Learning to Live on a Mars Day: Fatigue Countermeasures during the Phoenix Mars Lander Mission

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Study Objectives: To interact with the robotic Phoenix Mars Lander (PML) spacecraft, mission personnel were required to work on a Mars day (24.65 h) for 78 days. This alien schedule presents a challenge to Earth-bound circadian physiology and a potential risk to workplace performance and safety. We evaluated the acceptability, feasibility, and effectiveness of a fatigue management program to facilitate synchronization with the Mars day and alleviate circadian misalignment, sleep loss, and fatigue.
Design: Operational field study.
Setting: PML Science Operations Center.
Participants: Scientific and technical personnel supporting PML mission.
Interventions: Sleep and fatigue education was offered to all support personnel. A subset (n = 19) were offered a short-wavelength (blue) light panel to aid alertness and mitigate/reduce circadian desynchrony. They were assessed using a daily sleep/work diary, continuous wrist actigraphy, and regular performance tests. Subjects also completed 48-h urine collections biweekly for assessment of the circadian 6-sulphatoxymelatonin rhythm.
Measurements and Results: Most participants (87%) exhibited a circadian period consistent with adaptation to a Mars day. When synchronized, main sleep duration was 5.98 ± 0.94 h, but fell to 4.91 ± 1.22 h when misaligned (P < 0.001). Self-reported levels of fatigue and sleepiness also significantly increased when work was scheduled at an inappropriate circadian phase (P < 0.001). Prolonged wakefulness (≥ 21 h) was associated with a decline in performance and alertness (P < 0.03 and P < 0.0001, respectively).
Conclusions: The ability of the participants to adapt successfully to the Mars day suggests that future missions should utilize a similar circadian rhythm and fatigue management program to reduce the risk of sleepiness-related errors that jeopardize personnel safety and health during critical missions.
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INTRODUCTION

Space exploration presents physiological challenges for engineers, scientists and mission controllers. The Phoenix Mars Lander (PML) mission aimed to investigate the Martian arctic soils for history of water and potential for habitability.[1] In order to maximize personnel and communication efficiency as well as science output, mission control personnel were required to communicate with the solar powered Lander based on a Mars, rather than an Earth, day that lasts 24.65 h, almost 40 min longer per day than on Earth. Unfortunately for this mission, the human circadian system, which governs the daily timing of sleep, performance, and alertness, among many other functions, has evolved to synchronize strictly to a 24-h Earth day. Although early reports stated that the period of the human circadian pacemaker was close to 25 h (and therefore close to a Mars day),[2] more careful assessment of the circadian pacemaker in humans shows that the intrinsic circadian period is much closer to 24 h (24.2 h on average).[3,4] Synchronizing the circadian system to

a 24.65-h Mars day, and therefore the physiology, metabolism, and behavior it controls, requires resetting the clock later (phase delay) by 39 min per day, the equivalent of 2 time zones westward every 3 days. While this challenge appears modest, repeated failure to entrain to the Mars day over several days or weeks would soon result in desynchrony between the circadian system and the sleep-wake schedule, causing disrupted sleep, impaired cognition, and poor performance.[5-7] These problems were indeed experienced by the Jet Propulsion Laboratory (JPL) personnel and visiting scientists during previous Mars robotic missions (the Mars Pathfinder and Mars MER missions) who found the work schedule demands of a Mars day extremely challenging.[8,9] Those supporting the Sojourner Rover during the Mars Pathfinder Mission abandoned the Mars day schedule after only one month of the almost 3-month mission,[10] and many of the 250 MER controllers also found the schedule very difficult to maintain, with 82% reporting increased fatigue, sleepiness, and irritability, as well decreased levels of concentration and energy.[11] Clearly, without appropriate circadian rhythm and fatigue management countermeasures, maintaining daily life on the Mars day presents a significant challenge.

The physiological consequences of suboptimal adaptation to a Mars day are well documented. Laboratory simulations have shown that the near 24-h intrinsic circadian period (τ) in humans cannot entrain to the Mars day without specific intervention. Wright and colleagues reported that 100% (6/6) of subjects failed to entrain to the Mars day when exposed to dim light conditions

during wake episodes,[6,12] resulting in disturbed sleep and endocrine physiology, and impairment of alertness, mood, vigilance, cognitive function, and learning.[6,12] Increasing the light during wake episodes to ~100 lux, similar to typical indoor room light, was also insufficient to maintain appropriate entrainment.[7] More sophisticated photic countermeasures can facilitate entrainment to a Mars day, however, if the circadian phase response curve (PRC) to light is considered. The PRC predicts that evening light delays the circadian pacemaker (the direction required for most people to synchronize to a 24.65-h day), whereas morning light advances the clock.[13] Gronfier and colleagues reported that two 45-min evening pulses of bright white fluorescent light (~9,500 lux) could delay the intrinsic circadian period by 1 h per day, which would be sufficient for most individuals to entrain to the Mars day.[7] The same effect, enhancing a phase delay shift of the circadian pacemaker, can be achieved using less light if subjects are exposed to very dim light (~1.8 lux) for the first half of scheduled wakefulness and moderately bright light (~450 lux) for the remainder of the day, designed to enhance a phase delay shift of the circadian pacemaker.[5]

In August 2007, the Phoenix Mars Lander launched from Kennedy Space Center and landed inside the Arctic Circle on Mars on May 25, 2008.[1] A core of visiting scientists, University of Arizona personnel, and NASA JPL personnel worked around the clock on a Mars day schedule at the Science Operations Center (SOC) in Tucson, AZ, in support of the mission. The mission provided an opportunity to investigate the acceptability, feasibility, and effectiveness of a photic countermeasure as part of a fatigue management program in an operational environment, to alleviate circadian misalignment, sleep deficiency, sleepiness, decreased alertness, and performance impairment associated with working on a Mars day.

MATERIALS AND METHODS

Education and Recruitment

We provided 3 open educational sessions to the scientists, engineers, and support personnel working on the Phoenix Mars Lander project in the week prior to the mission. During those planned 1-h sessions, we provided information on sleep, circadian rhythms and appropriate countermeasures (e.g., photic [light] exposure, napping, use of caffeine) to facilitate entrainment to a Mars day schedule to maximize performance and alertness during work hours and maximize sleep during time off. We also invited those in attendance to volunteer to participate in the intervention study being conducted during the 78 days when personnel were required to live and work on the Mars day. The Partners Human Research Committee and the Committee for Protection of Human Subjects at NASA Johnson Space Center approved the procedures for the protocol.

Subjects

Twenty subjects volunteered to participate and provided written informed consent. One withdrew before data collection began. All were scientists or engineers working in support of the Phoenix Mars Lander at the SOC in Tucson, AZ, and 6 were local residents. Ophthalmological examinations were conducted pre- and post-mission to ensure subject safety. Subjects were asked to complete pre- and post-mission questionnaires to gather demographic information and subjective comments regarding work on the Mars day schedule.

Photic Countermeasure

The Science Operations Center (SOC) has typical office lighting although external windows in the work areas were blacked out. Access to windows was not restricted elsewhere in the building. At the start of the study, 16 participants were provided a portable light box to place at their work stations; the other 3 subjects indicated that the light box was not compatible with their job duties (e.g., required to move about the SOC during the working day). Participants were instructed to turn the light box on during their work shifts at the SOC. The light units consisted of an array of 276 blue LEDs mounted behind a plastic lens diffuser, housed within 50×60 cm panels (Apollo Health, American Fork, UT). Short-wavelength blue light was chosen for this operation because it had been shown that circadian resetting, melatonin suppression, and the alerting effects of light are short-wavelength sensitive in healthy human subjects[14-17] via stimulation of a novel non-rod, non-cone, melanopsin-based photoreception system located in specialized ganglion cells in the mammalian eye.[18,19] Each panel was mounted on an adjustable stand, and a 50-cm piece of string was attached to each light box to remind volunteers of the correct viewing distance. The light boxes emitted narrow-band short wavelength blue visible light (± 27 nm half-peak bandwidth) with a peak (λ_{max}) of 468 nm. The mean irradiance 50 cm from the light box was adjusted on-site at the SOC to an average of 505 ± 24 μW/cm^2 (1.04×10^{15} photons/cm^2/s) with an International Light Radiometer/Photometer (Newburyport, MA), a photon density known to produce robust circadian resetting and alerting effects.[14,17,20-22] Although photopic lux is not an appropriate measure of light for non-visual circadian, neuroendocrine, and neurobehavioral responses, the nominal lux (for qualitative comparison with other photic countermeasures) was approximately 377 lux measured 50 cm from the source. This measure underestimates the "active" stimulus for a narrow band light source with a short wavelength (blue) peak as the photopic light sensor is tuned to a peak sensitivity of 555 nm.[14-17] A Motionlogger-L ([ML] Ambulatory Monitoring, Inc., Ardsley, NY) with a battery-powered light sensor capable of detecting ambient light levels in the range of 0 to 4000 lux was attached to each light box as a means of verifying when it was turned on and off.

