm blue light exposure (B). Gray filled squares (■) in and A and B show the timing of LE relative to initial circadian phase in participant 3414V who was

excluded from all analyses due to LE being mistimed. The distribution of initial and final phase angle difference (PAD) in hours between endogenous circadian phase (DLMO) and the start of scheduled bedtime of each participant stratified by age category is shown in (C) and (D), respectively. Initial and final PAD were compared between advance and delay protocols using GLM. The box and whisker plots show the mean [filled red circle (●) within the box], 25th and 75th percentile (box limits), and the 10th and 90th percentiles (whiskers). Unfilled circles (○) and black filled circles (●) below each box show data from individual participants, stratified into older and younger age-categories, respectively. GR: Gradual, SL: slam, IM: Intermittent, RM: Room light, LE-EX: Light Exposure and Exercise, LE: Light exposure.

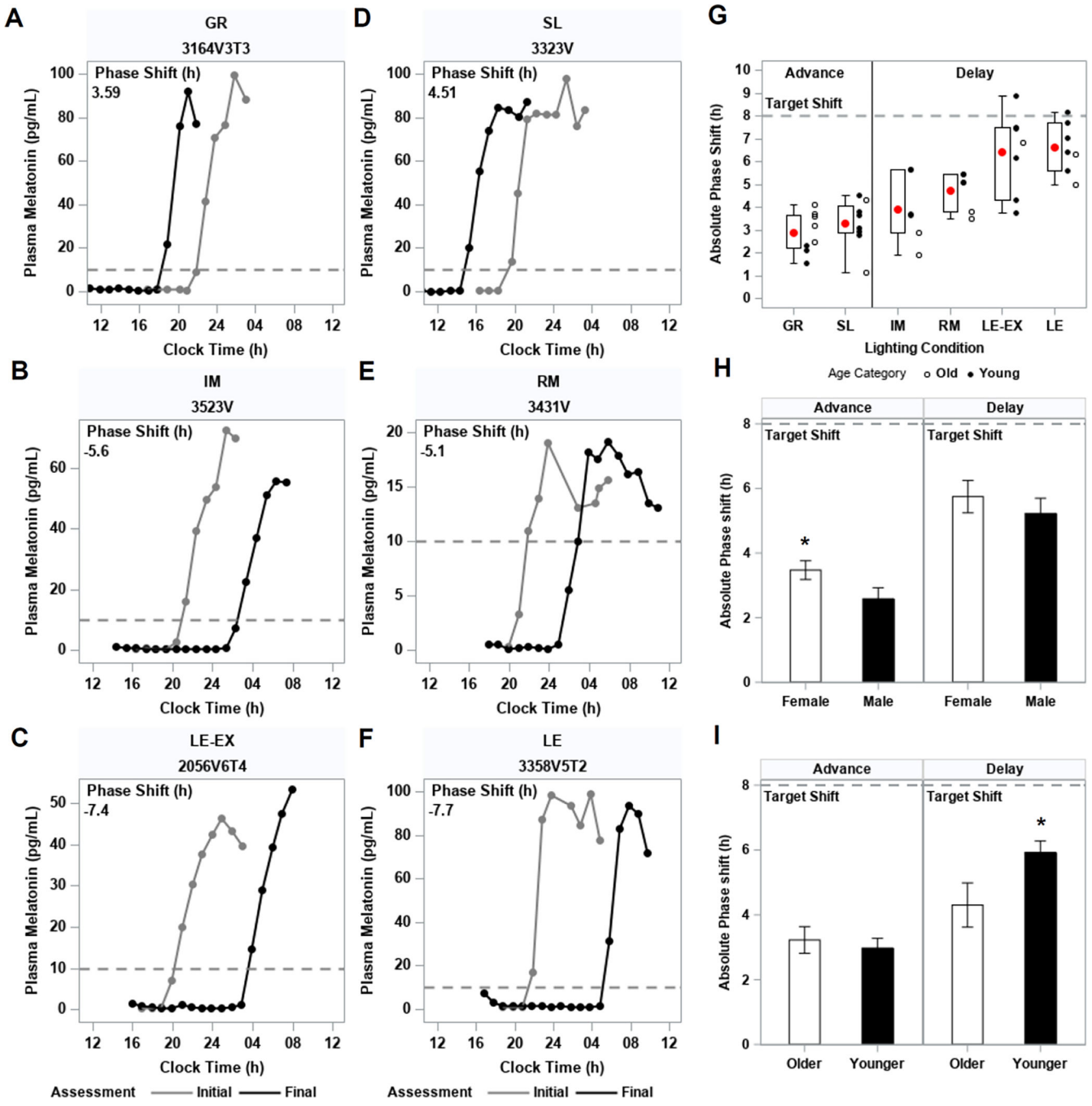

Figure 3. Individual and group-level circadian phase resetting.

Representative melatonin profiles from participants studied in each of the six protocols are shown in Figures 3A–F. Gray and black lines represent initial and final partial melatonin profiles for each participant, respectively. Gray dashed line indicates the 10-pg/mL threshold used to determine the onset of melatonin secretion under dim light (DLMO). The distribution in phase resetting in each of the 6 study protocols is shown in absolute hours of shift (G). Phase shift data were compared between conditions within each type of phase-shift protocol (i.e., advance or delay) using GLM with condition as the main effect. The box

and whisker plots show the mean (symbols within the box), 25th and 75th percentile (box limits), and the 10th and 90th percentiles (whiskers). Unfilled circles (○) and black filled circles (●) beside each box show data from individual participants, stratified into older and younger age-categories, respectively. Horizontal dashed line indicates target shift of 8 hours. Group mean (±SE) phase resetting stratified by sex and dichotomized age category pooled within the advance and delay protocols are shown in (H) and (I), respectively. Phase shift data were pooled between conditions within each type of phase-shift protocol (i.e., advance or delay) and tested for main effects of sex and age-category and their interaction using GLM. Post-hoc comparisons were Tukey-adjusted. M: Male F: Female, O: Older, Y: Younger. GR: Gradual, SL: slam, IM: Intermittent, RM: Room light, LE-EX: Light Exposure and Exercise, LE: Light exposure. * Signifies $p<0.05$.

Table 1.

Demographics and circadian phase of individual participants

ID	Age (years)	Sex	Protocol	Condition	Habitual Wake Time (hh:mm)	Initial Phase (hh:mm)	Final Phase (hh:mm)	Phase Shift (hours)
30H1V2T2	29	M	Advance	GR	7:02	20:56	18:23	1.56
3214V2T2	30	F	Advance	GR	6:11	19:35	16:28	2.11
3340V	26	F	Advance	GR	6:04	18:56	15:36	2.33
3183V3T2	42	M	Advance	GR	6:52	20:15	17:46	2.49
3351V	43	M	Advance	GR	5:54	18:45	14:33	3.20
3164V3T3	46	F	Advance	GR	7:50	22:50	18:15	3.59
3333V	44	F	Advance	GR	7:00	20:53	16:11	3.70
3365V	46	F	Advance	GR	4:16	17:57	13:50	4.11
28E6V2T3 *	30	M	Advance	GR	8:33	-	-	-
3414V	55	M	Advance	SL	7:14	23:26	5:05	−6.65
3324V	44	M	Advance	SL	7:52	19:39	17:30	1.16
3314V	30	F	Advance	SL	8:02	19:45	15:58	2.78
3379V	39	M	Advance	SL	7:02	19:45	16:48	2.95
3332V	30	M	Advance	SL	7:19	19:51	15:45	3.10
3308V	25	M	Advance	SL	7:51	21:53	18:15	3.63
3357V	36	F	Advance	SL	8:05	21:39	16:52	3.79
3341V	49	F	Advance	SL	7:39	21:49	16:29	4.33
3323V	26	F	Advance	SL	7:16	20:15	14:44	4.51
3515V	27	F	Delay	IM	5:58	20:08	0:48	−5.67
3523V	27	F	Delay	IM	6:24	21:51	2:29	−5.62
3534V **	26	M	Delay	IM	7:00	23:26	2:06	−3.68
3507V5T2	30	M	Delay	IM	7:03	20:39	23:18	−3.65
1317V5T3	52	M	Delay	IM	7:00	20:09	22:01	−2.86
3543V	51	F	Delay	IM	6:32	20:02	20:55	−1.88
3506V	30	F	Delay	RM	6:53	18:51	0:18	−5.44
3447V	36	M	Delay	RM	6:00	21:00	1:26	−5.42
3431V	27	M	Delay	RM	9:58	22:46	2:52	−5.09
3467V5T1 **	30	F	Delay	RM	8:15	22:23	3:26	−5.06
3545V	44	F	Delay	RM	5:30	18:58	21:44	−3.78
3443V	53	M	Delay	RM	6:00	18:39	21:09	−3.50
3635V7T3	31	F	Delay	EX	8:30	21:00	5:51	−8.86
3381V7T2	28	M	Delay	EX	10:02	23:56	7:26	−7.49
2056V6T4	37	M	Delay	EX	6:59	21:07	3:33	−7.43
3624V6T2	43	M	Delay	EX	5:29	19:52	1:41	−6.81
3661V6T3	28	F	Delay	EX	7:32	18:36	23:47	−6.17
3625V6T2	29	F	Delay	EX	6:57	20:54	0:13	−4.32

