

FINAL REPORT

Title: **Evaluation of Intermittent Bright Light Exposure as a Space Flight Countermeasure**

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INTRODUCTION

In order to enable astronauts to sustain high levels of performance throughout extended duration space missions it will be critical (1) to maintain an appropriate phase relationship of the human circadian pacemaker to the 24-hour sleep-wake/duty schedule aboard the space craft, and (2) to preserve the amplitude of the endogenous circadian timing system. On Earth, the amplitude of the endogenous circadian pacemaker and the phase relationship between the circadian pacemaker and the sleep-wake/duty schedule are preserved by exposure to the 24-hour, robust cycle of light and darkness associated with the Earth's rotation. During extended duration space station and exploration class space missions, astronauts will be exposed to markedly abnormal light/dark cycles in terms of both timing and intensity. Preliminary data suggest that such abnormal light/dark cycles are likely to result in a misalignment between the 24-h sleep-wake/duty schedules and the endogenous circadian timing system. Such circadian misalignment is known to produce sleep disturbances, daytime sleepiness, reduced attention, negative mood, slower reaction times, gastrointestinal disorders, and impaired daytime alertness. To prevent such misalignment, development of effective countermeasures to promote circadian entrainment is needed. Scheduled exposure to 5-h episodes of bright light has been shown previously to induce the necessary phase shifts and amplitude enhancement of the endogenous circadian pacemaker. However, energy and time constraints make such lengthy exposures to bright light impractical aboard the spacecraft.

We have previously shown ² that even room light can have a significant effect on the phase of the human circadian clock. New data we have gathered is now indicating that the human circadian timing system may be even more sensitive to light that we had originally hypothesized. Through support provided in part by the current grant, we recently found that half of the maximum resetting response achieved in response to bright light (~9,000 lux) during the early subjective night (i.e., 3.5 hours before the minimum of core body temperature) can be obtained with just 1% of this light, i.e., ordinary room light of ~100 lux ¹⁹. Moreover, we found that half of the maximum alerting response (estimated by the Karolinska Sleepiness Scale) achieved in response to bright light (~9,000 lux) can be obtained with room light of ~100 lux ⁵. Recent progress derived from experiments supported by our previous NASA grant (NAGW-4033) indicates that three consecutive days of exposure to short, intermittent pulses of bright light have a resetting effectiveness 4.5-5 times greater on a per minute basis than the continuous bright light exposure previously studied ¹⁶. However, these data could not allow us to quantify the effectiveness of a single sequence of intermittent light pulses given on a single day only.

Therefore, based on new data from our laboratory on the dynamics of photic stimulation on melatonin suppression ³ and phase shifting of the clock ¹⁴, the purpose of the project supported by the current grant was to test the hypothesis that a single sequence of six pulses of intermittent bright light exposure (15 minute light pulses separated by one hour of very dim light) administered during the early subjective night (6.5 hour episode of intermittent bright light exposure centered 3.5 hours before the nadir of the fitted endogenous circadian temperature rhythm) would induce a significant phase delay of the endogenous circadian timing system and the physiological variables it controls (i.e., melatonin, cortisol, core body temperature, alertness, and performance). Based on earlier data published by our laboratory ⁷, we anticipated a robust phase delay to continuous light given at this time and no change in phase in the controls who were exposed to continuous very dim light (<1 lux) during the intervention day. Moreover, the limit cycle oscillator model of the human circadian pacemaker developed by Kronauer and coworkers ¹⁴ predicted that the resetting effect of the intermittent light exposure would be more efficient as measured by the amount of shift induced per minute of bright light exposure than continuous bright light exposure. The results from this study are currently being used to refine our current model of the phase-shifting effect of light, and will allow estimation of the optimal duration of bright light needed for maximal phase shifting efficiency. This will lead to the development of a practical and efficient countermeasure to help maintain internal synchrony and prevent disruption of the circadian timing system. The results of the

conducted research have important implications on the health, productivity, and safety of astronauts during extended duration space missions.

MATERIALS AND METHODS

Overview of Study Design:

The purpose of this study was to test three specific hypotheses evaluating the effectiveness of intermittent bright light exposure in resetting the circadian timing system as a countermeasure to circadian misalignment likely to occur during space flight and long-term space missions. Our specific aims were the following:

- 1) Test the hypothesis that a single 6.5-hour episode of intermittent bright light exposure (six 15 minute bright light pulses / 60 minutes of very dim light) centered 3.5 hours before the nadir of the fitted endogenous circadian temperature rhythm will induce a significant phase delay of the endogenous circadian timing system.
- 2) Test the hypothesis that the phase-shifting response per minute of intermittent bright light exposure will be greater than that of continuous bright light exposure.
- 3) Test the hypothesis that the endogenous circadian rhythms of body temperature, plasma melatonin, plasma cortisol, alertness, and performance will phase delay shift by an equivalent amount in response to a single, 6.5 hour episode of intermittent bright light exposure centered 3.5 hours before the nadir of the fitted endogenous circadian temperature rhythm.

Twenty-one subjects (Appendix, Table 1) were empanelled in a randomized clinical trial. Upon admission to the Intensive Physiologic Monitoring (IPM) Unit of the Brigham & Women's Hospital on Experimental Day 1, subjects were maintained in an environment free of time cues until the end of the study on experimental day 10. Physiologic and neurobehavioral monitoring (as described in detail in the Specific Methodology section below) occurred throughout the duration of the study. Subjects were adapted to the laboratory with three baseline days (LD 16:8), during which time they continued to sleep and wake at their habitual times (Figure 1, solid black bars). In order to assess their endogenous circadian phase (ECP), subjects underwent a 26.2-h constant routine (procedure described in Specific Methodology Section) from day 4 to day 5. On day 5/6, a single 6.5-h