Sleep

Each participant was issued a handheld Palm Tungsten E2 Personal Digital Assistant (PDA; Palm, Inc., Sunnyvale, CA) on which to complete a daily sleep/work log. The questions were similar to those used in the Harvard Work Hours, Health, and Safety Group study of medical interns,[23] where there was 95% agreement between sleep self-reported in the diary and polysomnographically recorded sleep epochs.[23] The daily diary also included questions about subjective fatigue and the use of fatigue countermeasures, such as napping and caffeine.

Each participant wore the ML on his or her wrist on work days and on days off; the ML continuously recorded gross motor movement using a precision piezoelectric bimorph-ceramic cantilevered beam.[24] Sleep was estimated for each day using the

Action-W version 2.0 software (Ambulatory Monitoring, Inc., Ardsley, NY; UCSD algorithm with rescoring). Out of a possible 1,482 days (19 subjects × 78 days), we collected 1,314 days of actigraphy and 996 daily logs. Actigraphy loss was also due, in some instances, to equipment malfunction and subject error (e.g., forgetting to wear the device).

Light Exposure

The wrist-worn ML also included a light sensor that continuously recorded ambient light (lux). To verify individual light box exposures, the light levels recorded by the ML attached to the light box were compared to the light levels recorded by the ML worn by the individual at the times the individual reported being at work. Prior measures taken 50 cm from the light box (the approximate working distance from the light box) gave an average light level of 377 lux. The volunteer was therefore deemed to be exposed to the light box when he or she reported being at work (sleep/work diary), the light box surface-mounted ML was > 2000 lux and the individual's ML recorded ≥ 375 lux.

Performance

Performance tasks included the psychomotor vigilance task (PVT) and the Automated Neuropsychological Assessment Metrics (ANAM). The PVT detects changes in basic neurobehavioral performance involving vigilant attention, response speed, and impulsivity. The 10-min version of the PVT has been extensively validated in ground-based laboratory studies to detect cognitive deficits caused by a variety of factors, including restricted sleep, sleep/wake shifts, motion sickness, and residual sedation from sleep medications.[25-27] In the study reported here, participants were asked to complete a 5-min version of the PVT at least twice per day: at the beginning and end of each shift if at work, and during the morning and evening of their days off. This 5-min PVT has been previously validated.[28-31]

The ANAM is a library of computer based tests that measure cognitive processing efficiency. The ANAM evolved from computerized test batteries developed by the Department of Defense and correlates well with traditional neuropsychological measures.[32-35] Selected tests from the ANAM[36] were used to construct the Performance Assessment Work Station (PAWS), a computer-based test battery specifically designed for the assessment of cognitive performance in space or space-related operational environments.[37] PAWS was successfully used to explore cognitive deficits associated with bedrest[38] and during microgravity.[39] In addition, ANAM tests were used to construct the NASA Spaceflight Cognitive Assessment Tool for Windows (WinSCAT), a computer test battery designed to give astronauts an objective and automated means of assessing their cognitive functioning during space flight. The ANAM battery constructed for use in this study provided measures of simple reaction time (SRT) and nonverbal memory (M2S), as well as self-reported states of mood and sleepiness. For the mood and sleepiness scales, a scale of numbered blocks ranging from 0 to 6, with "0" having the verbal anchor "Not at all," the midpoint "3" labeled "Somewhat," and "6" labeled "Very much" was utilized. The volunteer was presented a series of adjectives, each adjective contributing to one of the mood categories, and was instructed to select the box/number that best represented the current state with respect to the presented adjective. Two computers in the study investigators' office in the Phoenix SOC were dedicated to ANAM testing. Volunteers were asked to come to that office to complete the ANAM battery at the beginning and end of each shift. ANAM batteries were not completed on non-work days.

Of a possible 2,964 PVT tests and 1976 ANAM tests (assuming a 4/2 work schedule with no travel), we collected 1435 and 744 tests, respectively. Some data were missed due to participant travel during the mission. All subjects completed ≥ 1 PVT test; the mean number of PVT tests competed per subject was 75.5 ± 52.0. All 19 subjects completed at least one ANAM battery; the average number of sessions completed per subject was 41.3 ± 33.1 sessions out of approximately 100, if 2 sessions were completed every work day. ANAM and PVT data that did not have corresponding time since awakening (i.e., no actigraphy data recorded for that day) or circadian phase (i.e., could not be estimated from available aMT6s data) were excluded from analysis.
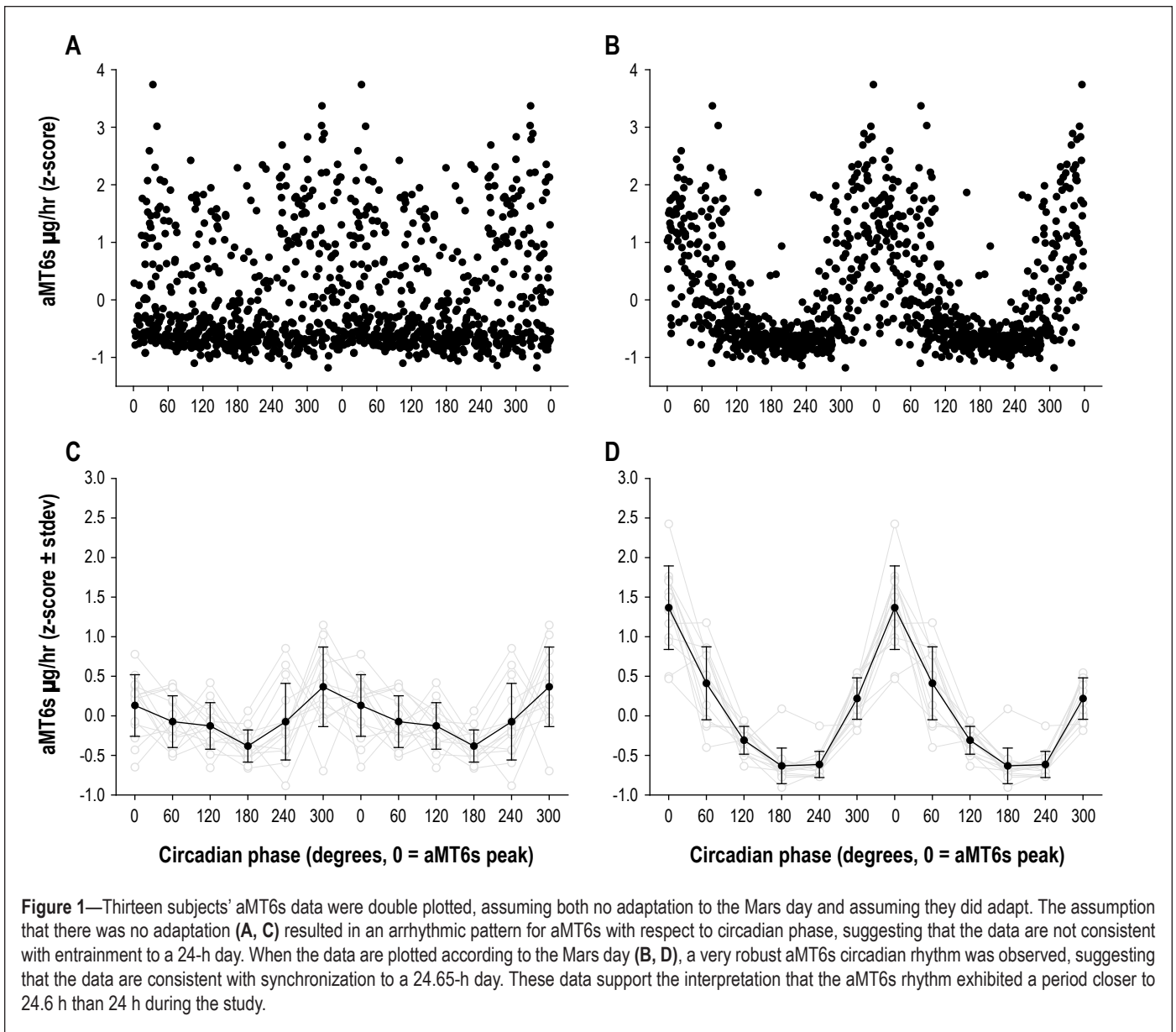
Circadian Phase

In order to determine if the participants' circadian pacemaker was able to adapt to the Mars day, we obtained a reliable measure of circadian phase throughout the mission by assaying urine samples for 6-sulphatoxymelatonin (aMT6s). Volunteers collected sequential 4-hourly urine samples (8-hourly overnight) for 48 h approximately every 2 weeks. These collections were scheduled at the convenience of the participant and may have occurred on work or non-work days. Collection duration and urine volume were measured, and a 5-mL sample saved and frozen (−20°C) until assayed. This method has been used successfully in prior studies of shiftworkers on North Sea oil rigs,[40-42] in shiftworking nurses,[43,44] in shiftworkers living in Antarctica,[45,46] and in many clinical populations and experimental protocols.[47-49]

