

Evidence Report:

Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload

Human Research Program
Behavioral Health and Performance Element

Approved for Public Release: Month DD, YYYY

National Aeronautics and Space Administration
Lyndon B. Johnson Space Center
Houston, Texas

Current Contributing Authors:

Erin Evans-Flynn, Ph.D	<i>NASA Ames Research Center</i>
Kevin Gregory, B.S.	<i>NASA Ames Research Center</i>
Lucia Arsintescu, M.A.	<i>San Jose State University Foundation</i>
Alexandra Whitmire, Ph.D.	<i>NASA Johnson Space Center</i>
Lauren B Leveton, Ph.D.	<i>NASA Johnson Space Center</i>

Previous Contributing Authors:

Laura Barger, Ph.D.	<i>Harvard Medical School and Brigham and Women's Hospital</i>
George Brainard, Ph.D.	<i>Jefferson Medical College, Thomas Jefferson University</i>
David F. Dinges, Ph.D.	<i>University of Pennsylvania School of Medicine and Drexel University</i>
Elizabeth Klerman, MD, Ph.D.	<i>Harvard Medical School and Brigham and Women's Hospital</i>
Camille Shea, Ph.D.	<i>Universities Space Research Association</i>

Table of Contents

I. PRD RISK TITLE: RISK OF PERFORMANCE DECREMENTS AND ADVERSE HEALTH OUTCOMES RESULTING FROM SLEEP LOSS, CIRCADIAN DESYNCHRONIZATION AND WORK OVERLOAD	7
II. EXECUTIVE SUMMARY	7
III. INTRODUCTION	9
IV. EVIDENCE	13
A. Spaceflight Evidence	13
B. Ground-based evidence	26
V. COMPUTER-BASED MODELING AND SIMULATION	49
VI. RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS	53
VII. GAPS	55
VIII. CONCLUSION	56
IX. REFERENCES	58
X. TEAM	72
XI. LIST OF ACRONYMS	73
APPENDIX A: MEASUREMENT OF SLEEP, CIRCADIAN PHASE AND WORKLOAD	75
APPENDIX B: INTERNATIONAL SPACE STATION LIGHTING	76

I. PRD RISK TITLE: Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization and Work Overload.

II. EXECUTIVE SUMMARY

Sleep loss, circadian desynchronization, and work overload occur to some extent for ground and flight crews, prior to and during spaceflight missions. Ground evidence indicates that such risk factors may lead to performance decrements and adverse health outcomes, which could potentially compromise mission objectives. Efforts are needed to identify the environmental and mission conditions that interfere with sleep and circadian alignment, as well as individual differences in vulnerability and resiliency to sleep loss and circadian desynchronization. Specifically, this report highlights a collection of new evidence to better characterize the risk and reveals new gaps in this risk as follows:

- *Sleep loss* is apparent during spaceflight. Astronauts consistently average less sleep during spaceflight relative to ground-based evaluation. The causes of this sleep loss remain unknown, however ground-based evidence suggests that the sleep duration of astronauts is likely to lead to performance impairment and short and long-term health consequences. Further research is needed in this area in order to develop screening tools to assess individual astronaut sleep need in order to quantify the magnitude of sleep loss during spaceflight; current and planned efforts in BHP's research portfolio address this need. In addition, it is still unclear whether the conditions of spaceflight environment lead to sleep loss or whether other factors, such as work overload lead to the reduced sleep duration. Future data mining efforts and continued data collection on the ISS will help to further characterize factors contributing to sleep loss.
- *Sleep inertia* has not been evaluated during spaceflight. Ground-based studies confirm that it takes two to four hours to achieve optimal performance after waking from a sleep episode. Sleep inertia has been associated with increased accidents and reduced performance in operational environments. Sleep inertia poses considerable risk during spaceflight when emergency situations necessitate that crewmembers wake from sleep and make quick decisions. A recently completed BHP investigation assesses the effects of sleep inertia upon abrupt awakening, with and without hypnotics currently used in spaceflight; results from this investigation will help to inform strategies relative to sleep inertia effects on performance.
- *Circadian desynchrony* has been observed during spaceflight. Circadian desynchrony during spaceflight develops due to schedule constraints requiring non-24 operations or 'slam-shifts' and due to insufficient or mis-timed light exposure. In addition, circadian misalignment has been associated with reduced sleep duration and increased medication use. In ground-based studies, circadian desynchrony has been associated with significant performance impairment and increased risk of accidents when operations coincide with the circadian nadir. There is a great deal of information available on how to manage circadian misalignment, however, there are currently no easily collected biomarkers that can be used during spaceflight to determine circadian phase. Current research efforts are addressing this gap.