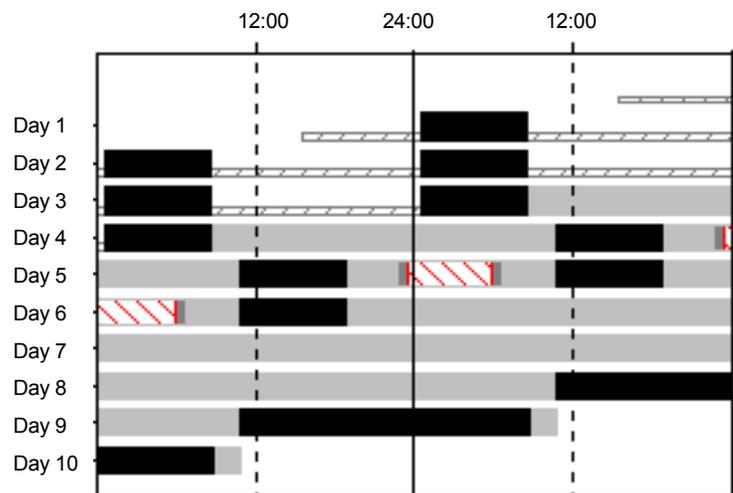


Figure 1: 10-day experimental protocol (double raster plot). Sleep episodes (8 hours) are illustrated as black bars. During the baseline days (days 1-3), subjects were exposed to ~150 lux (thin open gray bars with *inclined* lines). Except during the light exposure session, the subjects were exposed to ~2 lux (large gray bars) for the remainder of the study. A ~ 26.2-h constant routine (CR) was scheduled on days 4-5. The light exposure session (white bar with *inclined* lines) was scheduled on days 5-6, and consisted of 6.5 hours of exposure centered 3.5 hours before CBTmin. Subjects were exposed either to continuous **bright light** (~9,500 lux), **intermittent bright Light** [six 15-minute bright light (~9,500 lux) pulses separated by 60 minutes of very dim light (<1 lux)] or **very dim light** (<1 lux) (see Fig.2 for details of the light exposure sessions). Following the light exposure day, subjects underwent a 64-h CR and were discharged after a ~22-h recovery sleep episode.

light exposure session (Fig.2) was scheduled. Subjects were randomly assigned to either continuous bright light exposure, or to intermittent bright light exposure (Fig.3 for details), or to continuous very dim light exposure (7 subjects in each group) during their light exposure session. Following the light exposure day, subjects were scheduled to a 64-h constant routine to reassess their circadian phase and estimate the phase shift from the first ECP estimation. They were then discharged after a ~22-h recovery sleep episode.

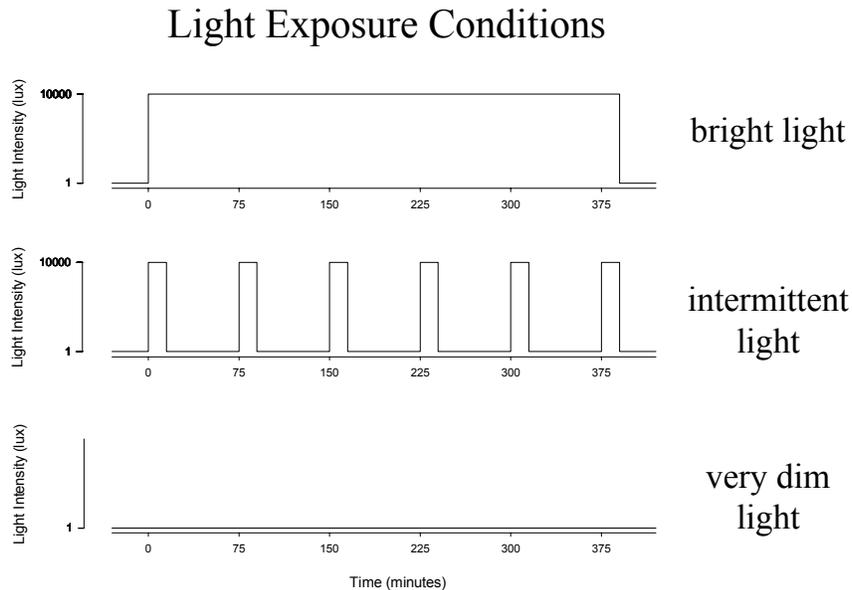


Figure 2: The 6.5-h light exposure session was centered 5.8 h before habitual wake time (~3.5 hours before CBTmin). Subjects were exposed either to continuous **bright light** (~9,500 lux), **intermittent bright Light** [six 15-minute bright light (~9,500 lux) pulses separated by 60 minutes of very dim light (<1 lux)] or **very dim light** (<1 lux).

Specific methodology:

Subject Recruitment: Healthy subjects were recruited for participation in this study. Potential subjects were intensively screened including a preliminary phone screening questionnaire and a physical exam. The physical included blood and urine tests, an EKG, and a full physical exam with a physician. A staff psychologist then examined the candidates still under consideration. Every attempt was made to acquaint each prospective subject with all of the procedures involved in this study in order to minimize the possible effect of uncertainty about the experimental procedures on the results. They were shown the sensors, the cameras, the intravenous catheter, the bright light level, etc., before consenting to participate in the experiment. Written informed consent was obtained from each subject before his/her study began. Each subject was told that he/she was free to discontinue participation in the experiment at any time and that the investigators also reserved the right to discontinue the study for medical or other reasons at any time.

Ambulatory physiologic monitoring. Subjects were required to maintain a regular sleep-wake schedule for 3 weeks prior to admission to the laboratory. Compliance to this protocol was monitored by evaluating a diary of sleep and wake times kept by the subjects. Furthermore, subjects were also required to call into a date/time-stamped answering machine just prior to going to bed and immediately upon awakening and the times were compared to sleep/wake logs on the day of admission. Finally, wrist activity and light exposure were monitored for 1 week immediately prior to admission to the laboratory with a portable data collection device (Actiwatch-L, Mini Mitter, Sunriver, OR).