Urinary aMT6s concentrations were measured by radioimmunoassay using the methods of Aldhous and Arendt.[50] Antiserum was supplied by Stockgrand, Ltd., University of Surrey (Guildford, UK). The intraassay coefficients of variation were 11.2, 7.3, and 9.4% at 4.2, 12.6, and 24.6 ng/mL (n = 21, each), respectively. The interassay coefficients of variation were 9.1, 6.2, and 8.3 at 4.4, 13.0, and 25.3 ng/mL (n = 10, each), respectively. Cosinor analysis of aMT6s values was used to determine acrophase (peak) time.[51] Regression analysis of significant (α set 0.10; 97% were $P < 0.05$) acrophases then determined observed period.[48]

When urine collection procedures were compromised (e.g., collection error), analysis methods were modified. In 17 of the 894 (1.9%) samples used to calculate acrophase time, the subject failed to record urine volume. In these cases, the mean urine volume for the 48-h collection period was substituted. The first data point for one subject in one 48-h collection period was removed prior to cosinor analysis due to the subject including the first morning void in the first sample of that collection period. In three 48-h urine collection periods in 3 separate subjects, the 24-h profile with no collection errors was double-plotted to provide a 48-h sequence for analysis. Finally, in two 48-h urine collections in one subject and one collection in a separate subject, one void was discarded by the subject and no sample was obtained. The subsequent sample was used for the missed collection interval in each of these 3 instances.

We were able to determine observed circadian period via linear regression in 15/19 subjects who had ≥ 3 valid phase assessments during the course of the study. Of a possible 133 col-

Figure 1—Thirteen subjects' aMT6s data were double plotted, assuming both no adaptation to the Mars day and assuming they did adapt. The assumption that there was no adaptation **(A, C)** resulted in an arrhythmic pattern for aMT6s with respect to circadian phase, suggesting that the data are not consistent with entrainment to a 24-h day. When the data are plotted according to the Mars day **(B, D)**, a very robust aMT6s circadian rhythm was observed, suggesting that the data are consistent with synchronization to a 24.65-h day. These data support the interpretation that the aMT6s rhythm exhibited a period closer to 24.6 h than 24 h during the study.

lections (19 subjects, each having a maximum of 7 collection periods), 77 sets of 48-h urine samples were collected, yielding valid aMT6s phase assessments with significant cosinor-derived acrophase (4.5 ± 1.2 per subject). The observed period in 2 subjects was segmented before and after transmeridan travel. Urine samples were not usable from one subject.

In many cases, the best fit regression line could have approximated a 24.65-h observed period or one closer to 24 h, assuming, respectively, that the subjects were or were not adapted to the Mars day. Subjects' raw aMT6s data were folded at 24 h (Figure 1A) and 24.65 h (Figure 1B). Figure 1D depicts the rhythmicity associated 24.65 h, as compared with the 24-h plot (Figure 1C), demonstrating the more likely 24.65-h observed period in this instance. Visual inspection of the rhythmicity of these plots revealed the best fit in cases of 2 potential observed periods.

Modeling

In addition to cosinor analysis, circadian phase was also estimated with a mathematical model. Sleep-wake (binary) and light exposure data (averaged in 1-h bins) collected from the MLs were used as input in a model of the effect of light on the circadian pacemaker that predicts core body temperature minimum as a marker of circadian timing (Circadian Performance Simulation Software [CPSS], version 1.2).[52-55] The model's phase and amplitude predictions have been experimentally correlated with established circadian markers.[56-60]

Analysis

To facilitate analysis by circadian phase and hours of wakefulness, outcome measures were assigned a time since wake (hours) and circadian phase (degrees). Beginning with the wake time from the main sleep episode, hours of wakefulness were assigned in eight 3-h bins. For circadian analysis, 0 degrees was assigned to the fitted daily acrophase of the aMT6s rhythm, and each circadian day was divided into four 90 degree (~6-h) bins. To estimate daily circadian phase, point-to-point lines were drawn between aMT6s acrophases and the acrophase interpolated on days without urine collections. In the case of missing acrophase data, the line was extended 3 days beyond last known acrophase (performance or mood data
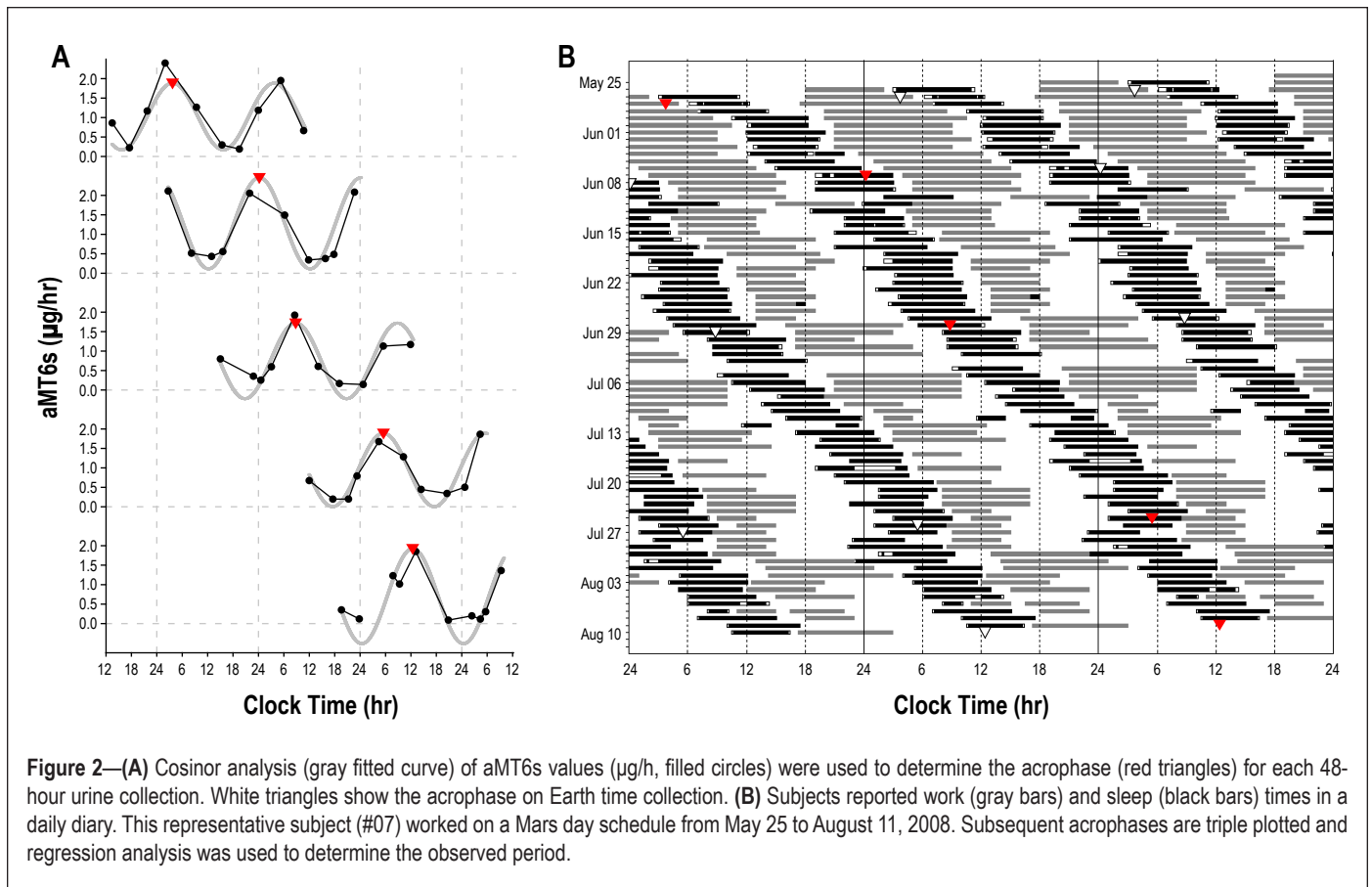
Figure 2—(A) Cosinor analysis (gray fitted curve) of aMT6s values (µg/h, filled circles) were used to determine the acrophase (red triangles) for each 48-hour urine collection. White triangles show the acrophase on Earth time collection. **(B)** Subjects reported work (gray bars) and sleep (black bars) times in a daily diary. This representative subject (#07) worked on a Mars day schedule from May 25 to August 11, 2008. Subsequent acrophases are triple plotted and regression analysis was used to determine the observed period.

collected beyond those 3 days was excluded). The duration of each circadian degree was adjusted based on the observed period between each fitted acrophase. Sleep duration, performance and mood data were analyzed according to these circadian and wake duration bins.[61,62]

Statistics

A mixed model analysis of variance was employed to determine the effects of time since awakening and circadian phase for all sleep, performance and mood variables (SAS Institute, Cary, NC, version 9.1.3). A Pearson correlation coefficient determined the association among observed periods estimated from aMT6s, the mathematical models, and between observed period and exposure to blue light. A Wilcoxon 2-sample test was used to compare categorical answers on the questionnaire. All errors are reported as standard deviation of the mean unless otherwise noted.