- *Work overload* has been documented during current spaceflight operations. NASA has established work hour guidelines that limit shift duration, however, schedule creep, where duty requirements necessitate working beyond scheduled work hours, has been reported. This observation warrants the documentation of actual work hours in order to improve planning and in order to ensure that astronauts receive adequate down time. In addition to concerns about work overload, ground based evidence suggests that work underload may be a concern during deep space missions, where torpor may develop and physically demanding workload will be exchanged for monitoring of autonomous systems. Given that increased automation is anticipated for exploration vehicles, fatigue effects in the context of such systems needs to be further understood.
- *Performance metrics* are needed to evaluate fitness-for-duty during spaceflight. Although ground-based evidence supports the notion that sleep loss, circadian desynchronization and work overload lead to performance impairment, inconsistency in the measures used to evaluate performance during spaceflight make it difficult to evaluate the magnitude of performance impairment during spaceflight. Work is underway to standardize measures of performance evaluation during spaceflight. Once established, such performance indicators need to be correlated with operational performance.
- *Individual differences* in sleep need and circadian preference, phase shifting ability and period have been documented in ground-based studies. Individual differences in response to sleep loss and circadian misalignment have also been documented and are presumed to be associated with genetic polymorphisms. No studies have systematically reported individual differences in sleep or circadian-related outcomes during spaceflight. More work is needed in this area in order to identify genetic or phenotypic biomarkers that predict resilience or vulnerability to sleep loss in order to personalize countermeasure strategies and mitigate performance impairment during spaceflight. Two laboratory and field investigations specific to this topic are currently ongoing; additional efforts, including an effort to mine existing biological data from spaceflight relative to sleep and circadian outcomes, is planned.
- *Sex differences* in sleep need and circadian period and phase have been reported in ground-based studies. The impact of these sex differences on performance is unclear. Sex differences in sleep need and circadian rhythms have not been systematically studied during spaceflight, presumably due to the small number of women that have flown in space. More research is needed in this area to evaluate whether any of the observed sex differences in physiology lead to altered performance in spaceflight and on the ground.
- *Countermeasures* to mitigate the impact of sleep loss, circadian desynchronization and work overload have been deployed on the International Space Station. The most prevalent countermeasure in use at the present time is sleep medication. Other countermeasures used by crewmembers include napping, sleep extension, caffeine and other wake-promoting drugs. Presently, the effectiveness of countermeasure use during spaceflight is unknown. Research is needed to evaluate the effectiveness and pharmacokinetics of sleep medication during spaceflight. New solid-state lighting arrays (SSLAs) are being deployed to ISS in order to promote circadian entrainment, phase shifting and to enhance alertness during critical operations. An additional flight investigation, also planned for 2016, will further evaluate the effectiveness, feasibility and acceptability of the SSLAs on the ISS, is planned to begin in 2016. Ground-based evidence suggests that other countermeasures may be useful to consider in future

spaceflight operations, including the use of millisecond pulses of light during sleep to facilitate circadian entrainment and phase shifting and comprehensive fatigue risk management systems as used by aviation and military personnel; accordingly, evidence reviews and early discussions are being held with military and content experts.

- *Biomathematical models* to predict fatigue show promise for aiding operational personnel in scheduling the timing of sleep and other activities. At the present time, while NASA has supported the development of two models specific to the needs of spaceflight, there is no comprehensive model that accurately predicts performance impairment arising from acute and chronic sleep loss, sleep inertia and circadian desynchrony. In addition, none of the models has been validated to predict individual differences in performance and few countermeasures have been incorporated into model predictions. There are numerous models in use in different sectors of government and industry. There is a need for information exchange between model users in order to identify the most appropriate models for guiding spaceflight operations. Planned efforts seek to validate the models prior to operational implementation in order to ensure that schedule-planning teams understand the capabilities and limitations of the models being used.