Inpatient environment and conditions. Upon admission to the study, subjects were isolated from external time cues, including clocks, radios, television, visitors, and sunlight, but maintained contact with staff members using techniques described elsewhere^{6,18}. Technicians were present 24 h per day to carry out the protocol; monitor the data acquisition system; collect biologic specimen; administer performance and short-term memory tests; polygraphically record each sleep episode; and administer bright light exposure at the scheduled times. All staff members were trained to avoid communicating time of day or the nature of the experimental conditions to the subjects. An extensive series of written protocols and checklists together with a computerized reminder system were used to insure uniformity in the execution of standard procedures (e.g., at bedtime and wake time) and to foster intra-staff communications (e.g., at shift change).

Lighting: The experimental suites in the Intensive Physiologic Monitoring Unit of the General Clinical Research Center at the Brigham and Women's Hospital have ceiling-mounted fluorescent fixtures that are controlled by a computer system. This system automatically turned the lighting on and off at scheduled times to the required pre-set intensity. The light intensity was that of normal indoor room light (~150 lux) during the baseline days, ~1.5 lux during CRs and light exposure day, and <1 lux and/or ~9,500 lux during the 6.5-h light exposure session (depending on experimental condition, see Fig.2). Light intensity was <0.03 lux during all sleep episodes. The 6.5 hours of exposure light exposure session was centered 5.8 h before habitual wake time (~3.5 hours before CBT_{min}). Subjects were exposed either to continuous bright light (~9,500 lux, defined as 100% bright light), or to intermittent bright light (six 15-minute bright light (~9,500 lux,) pulses separated by 60 minutes of very dim light (<1 lux), defined as 23% bright light) or to very dim light (<1 lux, defined as 0% bright light). Light exposure was administered with ceiling-mounted fluorescent lamps mounted in fixtures capable of providing ambient illumination of ~1 to 12,000 lux. A technician was present for all light treatments. This technician recorded light levels manually using an International Light 1400 photometer every five minutes to ensure subject compliance during light exposure sessions. The experimental suites were equipped with hand-held terminals for on-line event recording, a porthole for 24-h blood sample collection with minimal sleep disturbance, a video camera and a voice-activated audio system.

Wake episodes: During wake episodes, subjects were free to move about the suite as desired, except that they were asked not to lie down or nap during scheduled wake episodes. Subjects were restricted to light, sedentary physical activity; exercise was not allowed. Subjects' compliance with the protocol was monitored by means of closed-circuit cameras.

Temperature recording. Environmental temperature was maintained at 74 + 3° Fahrenheit. A real time, on-line data acquisition system utilizing IBM-PC-compatible, Pentium-based computers was employed to monitor and collect data. Core body temperature was continuously monitored by means of a rectal thermistor and room temperature by means of a permanent air temperature thermistor; both were stored every minute.

Sleep recording and scoring. During scheduled sleep episodes, subjects were instructed not to get out of bed, even if they awakened before the end of the scheduled sleep episode. If requested, a technician brought the subject a urinal or bedpan during the scheduled sleep episode. Sleep was recorded with polysomnography (PSG), including EEG, EOG, EMG, and EKG measures. All data were collected using Vitaport 2 or 3 digital recording systems (Temec, Netherlands).

Hormonal data. Blood samples were collected through an indwelling 18-gauge intravenous catheter every 30-60 minutes during designated portions of the protocol (e.g., the constant routines) using established techniques {2001}. A specially designed and manufactured 18-gauge intravenous placement unit with side portholes (Becton-Dickinson Vascular Access, Sandy, Utah) was used to facilitate the collection of

blood without disturbance of the subject, even during sleep. This intravenous placement unit was connected to a triple-stopcock manifold (Maxxim Medical, Atahens, TX) via an intravenous loop with a 12-foot extension cable (VMR Products, L.C., Fruit Heights, UT). The triple-stopcock manifold was connected to an intravenous microdrip to allow infusion of heparinized saline (0.45% sodium chloride, 10 units of heparin/ml) at a very slow rate (5-10 ml/h) between blood samples. Each subject's hematocrit was measured during the initial selection evaluation, on admission to the IPM, and every morning. No more than 2 pints of blood was taken over the course of each study. We provided participants with Ferrous Gluconate (324 mg) pills to be taken at breakfast and dinner: i) for a minimum of one week prior to participation in the inpatient research protocol; ii) during the inpatient portion of the protocol; and iii) for three weeks after the ending the protocol. During the study, we tested the subjects' hemoglobin levels every 1-2 day(s) when there was an indwelling intravenous catheter in place. If the hematocrit or hemoglobin values had fallen below 11.0 for men and 10.3 for women blood sampling would have been stopped, although this did not occur. Blood samples were assayed for melatonin and cortisol using radioimmunoassay techniques.

Constant routine procedure. To assess endogenous circadian phase accurately, each subject underwent two constant routines (CR). The initial CR was 26.2 hours (in order to center the 6.5-h light exposure session 5.8 h before habitual wake time (~3.5 h before core body temperature minimum) and the final CR was 64 h in length. The constant routine consisted of a regimen of enforced wakefulness in a semi-recumbent posture in constant very dim illumination (~1.5 lux). Subjects were not permitted to change this posture throughout the constant routine, and avoided standing up, sitting upright, lying on their side, etc. This posture was also maintained for urine samples and bowel movements. Subjects were maintained in a isocaloric diet. Nutritional intake was divided into hourly aliquots. Caloric and fluid intake was calculated for each subject to account for the sedentary nature of the constant routine. A staff member was always with the subject to help maintain wakefulness and to ensure that all protocol requirements were met.

Neurobehavioral Testing. We selected a battery of computer-based tests of performance and mood that are sensitive to the acute effects of misalignment of circadian phase and sleep disruption on performance. Standardized measures of performance and activation were included in the neurobehavioral test battery (NAB) administered every 2 hr all waking periods of every day. We have developed and extensively validated the NAB, which contains performance and subjective activation measures with the following characteristics: conceptually valid, relatively short duration, reliable, known psychometric properties, minimal practice/learning curves, reflect multidimensional aspects of performance and activation, and validated to be sensitive to both circadian phase and homeostatic sleep drive^{8,15,13}. The NAB computer ensemble also contained extensive data reduction analysis software that automatically extracted multiple performance (e.g., lapses) and activation subscale metrics, utilizing the appropriate criteria and transformations.