ID	Age (years)	Sex	Protocol	Condition	Habitual Wake Time (hh:mm)	Initial Phase (hh:mm)	Final Phase (hh:mm)	Phase Shift (hours)
3664V	33	M	Delay	EX	6:00	19:01	21:47	−3.77
3437V	28	F	Delay	LE	7:25	20:26	3:36	−8.16
3358V5T2	29	M	Delay	LE	7:51	21:20	5:02	−7.71
3469V5T2	37	F	Delay	LE	7:58	23:04	6:05	−7.02
3747V	30	F	Delay	LE	6:44	19:21	0:46	−6.43
3448V	55	F	Delay	LE	6:10	22:13	3:31	−6.31
3439V	35	M	Delay	LE	7:59	20:35	1:10	−5.57
3416V2T3	48	M	Delay	LE	7:01	19:58	23:57	−4.98

*An initial DLMO could not be calculated due to missing blood samples due to IV failure during the first scheduled sleep episode.

**Salivary melatonin

TABLE 2.

Calculated and measured characteristics of the light sources studied *

Lighting condition	Radiometric and Photometric Values (380–780 nm inclusive)				Retinal Photopigment Weighted Illuminances (α-opic EDI lux)					
	Photon flux photons/m^2/s	**Irradiance μW/cm^2**	**Photopic Illuminance lux**	**Measured CCT**	**S Cone**	**Rod**	**M Cone**	**L Cone**	**Melanopsin**	**DER**
4100K Ambient <15 lux[a]	1.35×10^{17}	4.6	12.2	3082K	5.3	8.5	10.3	12.6	8.1	0.66
2700K Pre-bed 50 lux[b]	5.28×10^{17}	17.8	51.6	2533K	14.8	30.8	40.2	52.9	26.3	0.51
4100K Ambient 90 lux[c]	7.25×10^{17}	25.3	78.0	3583K	42.6	53.4	67.4	78.8	48.6	0.62
4500K Control 90 lux[c]	8.23×10^{17}	29.1	94.0	4582K	59.5	69.3	85.2	93.1	64.6	0.69
4500K Pre-bed 50 lux[a]	4.50×10^{17}	15.9	51.4	4534K	31.2	38.2	46.8	50.8	35.4	0.69
6500K Active LE 750 lux[c]	7.16×10^{18}	260.0	750.8	6398K	794.3	690.5	724.2	751.1	703.8	0.94

*Values were derived from the CIE S 026 α-opic Toolbox – v1.049 – 2020/03/26 [63].

[a]Measures were taken 183 cm from the ground in the horizontal plane.

[b]Measures were taken at a height of 137 cm at the bed, ~152 cm from the light source in the vertical plane.

[c]Measures were taken at a height of 137 cm at the desk, ~61 cm from the light source in the vertical plane.

EDI = equivalent daylight (D65) luminance (lux); DER = daylight (D65) efficacy ratio.