III. INTRODUCTION

Sleep is a vital physiological requisite for humans, needed for survival like air, water and food. Sleep loss, disruption of circadian rhythms, and work overload are critical fatigue-causing factors that can compromise safety and lead to increased errors and degraded performance and productivity. Workers in safety-sensitive occupations, including truck drivers, shiftworkers, medical residents, and airline pilots are at increased risk for accidents due to lost sleep, circadian desynchrony, and work overload (Goel et al. 2009b). Furthermore, costs in lost workplace productivity due to poor and insufficient sleep can be substantial (Rosekind et al. 2010). The combination of sleep loss, circadian desynchrony and work overload associated with shiftwork has also been linked to both short and long-term health consequences including metabolic syndrome, diabetes, and cancer. These short and long-term consequences necessitate the careful management of each component of the risk during NASA missions.

There are four sleep-related determinants of alertness and performance including: 1) nightly sleep duration (chronic sleep loss); 2) number of hours awake (acute sleep loss); 3) sleep inertia (impaired performance upon waking) and 4) circadian phase (time of day). Studies of shift workers in a variety of industries have shown that compromising any one of these factors is sufficient to lead to performance decrements (Cohen et al. 2010). Work overload leads to extended duration work shifts, which in turn cause acute and chronic sleep loss and circadian misalignment. In combination, the fatigue resulting from these factors has been shown to have compounded consequences including increased lapses in attention and neurobehavioral impairment.

Chronic Sleep Loss. The average adult obtains approximately 8.5 hours of sleep per night when provided with extended sleep opportunity under optimal conditions (Klerman and Dijk 2005; Wehr et al. 1993). However, there is a wide range in individual sleep need, ranging from 6.1 to 10.3 hours when individuals are offered a controlled 16 hour daily sleep opportunity (Klerman and Dijk 2005). These findings support the notion that some people are natural short sleepers,

while others are natural long sleepers. There is a strong genetic basis underlying the regulation of normal sleep, along with influences of age and gender (Goel et al. 2013). A recent report from a panel of experts assembled by the American Academy of Sleep Medicine recommends that adults 18-60 years get 7 or more hours of sleep on a regular basis “to promote optimal health” (Watson et al. 2015). Similarly, the National Sleep Foundation advises 7-9 hours as the daily sleep need for most adults (Hirshkowitz 2015).

Despite these recommendations, work and life demands, poor sleep hygiene and sleep disorders result in most adults obtaining less sleep than they require, with nearly 30% of the US population reportedly obtaining six or fewer hours of sleep per night (Krueger and Friedman 2009; Luckhaupt et al. 2010). Analysis of time use data reveals that work and sleep time are inversely related and that evening television viewing is strongly correlated with the timing of sleep onset (Basner and Dinges 2009), suggesting that the majority of sleep loss is self-selected, not reflective of an individual’s actual sleep need.

When a person is not able to consistently achieve their required number of hours of sleep at night, a chronic sleep debt begins to accumulate. With each day of inappropriately short sleep, cognitive performance worsens (Belenky et al. 2003; Van Dongen et al. 2003). Laboratory studies illustrate that when healthy research subjects are restricted to four, six, or eight hours of time in bed per night, their performance steadily degrades, while their subjective feeling of sleepiness increases only modestly and then reaches a plateau (Belenky et al. 2003; Van Dongen et al. 2003). These findings suggest that most people are unable to accurately gauge how much sleep loss affects their performance.

Acute Sleep Loss. Acute sleep deprivation arises from spending too many continuous hours awake. This phenomenon occurs when a person stays awake beyond the maximum threshold of the homeostatic sleep drive. For example, under controlled laboratory conditions, the average number of continuous hours that a person can stay awake with sustained vigilance is approximately 16 hours, however, when a person who needs sleep after 16 hours stays awake beyond the 16 hour threshold, acute sleep deprivation occurs (Klerman and Dijk 2005). The functional consequence of this phenomenon has been demonstrated in laboratory studies where performance quickly degrades with increasing number of hours awake (Santhi et al. 2007). Other research has demonstrated that sustained wakefulness of only 19 hours can lead to performance decrements equivalent to those of someone with a blood alcohol concentration of 0.05% and when wakefulness is extended to 24 hours, performance on a simple reaction time task further declines to that of a person whose blood alcohol concentration is 0.10% (Dawson and Reid 1997).

Sleep Inertia. Sleep inertia is an impairment in alertness and performance that dissipates asymptotically from waking until approximately two to four hours after waking (Jewett et al. 1999). The brain does not fully wake immediately upon the transition to wakefulness and as a result performance impairments occur until the effects of sleep inertia have dissipated. The negative effects of sleep inertia are enhanced based on prior sleep history, the sleep stage from which one is awoken and circadian phase.