NAB performance tests include the following:

- a) *Psychomotor vigilance task (PVT).* Sustained attention performance was assessed throughout the protocol, using the psychomotor vigilance test (PVT) approach of Dinges and Powell⁹. The test has been demonstrated to be sensitive to circadian variation and sleep loss^{10,8}. Each PVT involved a 5-minute visual reaction time (RT) performance test in which the subject was required to maintain the fastest possible RT's to a simple visual stimulus. The inter-stimulus interval involved a high signal rate randomly varying between 2 and 10 seconds. A variety of performance metrics showing stable circadian variation were obtained from each PVT trial including the number of lapses, optimum response times, false alarms, and the characteristics of vigilance decrement functions (i.e., slope, y-intercept) as a result of time on task. Different transforms applied to variables reduced inter-subject variability and provided stable estimates of circadian variation. Data analyses focused on RT, errors,

and signal detection theory parameters. We separately analyzed anticipation errors (fast guesses) and non-responses (lapses).

- b) *Calculation Performance Task (ADD)*. This test, modeled after one described by Klein *et al.*¹², presented the subject with a series of randomly generated pairs of 2-digit numbers. The subject's task was to sum as many pairs as possible in the allotted 2-min time interval. The test was scored according to the number of calculations completed in the time allowed, irrespective of accuracy.

NAB subjective activation tests include:

- c) *Visual analog scales (VAS)*. VAS were used to assess the mood, alertness, and physical well being of the subjects. The scales consisted of a horizontal line drawn on the display with each end of the line labeled with the extremes of a subjective continuum (e.g., words or phrases such as "very alert" and "very sleepy"). The subject's task was to use the trackball to move an arrow to the position on the line between the two defined endpoints that best describes how he or she felt at that moment. The subject then pressed a keypad button, transforming the arrow into a hash mark intercepting the line.
- d) *Karolinska Sleepiness Scale (KSS)* was used as a highly sensitive subjective measurement scale for sleepiness¹.

Behavioral Event Recording. This system was designed to meet two goals: (1) immediate recording of the time that events occur during the study (e.g., showers, meals); and (2) direct communication between the subject and the technician about requests which might be influenced by the technician's subjective reaction to a verbal interaction. Recording the precise sequence in time of behavioral events, specimen collections and protocol markers was carried out via a centralized event recording system using multiple, inexpensive, hand-held (4" X 7"), commercially available terminals (TERMIFLEX/HT20, Nashua, NH) connected by standard RS-232-C cable to IBM-Compatible Intel Pentium file servers using software driven by a Next State Transition Table¹⁷. In addition, each request was displayed simultaneously on a computer monitor in the control room, indicating to the technician what each subject wanted and permanently recording the data in a computer file. This system was used to check whether various items scheduled in the protocol were carried out on time, and to remind the technician of the protocol schedule.

Statistical Analysis

- a) *Melatonin data.* We assessed circadian phase by determining melatonin onset (DLMOn) defined as the time at which the rising portion of the plasma melatonin profile crossed a level that was 25% of the fitted 3-harmonic amplitude of the melatonin rhythm measured during the first constant routine procedure¹¹ (Fig. 3). We also determined the melatonin offset (DLMOff), defined as the time at which elevated melatonin levels fell below 25% of the fitted 3-harmonic amplitude of the melatonin rhythm. The mean point between the DLMOn and the DLMOff was defined as the midpoint of the melatonin peak. We assessed melatonin suppression during light exposure session by comparing the area under the curve (AUC) of the melatonin profile measured during the 6.5-h light exposure session to the AUC of the same segment of time during the first CR (Fig. 3).
- b) *Core body temperature:* A dual harmonic regression model⁴ was used on core body temperature (CBT) recorded during CR1 and CR2 to estimate circadian phase (timing of temperature minimum, CBT_{min}). The timing of CBT_{min} measured on CR2 was compared to the timing of CBT_{min} measured during CR1 to determine the phase shift each subject achieved.
- c) *Neurobehavioral data.* Each of the tests (NAB) was administered automatically by computer at frequent intervals, and initial processing of test results were simultaneously calculated (exact time of administration; scoring of mood and alertness estimated with the VAS and KSS; number and correctness of sums (addition test) completed on the ADD; mean and median reaction time, number of lapses, and shortest and longest reaction times on the PVT). To account for subject variability on these tests, each subject's scores were referenced to his/her mean value and normalized in terms of variability (Z-scored) using the data from the baseline days

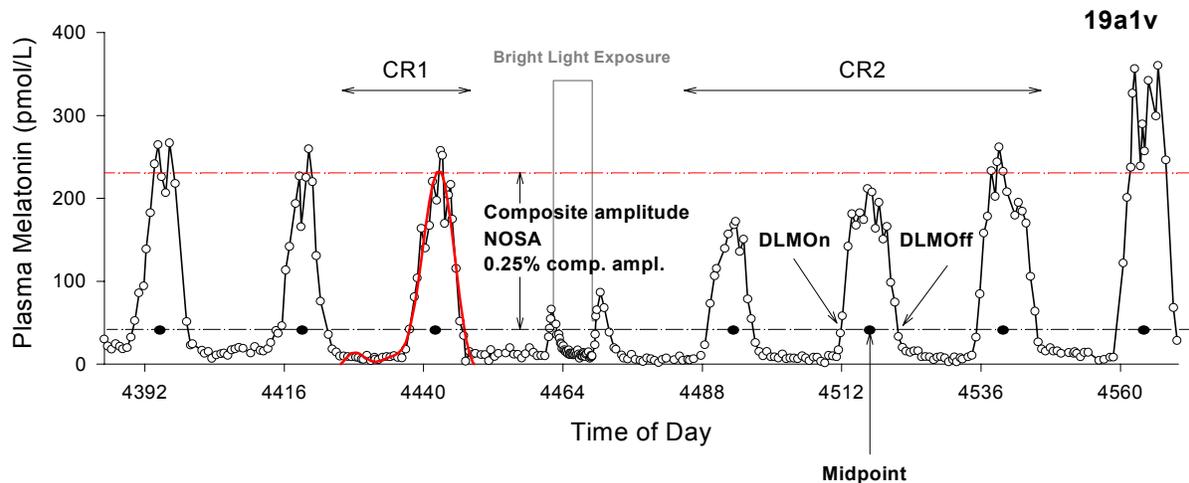


Figure 3: Method used for phase assessment using Dim Light Melatonin Onset (DLMO_{on}), Dim Light Melatonin Offset (DLMO_{off}) and Midpoint phase markers. The figure also illustrates the bright light exposure-induced melatonin suppression.