RESULTS

Detailed studies were conducted in a subset (n = 19, 6F, mean age ± SD = 36.8 ± 9.7 years), of ~13% of the approximately 150 ground crew mission personnel. The first Mars day began at ~17:00 when the Phoenix spacecraft landed on Mars. Two main shifts provided coverage, with each shift scheduled to start ~39 min later each day, although satellite communications necessitated variations in the schedule (Figure 2). Personnel were generally required to work 4-days-on/2-days-off for 78 days, before reverting to an Earth schedule on August 11, 2008. The average reported work shift duration was 8.6 ± 2.6 h, with ~30% of shifts lasting ≥ 10 hours.

Circadian Period

Most of the participants (13/15, 87%) exhibited circadian rhythms in urinary 6-sulfatoxymelatonin (aMT6s) that were synchronized to the Mars day (τ range, 24.58-24.83h; mean τ ± SD = 24.70 ± 0.07h; Table 1, Figures 2 and 3). Two of these subjects (#09 and #10) traveled to Europe in the middle of the mission and, while both were adapted to the Mars day prior to travel (τ = 24.78 h and 24.83 h), they were unable to re-adapt upon their return (τ = 24.08 and 24.37 h, respectively). Two subjects remained entrained to Earth time (τ = 23.98 and 23.93 h); one had a very erratic travel schedule throughout the mission (#06), and the other (#19) did not appear to adhere to a Mars day work schedule. Four subjects had insufficient urine data for assessment.

We also predicted circadian period from simulations using experimental sleep-wake and light-dark cycle data as input to a mathematical model of the effects of light on the human circadian pacemaker.[63] The mathematical model-based simulations were in agreement with the aMT6s acrophases, which showed that the majority of participants (17/19; 89%) were adapted to a Mars day (Table 1). The observed aMT6s circadian period was highly correlated with the model predictions ($r^2 = 0.86$, $P < 0.001$).

Sleep

For sleep episodes recorded by actigraphy, subjects slept an average of 6.2 ± 0.9 h per Mars day during their main sleep period, representing only 25% of each "day" (Figure 4). Subjects exhibited chronic sleep deficiency, with 50% of sleep episodes lasting ≤ 6 h, and only 23% lasting ≥ 7 hours.[26,64] Sleep duration was dependent on the circadian phase at which sleep was initiated (F = 16.96, P < 0.001; Figure 5). In those sleep periods when cir-

Subject	aMT6s	CPSS V1.2
01*	24.63 ± 0.14	24.62 ± 0.03
02	24.71 ± 0.12	24.63 ± 0.04
03	24.58 ± 0.27	24.60 ± 0.03
04	24.69 ± 0.26	24.65 ± 0.01
05	24.73 ± 0.22	24.62 ± 0.02
06	23.98 ± 0.08	23.99 ± 0.01
07	24.73 ± 0.28	24.74 ± 0.02
08	Insufficient data	24.66 ± 0.05
09**	24.78 ± 0.08	24.72 ± 0.03
10**	24.83 ± 0.81	24.69 ± 0.04
11**	24.72 ± 0.18	24.57 ± 0.03
12*	24.69 ± 0.13	24.83 ± 0.05
13	Insufficient data	24.81 ± 0.03
14	24.58 ± 0.44	24.74 ± 0.04
15	Insufficient data	24.67 ± 0.04
16	Insufficient data	24.65 ± 0.04
17	24.71 ± 0.18	24.67 ± 0.03
18	24.74 ± 0.14	24.71 ± 0.04
19	23.93 ± 0.14	23.81 ± 0.05

*aMT6s data span short transmeridian travel during Mars day work schedule.
**aMT6s data prior to transmeridian travel during Mars day work schedule; subjects 9 and 10 were unable to adapt to the Mars day after returning from travel; subject 11 did not have sufficient data to analyze post-travel.