Circadian Phase. Alertness and performance fluctuate with a circadian rhythm, such that during the time when the circadian drive to sleep is strongest, performance is worst (Johnson et al. 1992). Circadian misalignment is the term used to describe the phenomenon where a person attempts to initiate sleep and engage in wakefulness during times when there is circadian opposition to such activities. Jet-lag is a common situation in which this is experienced. The functional consequence of engaging in activities during adverse circadian phases is significantly impaired cognitive performance.

Sleep quality -- including the ability to fall asleep and remain asleep -- and sleep duration are dependent upon circadian phase, length of prior wake duration, and time within the sleep episode (Akerstedt and Gillberg 1979; Klerman et al. 2002; Wilkinson 1969). Quantification of this dependency has demonstrated that proper alignment of scheduled sleep episodes to the circadian pacemaker is important for sleep consolidation and sleep structure (Dijk and Czeisler 1994; Dijk and Czeisler 1995). High sleep efficiency is best maintained for eight hours when sleep is initiated approximately six hours before the endogenous circadian minimum of core body temperature (Dijk and Czeisler 1994; Dijk and Czeisler 1995). Sleep onsets before or after this time result in significantly lower sleep efficiencies, either due to increased wake during the sleep episode or shorter sleep episode durations. This phase relationship between the rest-activity cycle and the endogenous circadian timing system implies that even small circadian phase delays of the sleep propensity rhythm with respect to the rest-activity schedule can result in sleep onset insomnia or substantial wake after sleep onset.

Work Overload. Work overload poses an additional risk in operational settings and can be considered as a product of time on task, task complexity, and task intensity. Not easily measured, most studies that evaluate work overload primarily consider time on task or task duration measures (McDonald et al. 2011). Recent duty hour limit regulations in commercial trucking (FMCSA, 2011) and aviation (FAA, 2012) have attempted to address work overload by limiting hours of driving to 11 within a 14-hour duty period or by setting a maximum flight duty period based on the number of flight segments flown by a pilot (e.g., 4 segments limits to a 13-hour duty). For spaceflight operations, NASA utilizes “fitness for duty standards” that nominally limits crewmembers to 6.5 hours per day and recommends that crewmembers adhere to a 48-hour work week. Setting limits can be especially important during periods of critical operations. The NASA definition of a critical overload workload for a spaceflight crew is 10-hour work days that are undertaken for more than 3 days per week, or more than 60 hours per week (NASA STD-3001, Volume 1). Work underload can also pose issues as low levels of task-related arousal, monotony, and time-on-task can unmask underlying physiological symptoms of sleep loss and circadian desynchronization (Hutchins 2013).

The NASA Human Research Program (HRP) Behavioral Health and Performance (BHP) Element (<http://humanresearch.jsc.nasa.gov/about.asp>) aims to further characterize the risk of performance decrements and adverse health outcomes resulting from sleep loss, circadian desynchronization, and work overload, in preparation for Exploration missions beyond lower earth orbit, including to Mars. Operationally relevant monitoring technologies that detect sleep quantity and quality, and individualized countermeasures that prevent or mitigate the risk in long-duration isolated environments, will equip crews for optimal behavioral health and performance. Focused

laboratory and ground analog studies as well as spaceflight studies will provide valuable insights into developing these technologies and countermeasures.

The NASA HRP BHP element is tasked with the responsibility of managing three risks. These are the risk of: (1) performance decrements and adverse health outcomes resulting from sleep loss, circadian desynchronization, and work overload; (2) performance and behavioral health decrements due to inadequate cooperation, coordination, communication, and psychosocial adaptation within a team; and (3) adverse cognitive or behavioral conditions and psychiatric disorders. As each of these risks is addressed in a separate evidence report chapter, they should not be construed to exist independently of one another but, rather, should be evaluated in conjunction with the other. Furthermore, the BHP risks overlap with the risks in other HRP Elements and, as such, must also be considered in conjunction with these other risks (see figure 3-1 for an example of these possible overlaps).

BHP's relationships with other elements are further outlined in the HRP Human Research Roadmap (<http://humanresearchroadmap.nasa.gov/>). The nature of the Roadmap implies that BHP is continually reviewing and updating integration points with other Elements. Current research efforts are under way through collaborative efforts with the Exploration Medical Capabilities (ExMC) Element, Human Health and Countermeasures (HHC) Element, as well as the Space Human Factors & and Habitability Element (SHFH) Element. While current research is designed to address identified gaps, it will be necessary to update and review BHP's risk mitigation strategy as new evidence emerges. Such information may also inform the current medical operations, as new or revised mitigations for issues pertinent to current spaceflight, become available.