RESULTS

Twenty-one subjects completed the study; each was randomly assigned to either the bright light exposure condition, the dim light exposure condition or the intermittent bright light exposure condition (see Appendix, Table 1).

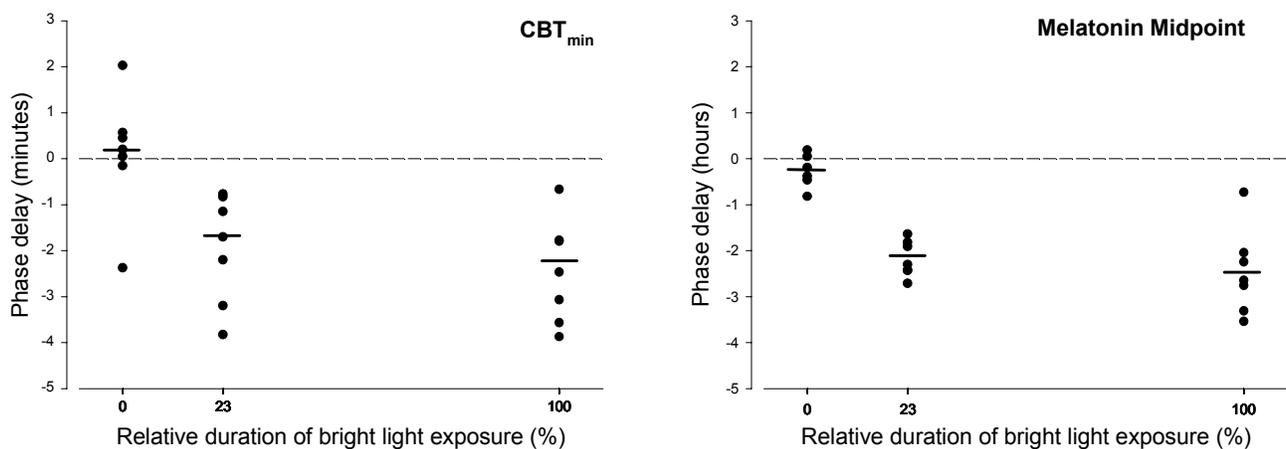


Figure 4: Resetting responses of 21 subjects to the 0% (very dim light), 23% (intermittent bright light) and 100% (bright light) conditions, measured with core body temperature minimum (CBT_{min}, left figure) and melatonin midpoint (right figure). Phase-advance shifts are plotted as positive values, whereas phase-delay shifts are plotted as negative values. Horizontal bars represent the median phase shift observed in each condition.

As expected at that phase of light exposure, all bright light-exposed groups demonstrated phase delays of their endogenous circadian rhythms of core body temperature (CBT) and melatonin (Fig. 4, Appendix table 1). The resetting responses measured with CBT were more variable than that measured with melatonin; however we found a significant linear relationship between the two markers (Fig. 5).

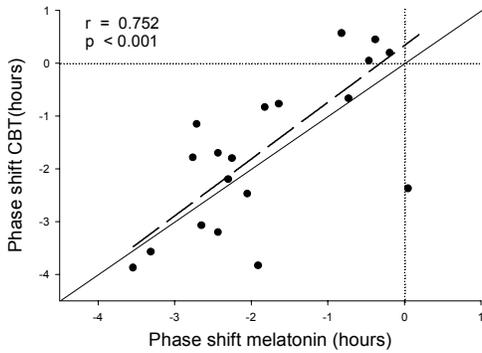


Figure 5: Linear relationship ((dashed line)) between phase shifts of melatonin and CBT rhythms. Phase-advance shifts are plotted as positive values, whereas phase-delay shifts are plotted as negative values.

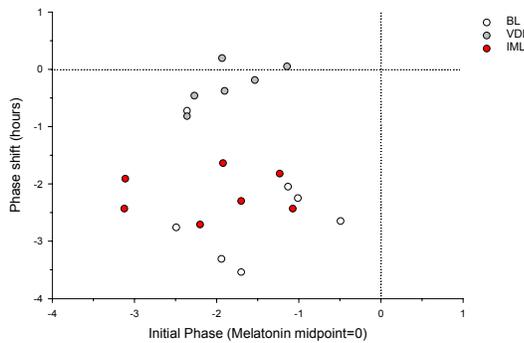


Figure 6: Phase shifts (melatonin midpoint) measured in 21 subjects under bright light exposure condition (BL), very dim light condition (VDL) and intermittent bright light condition (IML) as a function of initial phase. Phase-advance shifts are plotted as positive values, whereas phase-delay shifts are plotted as negative values.

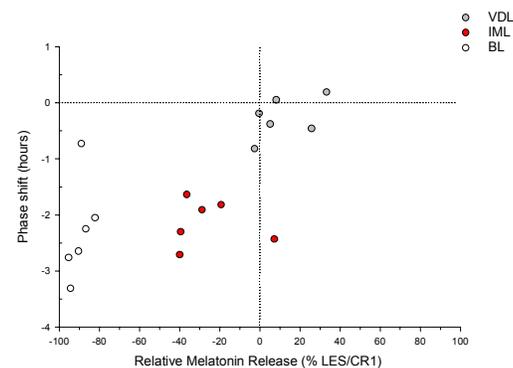


Figure 7: Phase shifts (melatonin midpoint) measured in 21 subjects under either bright light exposure condition (BL), or very dim light condition (VDL) or intermittent bright light condition (IML) as a function of melatonin suppression during the light exposure session (LES). Phase-advance shifts are plotted as positive values, whereas phase-delay shifts are plotted as negative values. CR1: constant routine 1.