use. Across the 78 days of Mars days, subjects were nominally scheduled to work ~52 days on a 4on/2off schedule; the light boxes were switched on an average of 25.3 ± 12.4 days of the 78-day mission. On those days, it was switched on for an average of 4.0 ± 1.8 hours. The subjects' average exposure to the light box, calculated from ML light exposure data, was slightly less in number of days (21.1 ± 10.5 days) and hours per day (2.2 ± 1.1 h). Short-wavelength light exposure duration may be underestimated, as light exposures could not be quantified on days when actigraphy was not collected. Additionally, the light sensor was part of the ML worn on the wrist; it was thus not a perfect measure of light exposure to the eye and may have further underestimated exposure.
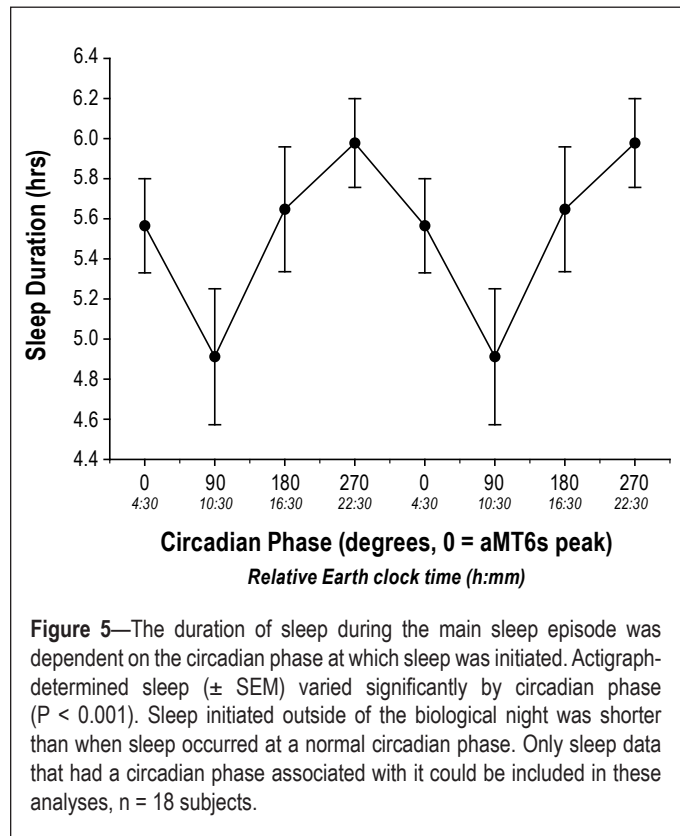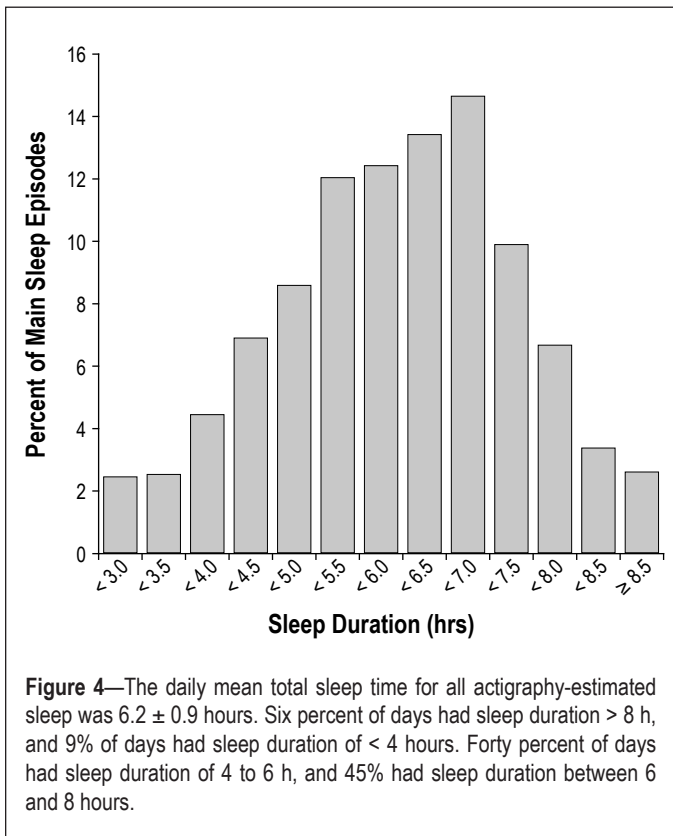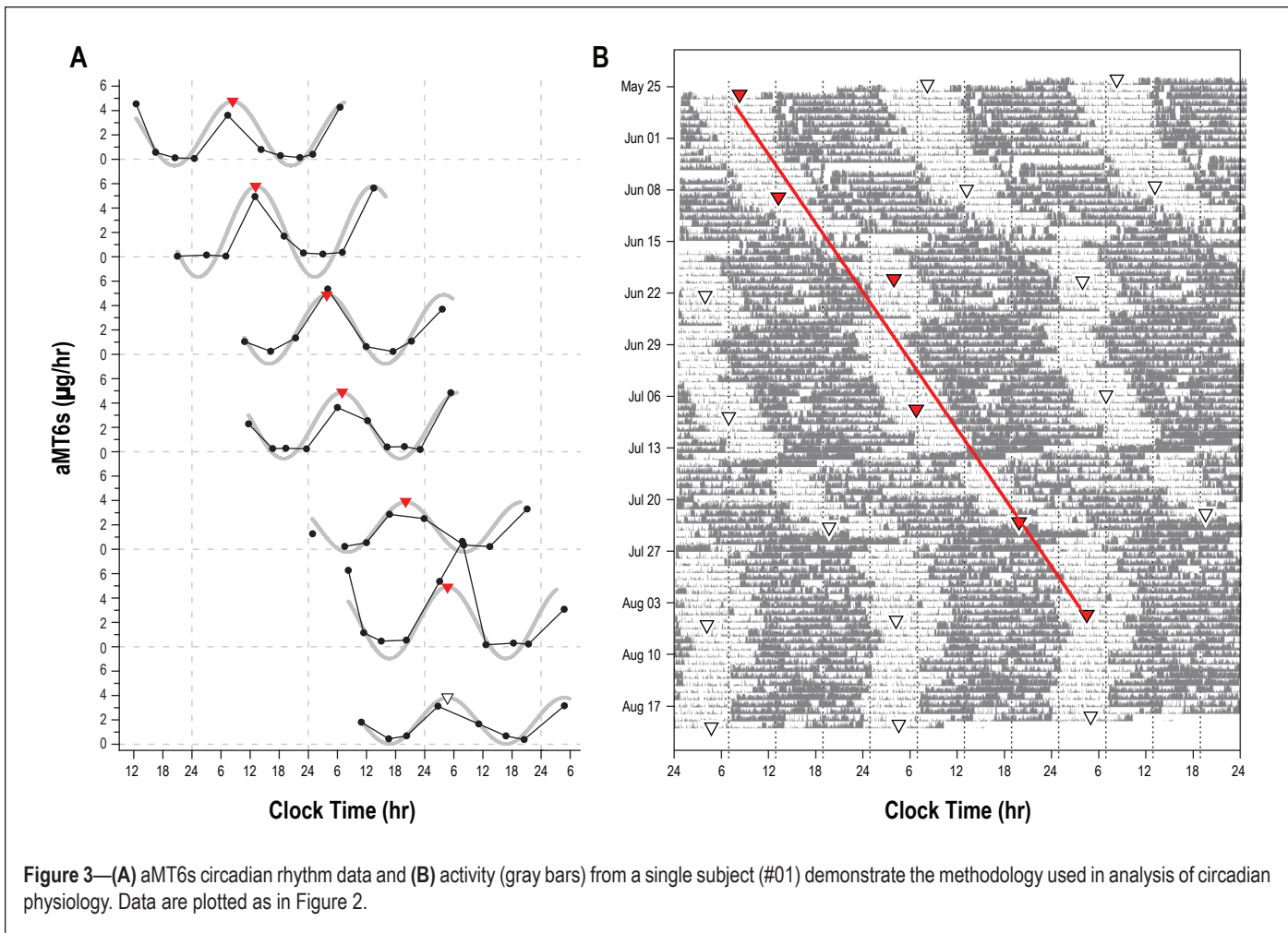
There was no significant association between an individual's exposure to the light box and the observed circadian period. Two of the 3 participants who did not receive a light box adapted to the Mars day work schedule, according to aMT6s-estimated observed period (#02 and #03). We were unable to analyze the urine collected from the third participant who did not receive a light box (#08), but the subject did appear to adapt to the Mars day work schedule according to the circadian model estimates, based on wrist light exposure and actigraphy-estimated sleep-wake timing (Table 1).
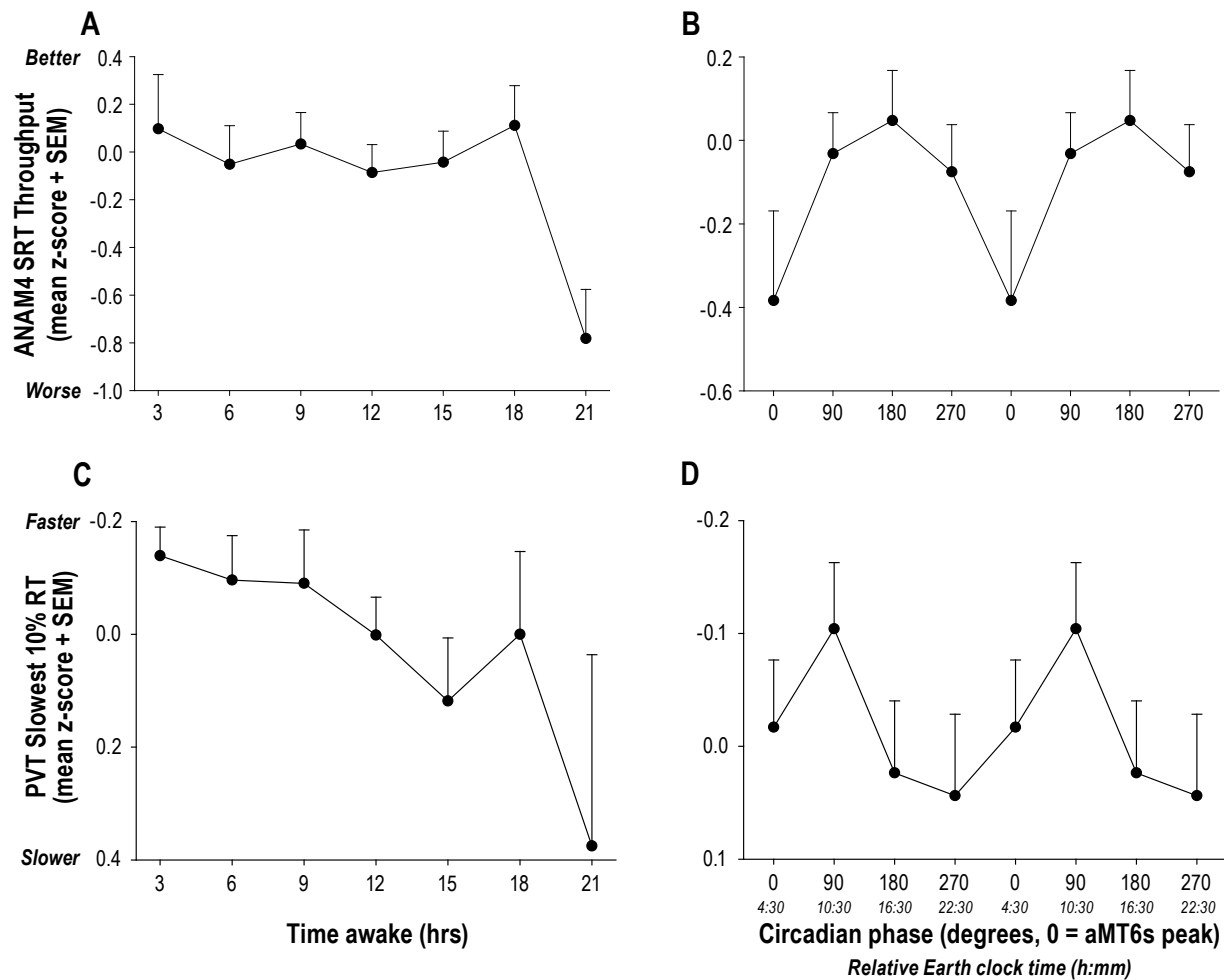
Questionnaires

According to the sleep/work log, volunteers reported 2.16 ± 0.35 servings of caffeine per day (1 serving = 1 cup of coffee/tea or 1 caffeinated soda) which trended slightly higher on work (2.23 ± 0.36 servings) compared to non-work days (1.91 ± 0.36 servings; P = 0.06). Volunteers also completed a post-mission questionnaire (response rate 74%, [14/19]). Most (64%) reported that working on a Mars day was "somewhat easy" or "very easy," 29% reported it to be "somewhat difficult." Fatigue was reported "strongly increased" or "moderately increased" for 64% of respondents. Twenty-eight additional support personnel (out of the 52 present when surveys were distributed; 54% response rate) who did not volunteer for the full study also completed the questionnaire, and 75% reported that fatigue "strongly increased" or "moderately increased" during Mars day operations. Of those individuals, 42% reported it was "somewhat difficult" to work on a Mars day and 8% reported it was "very difficult." Thus, in this limited sample, those who did not volunteer for the fatigue management program reported greater difficulty working on the Mars day than the study volunteers (Z = −2.01, P = 0.044).

cadian phase was available, main sleep duration was 5.98 ± 0.94 h when synchronized but fell to 4.91 ± 1.22 h when misaligned (P < 0.001), a decrease of 18% when sleep was initiated during the biological day (Figure 5). Seventeen of the 19 subjects used naps as a fatigue countermeasure, as was recommended in the pre-mission education. Each nap lasted 1.3 ± 0.6 h, and participants used this countermeasure on an average of 6.2 ± 5.0 days.