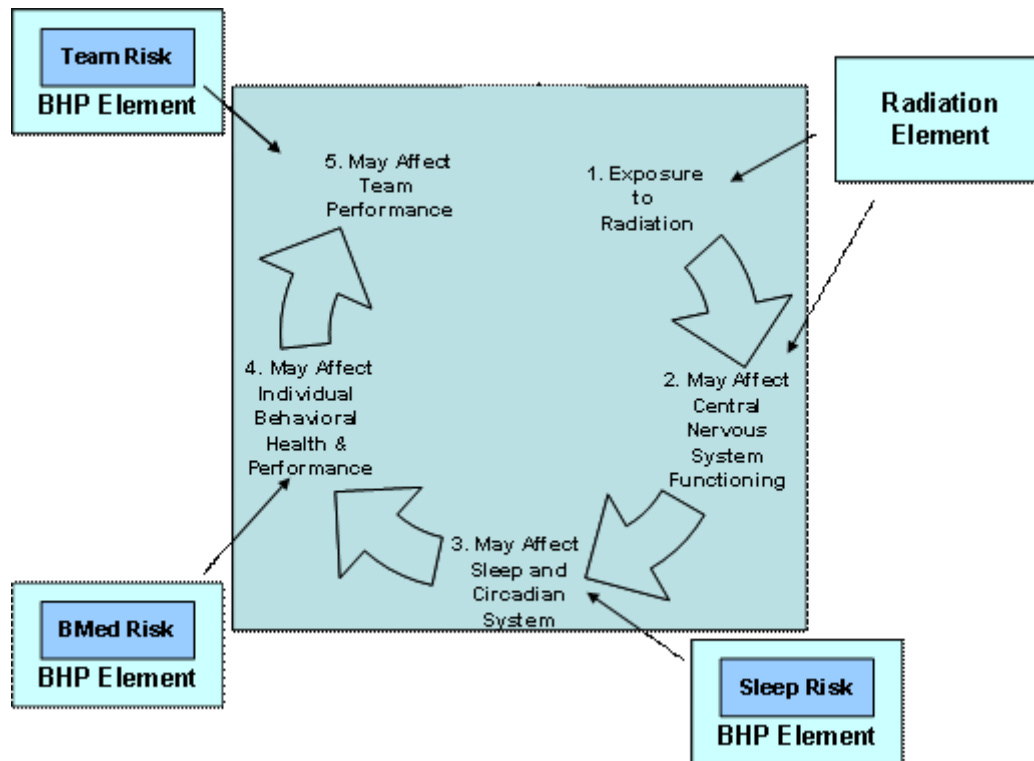


Figure 1. Sample integration within the BHP element, and with other HRP elements.

IV. EVIDENCE

A. Spaceflight Evidence

1. Occurrence of Sleep Loss During Spaceflight

Throughout the history of spaceflight numerous studies have been conducted to describe the nature of sleep in space and to quantify the frequency and magnitude of sleep loss. These studies have employed a variety of measures to evaluate sleep including polysomnography, actigraphy, subjective scales and questionnaires/interviews (for a description of these measures, see Appendix 1). Results from seven Category II and Category III studies ($n = 177$) are summarized in Table 1. These studies show that astronauts sleep an average of about six hours while in space, irrespective of the spaceflight mission examined or methodology used to quantify sleep. This amount of sleep is less than the amount recommended by the National Sleep Foundation and American Academy of Sleep Medicine to maintain satisfactory alertness, performance and health. *It is also nearly two hours less than the eight hours recommended for astronauts per NASA-STD-3001, Volume 1.* Collectively, these studies suggest that astronauts experience chronic sleep loss during spaceflight.