The median phase-delay shift observed from the core body temperature data was -0.20 h (phase advance) in the group of subject exposed to very dim light (0% bright light), 1.75 h in the group exposed to the intermittent bright light 23% duty schedule and 2.47 h in the group exposed to the continuous bright light exposure 100% schedule (Fig. 4, left panel).

The median phase-delay shift observed from the plasma melatonin was 0.28 h in the group of subject exposed to very dim light (0% bright light), 2.30 h in the group exposed to the intermittent bright-light 23% duty schedule and 2.65 h in the group exposed to the continuous bright light exposure 100% schedule (Fig.4, right panel). The bright light exposed groups showed significantly larger phase delays compared to the very dim light group ($p < 0.0002$), however, no statistical difference was found between the phase shifts measured under bright light and intermittent light conditions ($p = 0.41$). Thus, the phase delays observed after intermittent bright light exposure were comparable to those measured after continuous bright light exposure (Fig.7), even though the bright light represented only 23% of the 6.5 h exposure. Given that the median phase delay was 2.65 h under continuous bright light condition (6.5 hours) and was 2.30 h under intermittent bright light (1.5 h of bright light), the phase resetting ability of intermittent bright light exposure was 3.7 times greater than that of continuous bright light exposure on a per minute of bright light exposure basis.

Figure 6 illustrates the phase delays measured in the three groups as a function of the initial phase of the subjects (melatonin midpoint measured during CR1). We found no significant linear correlation (N.S.) between initial phase and phase shift for each of the three experimental groups, indicating that the magnitude of the phase shifts was not related to a difference in timing of the light exposures but was rather associated to the light exposure condition itself.

As expected, melatonin levels were significantly lowered by bright light exposure compared to very dim light exposure (Appendix, Table 3). On average, melatonin was suppressed by $89 \pm 2\%$ in the bright light exposure group, and by only $27 \pm 6\%$ in the intermittent light exposure ($p < 0.0002$). As a result, as shown in Figure 7, the magnitude of the phase shifts is not a linear function of the degree of melatonin suppression.

Analyses of sleep and neurobehavioral data are ongoing and the results could not be integrated in the present report.

DISCUSSION

These results demonstrate that intermittent bright light exposure is effective in inducing phase shifts of the circadian timing system and that intermittent pulses of bright light have a greater resetting effectiveness on a per minute basis than the continuous bright light exposure. They also suggest that the magnitude of phase shifts is not a linear function of melatonin suppression.

These findings have important implications as they provide a greater understanding of the effects of brief episodes of light on the human circadian timing system. These findings will facilitate the design of circadian resetting strategies that most efficiently utilize bright light exposure. These strategies are critical in situations in which circadian misalignment is problematic, such as long-duration space missions and shift work. During long-duration space missions, astronauts are exposed to a low-intensity light/dark cycle. Such exposure may result in a loss of synchronization between the internal circadian clock and the external light/dark cycle. This type of misalignment can result in problems in the performance, health, and safety of astronauts. By using brief episodes of light exposure, the present results indicate that it may be possible to prevent such misalignment from occurring. As previously discussed, this will be very important on long-duration space missions in which daily exposures to extended episodes of bright light exposure is untenable in terms of both energy and time. Misalignment of circadian phase and sleep-wake/duty cycle can also occur here on Earth. Shift workers who are exposed to unusual patterns of light and dark due to the nature of their jobs could be helped to keep their internal rhythms better aligned with that of their sleep/wake schedule by utilizing maximally effective brief pulses of light. Such strategies could also be used not only to treat misalignment associated with transmeridian travel, but also in Advanced and Delayed Sleep Phase Syndrome (ASPS and DSPS, respectively). These two pathologies are characterized by a marked difficulty in maintaining appropriate timing of sleep during the desired night-time hours due to a misalignment or circadian phase. Our research also addresses fundamental questions about the basic properties of the human circadian timing system.

CITED REFERENCES

1. Åkerstedt T, Gillberg M. Subjective and objective sleepiness in the active individual. *Int J Neurosci* 1990;52:29-37.
2. Boivin DB, Czeisler CA. Resetting of circadian melatonin and cortisol rhythms in humans by ordinary room light. *Neuroreport* 1998;9:779-782.
3. Brown EN, Choe Y, Shanahan TL, Czeisler CA. A mathematical model of diurnal variations in human plasma melatonin levels. *Am J Physiol* 1997;272:E506-E516.
4. Brown EN, Czeisler CA. The statistical analysis of circadian phase and amplitude in constant-routine core-temperature data. *J Biol Rhythms* 1992;7:177-202.
5. Cajochen, C., Zeitzer, J. M., Czeisler, C. A., and Dijk, D.-J. Dose-response relationship for light intensity and alertness and its ocular and EEG correlates. *Sleep Res Online* 2(Suppl.1), 517. 1999.
6. Czeisler, C. A. Human circadian physiology: internal organization of temperature, sleep-wake, and neuroendocrine rhythms monitored in an environment free of time cues. 1-346. 1978. Ph.D. Dissertation. Stanford University.
7. Czeisler CA, Kronauer RE, Allan JS, Duffy JF, Jewett ME, Brown EN, Ronda JM. Bright light induction of strong (type 0) resetting of the human circadian pacemaker. *Science* 1989;244:1328-1333.
8. Dinges DF, Kribbs NB. Performing while sleepy: Effects of experimentally-induced sleepiness. In: Monk TH, ed. *Sleep, Sleepiness and Performance*. Chichester, UK: John Wiley and Sons, Ltd.; 1991:97-128.
9. Dinges DF, Powell JW. Microcomputer analyses of performance on a portable, simple visual RT task during sustained operations. *Behav Res Meth Instr Comp* 1985;17:652-655.