Alertness and Performance

Performance on the nonverbal memory (M2S) and serial reaction time (SRT) tasks deteriorated with increased time awake ($F_{6,128} = 2.42$, P = 0.030; $F_{6,135} = 2.35$, P = 0.024, respectively; Figure 6) as did the response time of the slowest 10% of PVT trials ($F_{6,1161} = 2.76$, P = 0.012; Figure 6). Self-reported ratings for anxiety, sleepiness and vigor also worsened with increased time awake ($F_{6,127} = 2.37$, P = 0.04; $F_{6,170} = 13.97$, P < 0.001; $F_{6,131} = 8.21$, P < 0.0001, respectively). Self-reported Karolinska Sleepiness Scale (KSS) ratings were dependent on both time since awakening ($F_{6,1178} = 30.58$, P < 0.0001) and circadian phase ($F_{3,1178} = 6.81$, P = 0.0001), as were self-reported ratings of fatigue ($F_{17,120} = 1.84$, P = 0.03; [interaction]; Figure 7). Sleepiness and fatigue were greater with increased time awake and when assessed during the biological night.

Short-Wavelength (Blue) Light Exposure

The use of the light boxes varied by participant; some switched it on when at work almost all the time, some switched it on sporadically, while others started and then discontinued

DISCUSSION

The ground operations were linked with to the 24.65-hour Mars day in order to optimize the work of the solar powered lander, and to maximize the Lander time and the amount of science that can be conducted in the Martian environment that was limited by the imminent Martian winter. That is, the Lander is solar powered and operations on Mars could only occur during the daylight hours or shortly thereafter. After the data were transmitted to Earth each day; they then had to be assessed before scientific and operational decisions could be made, prioritized, programmed, and uploaded to the spacecraft to maximize scientific operations. Additionally, the expertise in each Lander system was limited, such that there were not

Figure 3—**(A)** aMT6s circadian rhythm data and **(B)** activity (gray bars) from a single subject (#01) demonstrate the methodology used in analysis of circadian physiology. Data are plotted as in Figure 2.

Figure 4—The daily mean total sleep time for all actigraphy-estimated sleep was 6.2 ± 0.9 hours. Six percent of days had sleep duration > 8 h, and 9% of days had sleep duration of < 4 hours. Forty percent of days had sleep duration of 4 to 6 h, and 45% had sleep duration between 6 and 8 hours.

Figure 5—The duration of sleep during the main sleep episode was dependent on the circadian phase at which sleep was initiated. Actigraph-determined sleep (± SEM) varied significantly by circadian phase (P < 0.001). Sleep initiated outside of the biological night was shorter than when sleep occurred at a normal circadian phase. Only sleep data that had a circadian phase associated with it could be included in these analyses, n = 18 subjects.

Figure 6—Performance was dependent on the number of continuous hours awake. The slowest 10% response times (mean + SEM) significantly increased (**A**; P = 0.012) and throughput on the ANAM SRT decreased (**C**; P = 0.024) as a function of time awake. Both performance measures also exhibited evidence of circadian modulation, with a trend for decreased performance during biological night **(B and D)**.

enough personnel qualified to accomplish the work in a typical terrestrial shift schedule.

Adapting the human sleep-wake and performance cycle to a 24.65-h Mars day represents a substantial physiological challenge, with individuals requiring as much as an hour per day delay in their intrinsic circadian pacemaker. While successful countermeasures have been simulated previously in the laboratory, the Mars Phoenix Lander mission provided an opportunity to test the acceptability, feasibility, and effectiveness of a fatigue management program to facilitate synchronization with the Mars day in an operational environment. Eighty-seven percent of the subjects who participated in our study, as part of the Mars Phoenix Lander fatigue management program, were able to synchronize to a Mars day schedule as assessed using both physiological measures of circadian phase and mathematical modeling. As expected, when subjects' work and sleep schedules were appropriately synchronized with the circadian pacemaker, they exhibited longer sleep duration, better alertness, and reduced fatigue. Overall, daily sleep duration averaged just over 6 hours across the study, not unexpectedly reflecting sleep deficiency in modern society.[65,66]

Prior missions have demonstrated that working Mars day schedules without appropriate countermeasures can cause se-vere problems with sleep, performance, and compliance. Reports from the earlier Mars Pathfinder missions that did not employ dedicated circadian and sleep countermeasures indicated less success in adaptation to the Mars day schedule than our current study. Based on NASA surveys of 24 Mars Pathfinder veterans, those supporting the Sojourner Rover indicated that fatigue significantly affected their performance at work to the extent that they discontinued work on the Mars day schedule after only one month and described the schedule as "broken."[8] JPL managers described the scientists' and engineers' discontinuation of the Mars day schedule as a "rebellion."[10]

The 2004 MER mission personnel appeared more successful than those supporting the Pathfinder in adapting to a Mars day. Nine subjects participated in the objective measurement of sleep during the mission using actigraphy, and 22 subjects completed questionnaires. Actigraphy-based sleep/wake period reportedly increased from 24.08 h during a 2-week baseline Earth schedule to 24.84 h during the approximately 90-day Mars day schedule.[9] Although these data suggest that the circadian systems of these participants were able to adjust to the Mars day schedule, the sleep-wake cycle is a relatively poor measure of circadian phase,[67] especially when risk of desynchrony is high.[43,68] Despite the apparent entrainment, the survey
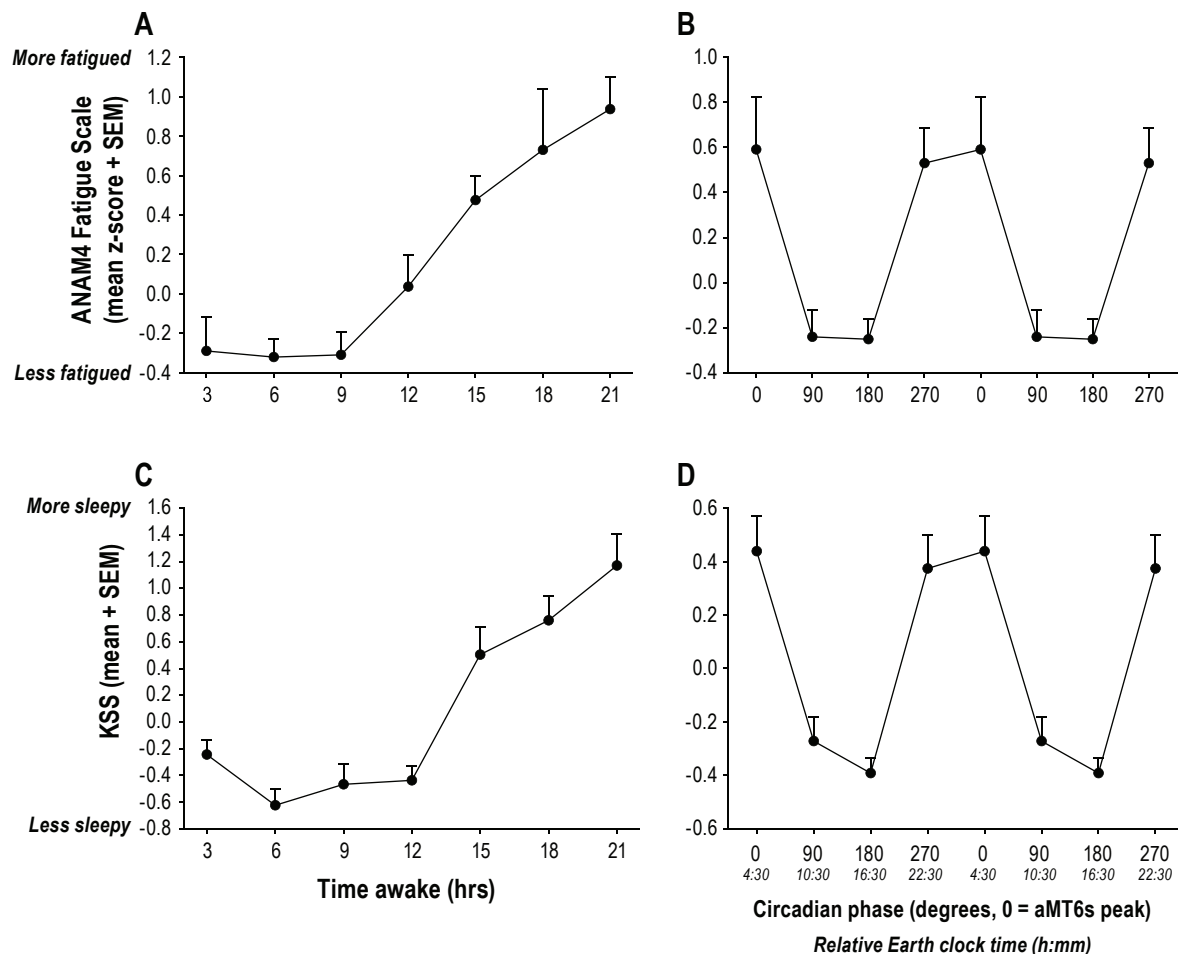
Figure 7—Subjective sleepiness and fatigue ratings were dependent on the number of continuous hours awake and circadian phase. Self-reported sleepiness significantly increased with time awake on both the KSS (**A**; P < 0.0001) and the ANAM Fatigue scale (**C**; P = 0.0001). Both measures also exhibited a robust circadian rhythm, with highest sleepiness reported when subjects were awake during the biological night (**B**, P = 0.0001; and **D**, P = 0.0003).

responses indicated that fatigue and stress problems were greater than in the previous Pathfinder mission.[9] Notably, in our current study, Phoenix support personnel who did not participate in the fatigue management program reported nearly double the rate of difficulty in working on a Mars day (50% versus 29%, respectively) and more fatigue (75% versus 64%, respectively) than those who participated in our program.