Table 1. Summary of Spaceflight Sleep Studies and Category of Evidence

Source	Average Hours of Sleep (Ground)	Average Hours of Sleep (Spaceflight)	Missions	Subjects (N)	Measurement Tool	Category of Evidence
Barger et al., 2014	6.3	6.0	<i>STS-104, -109, -111, -112, -113, -114, -115, -116, -118, -120, -121, -122, -123, -124</i>	64	Actigraphy	II
Barger et al., 2014	6.4	6.1	<i>ISS</i>	21	Actigraphy	II
Dinges, et al., 2013	6.7	6.4	<i>ISS</i>	18	Sleep logs	III
Dijk et al., 2001	6.8	6.5	<i>STS-90, -95</i>	5	Polysomnography, actigraphy	II
Monk et al., 1998	6.5	6.1	<i>STS-78</i>	4	Polysomnography	II
Gundel et al., 1997	6.4	6.1	<i>Mir</i>	4	Polysomnography	II
Santy et al., 1988	n/a	6.0	Space shuttle	58	Post-flight debriefing	III
Frost et al., 1976	6.9	6.0	Skylab	3	Polysomnography	II

Although there is a general consensus between studies that sleep duration in space is approximately six hours, it is unclear whether this is due to a majority of astronauts requiring less sleep than the general population, or whether factors related to spaceflight, such as work overload, the habitability of the sleep environment, and/or microgravity, lead to reduced sleep duration. Each study that has been completed provides unique information on why sleep duration in space may be shorter than recommended.

It is possible that the astronaut population is over-represented by individuals who require less sleep than the general population, however, all studies completed to date have shown that astronauts sleep less during spaceflight relative to on Earth. A post-flight debriefing survey that was conducted in 1988 (Category III) found that 58 crewmembers from nine space shuttle missions (ranging in duration from 4 to 9 days) reported sleeping on average 6 hours per day while in space compared to 7.9 hours terrestrially (Santy et al. 1988). Sleep was most reduced during the first and last days of a mission (total 5.6 and 5.7 hours, respectively). Many crew members reported fewer than five hours sleep on some nights, and some crewmembers slept two hours or less (Santy et al. 1988). The variability in the duration of sleep episodes suggests that some proportion of sleep loss arises from external factors rather than differences in intrinsic sleep need.

Recent evidence validates the findings of the survey study conducted by Santy and supports the notion that sleep loss during spaceflight is present even on recent spaceflight missions. Barger and colleagues completed the largest study of sleep in space using actigraphy and sleep logs over ten years of spaceflight on Shuttle and ISS (Category II). They found that Shuttle astronauts averaged about 20 minutes less in space relative to a two-week preflight period and about 47 minutes less relative to the week after landing (Barger et al. 2014). This finding does not appear to be strictly related to work overload on short-duration Shuttle missions. During long-duration missions on ISS, Barger and colleagues reported that astronauts averaged about 19 minutes less sleep during spaceflight relative to a two-week pre-mission period and about 52 minutes less relative to the first week after landing (Barger et al. 2014). These findings are very similar to a report by Dinges and colleagues, who completed a study using subjective sleep logs (Category III) among 18 ISS astronauts (4F) and reported an average sleep duration of about 20 minutes less during spaceflight relative to preflight (Dinges et al. 2013). In both of these studies the pre-flight data collection occurred during the training flow for the mission, which could have caused sleep loss during the pre-flight interval.

Similar findings were also reported during earlier missions. Kelly studied four (1F) Shuttle astronauts during a 10-day mission using logbook reports and found that in-flight sleep was reduced by 15% compared to pre-flight (Category III, (Kelly et al. 2005). Gundel reported that the in-flight polysomnographic sleep duration for four astronauts aboard Mir averaged about 16 minutes less than baseline (Category II (Gundel et al. 1997)). A study of three astronauts on three separate Skylab missions (Category II), with varied mission lengths, revealed that in-flight polysomnographic sleep averaged about an hour less than pre-flight although this may have been due to reduced time in bed during that mission (Frost et al. 1976).

Despite the observation that astronaut sleep duration on the ground is longer relative to during spaceflight, it should be noted that the majority of studies have reported that astronauts sleep less than seven hours on the ground. It is possible that this reflects a shorter sleep need relative to the general population, but it may reflect reduced opportunity for sleep due to work overload and for ISS astronauts, overseas training, during preflight preparations. Dijk and colleagues evaluated five astronauts (Category II) during STS-90 and STS-95 using PSG and actigraphy and found that in-flight sleep duration averaged about 13 minutes less than preflight (Dijk et al. 2001). Notably, they found that astronauts slept longer when they were assigned to wear electrodes for the collection of sleep data. This finding suggests that the astronauts studied during these missions were capable of sleeping longer during spaceflight, but did not do so when their sleep was not being actively evaluated through PSG. This finding suggests that it is possible for astronauts to sleep longer than six hours during spaceflight and that other mission-related factors account for some of the observed sleep reduction in space.