10. Dinges DF, Powell JW. Sleepiness impairs optimum response capability--It's time to move beyond the lapse hypothesis. *Sleep Res* 1989;18:366.
11. Hughes, R.J., Sack, R. L., Singer, C. M., McArthur, A. J., and Lewy, A. J. Preservation of normal endogenous melatonin profiles in older "low producers". *Sleep Res* 1997;26:718-718.
12. Klein T, Martens H, Dijk D-J, Kronauer RE, Seely EW, Czeisler CA. Circadian sleep regulation in the absence of light perception: Chronic non-24-hour circadian rhythm sleep disorder in a blind man with a regular 24-hour sleep-wake schedule. *Sleep* 1993;16:333-343.
13. Kribbs NB, Dinges DF. Vigilance decrement and sleepiness. In: Harsh JR, Ogilvie RD, eds. *Sleep onset mechanisms*. Washington: American Psychological Association; 1994:113-125.
14. Kronauer RE, Jewett ME, Czeisler CA. Modeling human circadian phase and amplitude resetting. In: Touitou Y, ed. *Biological Clocks, Mechanisms and Applications*. Amsterdam: Elsevier Science B.V.; 1998:63-72.
15. Lieberman HR, Wurtman JJ, Teicher MH. Aging, nutrient choice, activity and behavioral responses to nutrients. *Nutrition and the chemical senses in aging*. *Ann NY Acad Sci* 1993.
16. Rimmer DW, Boivin DB, Shanahan TL, Kronauer RE, Duffy JF, Czeisler CA. Dynamic resetting of the human circadian pacemaker by intermittent bright light. *Am J Physiol* 2000;279:R1574-R1579.
17. Ronda JM, Shampine WT, Kennedy WA, Czeisler CA. A next state transition table method for precise event recording utilizing hand-held terminals. *Sleep Res* 1985;14:278-278.
18. Weitzman ED, Czeisler CA, Zimmerman JC, Ronda JM, Knauer RS. Chronobiological disorders: analytic and therapeutic techniques. In: Guilleminault C, ed. *Disorders of Sleeping and Waking: Indications and Techniques*. Menlo Park, CA: Addison-Wesley; 1982:297-329.
19. Zeitzer JM, Dijk D-J, Kronauer RE, Brown EN, Czeisler CA. Sensitivity of the human circadian pacemaker to nocturnal light: Melatonin phase resetting and suppression. *J Physiol (Lond)* 2000;526:695-702.

REFERENCES SUPPORTED IN PART BY THIS NASA GRANT

1. Cajochen C, Zeitzer JM, Czeisler CA, Dijk DJ. Dose-response relationship for light intensity and alertness and its ocular and EEG correlates. *Sleep Research Online* 1999; 2(Suppl.1):517.
2. Czeisler CA, Dijk DJ. Human circadian physiology and sleep-wake regulation. In *Handbook of Behavioral Neurobiology: Circadian Clocks*. Takahashi JS, Turek FW, Moore RY (eds), 1999, in press.
3. Czeisler CA, Khalsa SB – The human circadian timing system and sleep-wake regulation. In *Principles and Practice of Sleep Medicine*. Kryger MH, Roth T, Dement WC (eds), 2000.
4. Czeisler CA, Klerman EB. Circadian and sleep-dependent regulation of hormonal release in humans. *Recent Prog Horm Res* 1999;54:97-132.
5. Ho AH, Gronfier C, Czeisler CA. Effects of prolonged sleep deprivation on cortisol secretion in Humans. *Sleep* 2001;24(Suppl.):A89-90.
6. Kronauer RE, Jewett ME, Czeisler CA. Modeling human circadian phase and amplitude resetting. In: *Biological clocks, Mechanisms and applications*, edited by Touitou Y, Elsevier Science BV, 1998,pp.63-72.
7. Rimmer,D.W., D.B.Boivin, T.L.Shanahan, R.E.Kronauer, J.F.Duffy, and C.A.Czeisler. Dynamic resetting of the human circadian pacemaker by intermittent bright light. *Am J Physiol* 2000;279: R1574-R1579.
8. Zeitzer JM, Daniels JE, Duffy FD, Klerman EB, Shanahan TL, Dijk DJ, Czeisler CA. Do plasma melatonin concentrations decline with age? *Am J Med* 1999, 107:432-436.
9. Zeitzer JM, Kronauer RE, Czeisler CA. Photopic transduction implicated in human circadian entrainment. *Neurosci Lett* 1997;232: 135-138.

10. Zeitzer JM. Physiology and anatomy of human circadian photoreception and melatonin regulation. Ph.D. Dissertation, Harvard University, Boston MA, 1999.
11. Zeitzer, J.M., D.-J. Dijk, R.E. Kronauer, E.N. Brown, and C.A. Czeisler. Sensitivity of the human circadian pacemaker to nocturnal light: Melatonin phase resetting and suppression. *J. Physiol. (Lond.)* 2000;526: 695-702.