Performance data were not reported in the MER technical report, although Bass and colleagues reported one MER team member was injured after a series of Mars time shifts when he mistakenly walked into a wall and another reported falling asleep at the onramp to the freeway.[11] A previous two-week "Mars analog" study (but conducted on Earth time) in four subjects did not show decrements associated with time awake in PVT performance or subjective sleepiness (KSS). The authors attributed this result to the high motivation of the crew,[69] although motivation has limited ability to override circadian and homeostatic regulation of alertness and performance and is, in fact, subject to these influences itself.[70] Seven crewmembers at the Flashline Mars Arctic Research Station on Devon Island, Canada, lived on a Mars day for 37 days. O'Griofa and colleagues reported improved alertness and reduced fatigue from diary data and improved decision speed in performance test-

ing.[71] Objective cardiopulmonary monitoring of sleep was conducted on four of the crewmembers and showed no statistical differences between pre-mission and the Mars day.[71] These data, collected relative to the sleep-wake cycle of the study participants, are difficult to interpret. As demonstrated in our current study, although the average circadian period may be synchronized to the Mars day, subjects' sleep-wake and work schedules sometimes occur at an abnormal circadian phase, resulting in reduced sleep and poorer alertness and performance. Quantifying these important distinctions is not possible in studies that do not measure a marker of endogenous circadian phase in addition to sleep. Although the measurement of circadian phase can be challenging in operational settings and melatonin's sensitivity to light may be considered a potential confounder in the analysis of aMT6s results, the method has been successfully used in a multitude of field studies (See supplemental matierals for additional information on light as a potential confounding factor in interpreting aMT6s data).[40-49] We would recommend inclusion of a circadian marker in all future analog studies and spaceflight missions in order to interpret sleep, alertness, and performance data most accurately.

The consequence of misalignment between sleep and circadian phase on alertness and performance were illustrated in

the current study. The time course and pattern of alertness and performance are regulated by the interaction of two oscillatory processes—the circadian clock and a homeostatic hourglass regulator—as described in the two-component model of sleep-wake regulation.[61,72-74] The circadian system regulates the daily pattern of sleep propensity, such that alertness and performance are worst during the biological night, when sleep usually occurs. The homeostatic component predicts alertness and performance based on the duration of wake and sleep; performance worsens with increasing time awake and improves after greater time asleep. These factors interact in a nonlinear manner[75] and are further exacerbated by chronic sleep deficiency.[76] Despite the operational setting and large number of factors that could affect alertness and performance in the workplace (e.g., unlimited access to caffeine, light, mission anxiety and other potential confounders), we were able to detect significant changes in alertness and fatigue with respect to both time awake and circadian phase. When subjects worked after an extended time awake (≥ 21 h), or worked during the biological night (Figures 6, 7), alertness and fatigue worsened, as predicted.[73,77] Significant circadian variations were not observed in all performance metrics, most likely due to study power, although performance was slowest when wake time occurred during the biological night as predicted from prior laboratory[6,62,78-80] and field studies[61,81] of circadian misalignment. The biological principles that underlie alertness and performance are therefore apparent in an uncontrolled operational setting, even among such highly trained and highly motivated professionals.

The success of manned and unmanned space missions depends on the ability of the crew and the support team to be alert and maintain high levels of cognitive function while operating complex, highly technical equipment, regardless of whether they are in-flight or part of mission control. Human error is a common cause of accidents and injuries,[82] and even relatively simple mistakes can jeopardize critical mission operations that have often taken decades to plan, at a cost of hundreds of millions of dollars. The risks to sleepiness and performance conferred by unusual work schedules have been extensively documented.[9-11,83,84] Our current data show that the risk of making a sleepiness-related error is not random and is predicted by sleep and circadian principles, and therefore may be prevented with the application of appropriate countermeasures. Such risk mitigation should be considered an integral part of future mission planning, particularly when there is a risk of circadian desynchrony due to working on a non–24-hour schedule in space and other environments, such as submarines[85] and polar regions.[45,86]

A major component of our planned intervention was a timed photic countermeasure, provided via a portable blue light box. Placing the light box at the work station was only feasible for 84% (16/19) of the participants in the study, and many jobs required them to move about the SOC frequently away from this light stimulus. Light box use was highly variable among participants, averaging just over two hours of blue light exposure per day. Although the majority of volunteers successfully adapted to the Mars day schedule as measured by aMT6s analysis, there was no significant relationship between the number of hours of light box exposure and the observed circadian period. Outside of the SOC, natural light was also freely available in the Tucson summer which could enhance or inhibit appropriate adaptation,

depending on the circadian phase of exposure.[13] We provided education sessions to explain these circadian principles and gave generic advice when to seek and when to avoid light exposure. Given that two of the three who were not provided with a light box also adapted to the Mars day, the effects of all environmental light exposure (measured with the Motionlogger-L) was evaluated with a mathematical model, which demonstrated that appropriate exposure to external light may have provided sufficient entraining stimulus. In future missions, a more integrated lighting countermeasure that could benefit the entire ground crew would be preferable, for example by retrofitting existing fixtures with white-appearing, blue-enriched lamps[87] or developing new state-of-the-art programmable smart lighting systems.[88]

Environmental factors other than light may also have contributed to the adaptation to the Mars day schedule, given that knowledge of time of day, exercise, living routine, social communication, and group habitation can influence the human circadian system, albeit weakly.[89] Bass and colleagues suggested that personnel who temporarily locate to the mission operations center have less difficulty working on the Mars day schedule,[11] possibly due to lack of competing family and personal commitments that continued on an Earth schedule. The Phoenix Mars Lander mission was the first Mars robotic mission based outside the NASA JPL, perhaps lessening the number of workers living with their families; approximately two-thirds of our participants did not permanently live in Tucson. Future studies should consider the influence of these social pressures and account for them in study designs. Operational constraints prevented us from implementing a randomized control study design. As such, we cannot rule out that outcomes were not influenced by a study or placebo effect.[90] It is unlikely, however, that adaptation to the Mars day results were under this influence. Circadian adaptation and melatonin regulation (assessed in this study by measurement of urinary aMT6s) have been shown to be quite resistant to placebo effects.[91,92] Additionally, we cannot determine the relative contribution of each aspect of the fatigue management program (e.g., education, photic countermeasure) on adaptation to the Mars day. Laboratory studies have shown that scheduling alone, without sufficient light, is inadequate for adaptation to a Martian schedule.[6,7]

NASA has an ambitious Mars exploration program. The Mars rover, Curiosity, landed on Mars in August 2012, and both unmanned and manned missions are in the planning stages.[84,93,94] Thus, the challenges of living and working on a Mars day will require additional investigation and resources. In the near-term, we would recommend development of an extensive education and integrated countermeasures program for forthcoming missions. An ongoing circadian rhythm and fatigue management program that would continually monitor individual performance and provide rapid feedback and countermeasure adjustment as a mission progresses is also recommended. Our study demonstrates that it is possible to collect precise circadian phase and sleep data during a high-tempo, dynamic, and operational mission environment. These data are critically important for the identification and mitigation of performance and sleepiness-related risk. Missions of this importance and cost demand a dedicated, integrated fatigue management program with appropriate countermeasures to prevent avoidable and potentially catastrophic fatigue-related error.

DISCLOSURE STATEMENT

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Is Light a Confounding Factor in Interpretation of aMT6a Data?

Suppression of melatonin by light is a potential confounding factor in interpreting the urinary 6-sulfatoxymelatonin (aMT6s) data. We examined whether circadian amplitude changed systematically during the study as might be expected if the light-dark cycle was affecting melatonin level. First, we examined whether there was a systematic change across the study. As shown in Figure S1, no simple systematic change was apparent. Subjects began the study at different circadian phases (n = 14, initial 48-h collection period within 5/24-28/2008, 5.6 am ± 1.9 h, range 3.7-9.7 am, median 4.8 am; the majority of participants were not local Tucson residents).

We then examined whether the amplitude varied with the timing of the melatonin peak (acrophase); if light was suppressing melatonin, one might expect that the melatonin amplitude would be lower when melatonin peaked in the daytime. As shown in Figure S2, there was no evidence of reduced amplitude during daytime peaks when controlled for inter-individual differences in melatonin level.

Given that the Mars day work schedule was not aligned with the 24-h light-dark cycle, the relevance of examining amplitude with respect to day and night could be questioned. The next step, therefore, was to examine whether the amplitude changed as a function of whether it occurred during sleep episodes, in the dark, or a wake episode, when it would be more likely to be light. If light was systematically suppressing melatonin, one might hypothesize lower amplitudes when the peak time occurred during wake episodes as compared to sleep episodes. As shown in Figure S3, there was again no systematic change in amplitude with respect to the light-dark cycle.

In a subset of 7 subjects, we assayed the same urine samples for cortisol, which is much less confounded by light, Figure S4. The acrophases for aMT6s and cortisol were significantly correlated (average Pearson r ± STDEV, 0.98 ± 0.01) in these sighted subjects, as we have previously reported for these urinary markers in the blind.[1] Cortisol data were not reported in this manuscript because financial restrictions only allowed analysis of a subset of participants.

Additionally, this method has been used successfully to assess circadian phase in multiple real-world studies, including studies of shiftworking nurses, in shiftworkers on North Sea oil rigs, and in shiftworkers living in Antarctica. It has also been used to assess melatonin levels and circadian rhythms in children, including patients with autism, blindness, and epilepsy and in many other clinical populations and experimental protocols.[3-23]

Furthermore, we plotted the aMT6s data assuming no adaptation to the Mars day (i.e., on a ~24-h scale) and assuming that they did adapt (i.e., on a ~24.65-h scale). As illustrated in Figure 1, the assumption that there was no adaptation (Figure 1, Panels A, C) resulted in an arrhythmic pattern for aMT6s with respect to circadian phase, suggesting that the data are not consistent with entrainment to a 24-h day. When the data are plotted according to the Mars day (Figure 1, Panels B, D), a very robust aMT6s circadian rhythm was observed, suggesting the data are consistent with synchronization to a 24.65-h day.
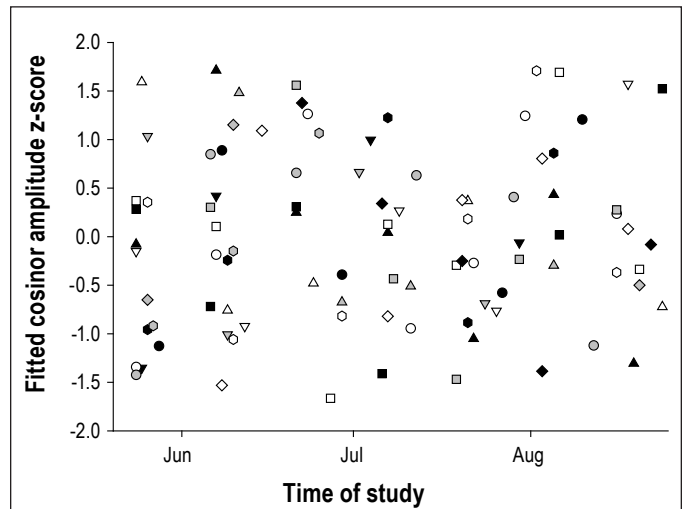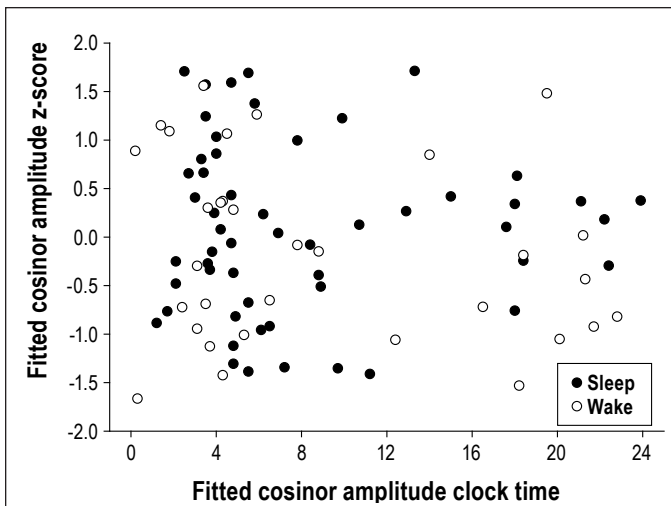

Figure S1—aMT6s amplitudes at fitted acrophase for all subjects (n = 18, aMT6s μg/hr z-score) plotted across duration of study. Each symbol represents a different subject (symbols consistent with Figures S2 and S4)
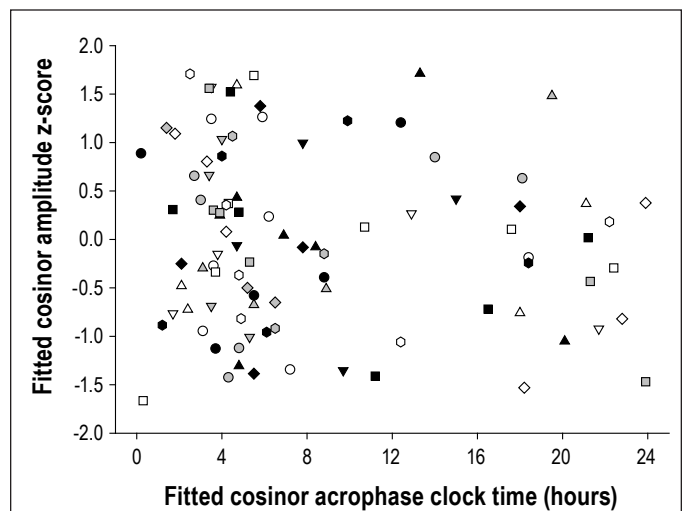
Figure S2—aMT6s amplitudes at fitted acrophase for all subjects (n = 18, aMT6s μg/hr z-score) plotted across time of day of fitted acrophase. Each symbol represents a different subject (symbols consistent with Figures S1 and S4).

Finally, it is well established from highly controlled laboratory studies conducted in dim light that sleep duration and alertness change in a predictable manner with respect to circadian melatonin rhythm, such that sleep is longest when the sleep episode coincides with the biological night, indicated by the melatonin peak, and shortest when sleep occurs during the biological day, when no melatonin is produced.[2] As illustrated in Figure 4, these predicted relationships persist in the current data.
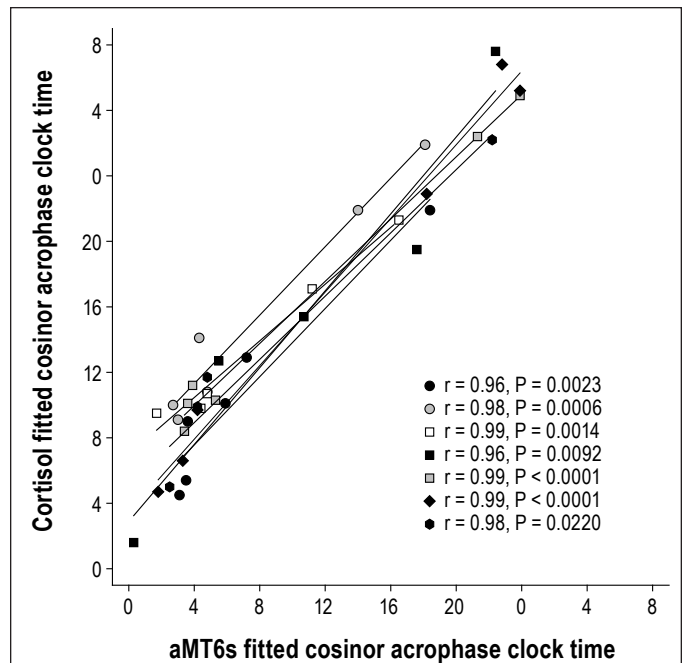
Thus, although that suppression of melatonin by light is a potential confounder in interpreting the aMT6s data, we do not believe it is a factor in this study.

Figure S3—aMT6s amplitudes at fitted acrophase for all subjects (n = 18, aMT6s µg/hr z-score, 8 acrophases excluded due to missing actigraphy to categorize sleep/wake). Closed circles indicate acrophases that occurred during sleep and open circles indicate acrophases that occurred during wake. There was no difference in amplitude when the peak occurred during wake or sleep (unpaired Student's *t*, P = 0.25).

Figure S4—aMT6s acrophase times vs. cortisol acrophase times for 7 subjects. Each symbol represents a different subject (symbols consistent with Figures S1 and S2).

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