LIST OF PRESENTATIONS SUPPORTED IN PART BY THIS NASA GRANT

1. Cajochen C, Zeitzer JM, Czeisler CA, Dijk DJ. Dose-response relationship for light intensity and alertness and its ocular and EEG correlates. World Federation of Sleep Research Societies 3rd International Congress, Dresden (Germany), October 5–9, 1999.
2. Czeisler CA. Student Day Discussion Groups: “Interaction of Sleep and Circadian Rhythms”. World Federation of Sleep Research Societies 3rd International Congress, Dresden (Germany), October 5–9, 1999.
3. Czeisler CA. Symposium – Evidence for Interaction between Sleep and Circadian Systems: “Nature of Interaction in Humans”. American Physiological Society Conference, Ft. Lauderdale, FL, October 19–22, 1999.
4. Czeisler CA. Trainee Symposium Interactive Workshops: “Circadian and Sleep/Wake Regulation of Endocrine Functions”. 13th Annual Meeting of the Associated Professional Sleep Societies, Orlando, FL, June 19–24, 1999.
5. Czeisler, C.A. Student Day Discussion Groups: “Interaction of Sleep and Circadian Rhythms”. World Federation of Sleep Research Societies 3rd International Congress, Dresden (Germany), October 5–9, 1999.
6. Forger DB. An alternate model of the human circadian clock. Workshop on Biomathematical models of circadian rhythmicity, sleep regulation and neurobehavioral function in humans, Dedham MA, May 18-21, 1999.
7. Gronfier C, Kronauer RE, Wright KP, Czeisler CA. Phase-shifting effectiveness of intermittent light pulses: relationship to melatonin suppression. Meeting of the Society for Research on Biological Rhythms, Amelia Island Plantation, FL, May 11-13, 2000.
8. Ho AH, Gronfier C, Czeisler CA. Effects of prolonged sleep deprivation on cortisol secretion in Humans. 15th Annual Meeting of the Associated Professional Sleep Societies, Chicago, IL June 5-10, 2001.
9. Jewett ME, Dijk DJ, Kronauer RE, Czeisler CA. Sigmoidal decline of homeostatic component in subjective alertness and cognitive throughput”. 13th Annual Meeting of the Associated Professional Sleep Societies, Orlando, FL, June 19–24, 1999.
10. Jewett ME, Kronauer RE. Interactive mathematical models of subjective alertness and cognitive throughput in humans. Workshop on Biomathematical models of circadian rhythmicity, sleep regulation and neurobehavioral function in humans, Dedham MA, May 18-21, 1999.
11. Kronauer RE, Forger DB, Jewett ME. Quantifying human circadian pacemaker response to brief, extended, and repeated light episodes over the photopic range. Workshop on Biomathematical models of circadian rhythmicity, sleep regulation and neurobehavioral function in humans, Dedham MA, May 18-21, 1999.
12. Kronauer RE, Jewett ME, Czeisler CA. Modeling human circadian phase and amplitude resetting. International Congress on Chronobiology, Paris, France, Sept. 7-11, 1997.

LIST OF STUDENTS/TRAINEES SUPPORTED IN PART BY THIS NASA GRANT

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APPENDIX

Subject Code	Condition	Gender	Age
19a1v	BL	female	20
19b1v	VDL	male	21
19b9v	IML	male	31
19c3v	VDL	male	23
19c4v	IML	female	25
19d9v	BL	male	40
2004v	IML	male	22
2006v	BL	male	28
2008v	VDL	female	19
2012v	BL	female	27
2018v	VDL	male	24
2024v	IML	male	21
2035v	IML	male	27
2036v	BL	male	21
2038v	VDL	male	30
2039v	VDL	male	31
19c9vot2	IML	male	28
2041v	BL	female	26
2042v	IML	female	23
2043v	BL	male	19
2056v	VDL	male	21

Table 1: Experimental condition (BL, bright light; IML, intermittent light; VDL, very dim light), gender and age of the 21 subjects studied. Seven subjects were studied in each group for a total of six females and 15 males.

Subject Code	Condition	Phase shift Melatonin	Phase shift CBT
19a1v	BL	-3.15	-3.07
19b1v	VDL	-0.33	0.05
19b9v	IML	-2.12	-1.15
19c3v	VDL	-0.52	0.20
19c4v	IML	-2.88	-1.70
19d9v	BL	-0.82	-0.67
2004v	IML	-2.45	-3.83
2006v	BL	-2.70	-2.47
2008v	VDL	-0.24	-2.37
2012v	BL	-3.36	-3.57
2018v	VDL	-0.29	0.45
2024v	IML	-2.14	-0.77
2035v	IML	-2.98	-2.20
2036v	BL	-2.92	-1.78
2038v	VDL	0.06	2.03
2039v	VDL	-1.09	0.57
19c9vot2	IML	-2.28	-0.83
2041v	BL	-2.48	-1.80
2042v	IML	-2.34	-3.20
2043v	BL	-3.72	-3.87
2056v	VDL	-	-0.15

Table 2: Individual phase shifts of the endogenous circadian rhythms of temperature (CBT_{min}) and melatonin (midpoint) in the bright light (BL), intermittent light (IML) and very dim light (VDL) exposure groups. Note that due to missing blood samples, the melatonin midpoint couldn't be calculated for subject 2056v.

Subject Code	Condition	AUC CR1	AUC LES	%CR1/LES
19a1v	BL	1181.2	113.4	-90%
19b1v	VDL	1017.5	1280.8	26%
19b9v	IML	293.7	176.7	-40%
19c3v	VDL	1598.7	1593.7	0%
19c4v	IML	1342.4	1441	7%
19d9v	BL	390	42.9	-89%
2004v	IML	1440.6	1026.4	-29%
2006v	BL	2163.9	387.9	-82%
2008v	VDL	828.2	897	8%
2012v	BL	1922	107.9	-94%
2018v	VDL	1458.2	1534.7	5%
2024v	IML	2081.3	1323.7	-36%
2035v	IML	1324.3	803.4	-39%
2036v	BL	2574.5	122.6	-95%
2038v	VDL	944.8	1259.7	33%
2039v	VDL	896.5	873.4	-3%
19c9vot2	IML	1732.6	1398.8	-19%
2041v	BL	1888	250.8	-87%
2042v	IML	1133.18	756.4	-33%
2043v	BL	604.75	90.47	-85%
2056v	VDL	903.91	1064.11	18%

Table 3: Individual area under the curves (AUC in pmol/ml/6.5h) measured during the 6.5-h light exposure session (LES) and during the comparable time window during constant routine 1 (CR1), in the bright light (BL), intermittent light (IML) and very dim light (VDL) exposure groups. A negative value in the ratio CR1/LES (right column) indicates melatonin suppression during the light exposure session whereas a positive value indicates a melatonin increase.