In order to identify factors related to sleep loss during spaceflight, Whitmire and colleagues gathered subjective reports of sleep experiences during Shuttle operations from 74 astronauts using a survey and interview (Category III). Approximately half (54%) agreed that it was easy to fall asleep in space and about half (47%) reported that it was easy to stay asleep in space (Whitmire 2013). Various factors were reported as interfering with the ability to fall asleep including “thinking/active mind,” mission-related work issues, physical discomfort, lighting and unfamiliarity with the shuttle environment and microgravity. A lack of time to 'wind down' was

also cited as an issue for some, while 20% reported no issues with falling asleep. Shuttle noise, such as from alarms, was most reported as disturbing sleep while noises from the galley water pump or the A/G communication bleed did not disrupt sleep. A number of respondents mentioned using earplugs although some felt they were uncomfortable.

2. Occurrence of Sleep Inertia During Spaceflight

There have been no studies that have systematically documented the impact of sleep inertia on performance during spaceflight. Despite this, astronaut journal reports suggest that sleep inertia and an inability to quickly transition from sleep to wake does occur. For example, one astronaut reported “The morning started disastrously. I slept through two alarms, one set for 0600 and another a half-hour later to remind me to take some CEO pictures. My body apparently went on strike for better working conditions (Stuster 2010).”

This lack of information on the impact of sleep inertia represents a gap in understanding, particularly since astronauts could be required to respond to an emergency at any time of day or night. Sebok notes that “understanding and managing sleep inertia is highly relevant to spaceflight operations as there is no way to know when a failure could occur and there is about a 30% chance that it could be during the astronauts’ sleep period and their ability to react could be impaired when quick actions are needed (Sebok 2013)”.

3. Occurrence of Circadian Desynchronization During Spaceflight

Circadian desynchronization can arise from two situations. First, the imposed sleep-work schedule can lead to a scheduled wakefulness occurring during the circadian nadir and scheduled sleep occurring during the wake-promoting portion of the circadian rhythm. Second, under a stable sleep-wake schedule, the endogenous circadian rhythm can drift to an earlier or later phase due to insufficient or inappropriately timed light exposure. Both of these causes of circadian desynchronization have been observed during spaceflight.

Sleep-work schedules were responsible for considerable sleep disruption and circadian misalignment during the Gemini missions due to the need for one member of a two-crew operation to be awake at all times. On Gemini IV, the astronauts slept in four-hour shifts, with one crewmember sleeping while the other was awake (Hacker and Grimwood 1977). This led to substantial fatigue, likely related to circadian desynchronization and resulting sleep loss. A similar problem was apparent on Gemini V, but given the severity of the astronaut’s sleep disruption due to the poor sleeping environment, the astronauts worked with mission control to change their schedule and allow them to sleep at the same time (Hacker and Grimwood 1977). This resulted in each astronaut experiencing a longer, more consolidated sleep. Although some subsequent NASA missions varied between a split-sleep watch schedule and having all astronauts sleep at the same time, the majority of recent missions on ISS, shuttle and Mir involved having all crewmembers sleep at the same time, although not always on a 24-hour schedule.

Few investigators have examined biomarkers of circadian rhythms during spaceflight, but each study that has been reported has revealed evidence of circadian misalignment. In a case

study of an astronaut studied for eight days aboard the Space Station Mir (Category III), Gundel and colleagues reported a circadian phase shift of 2-3 hours in the body temperature rhythm and in subjective mood ratings relative to baseline, despite a 24-hour imposed sleep-wake schedule (Gundel et al. 1993). In a subsequent Category III study of four astronauts aboard Mir, studied for 103, 30, 23 and 7 nights, Gundel and colleagues reported that three of four astronauts had an average phase delay of two hours in the circadian rhythm of core body temperature compared to baseline (Gundel et al. 1997). In this study, participant's phase assessments were conducted throughout each individual's mission. The participant that did not appear to have a phase delay relative to baseline had an approximately eight-hour range in baseline circadian phase over four days of data collection, suggesting that that participant may have experienced some schedule or workload-induced circadian misalignment prior to spaceflight. This circadian misalignment was associated with a reduction in sleep efficiency, despite the fact that the astronauts had a longer sleep opportunity during spaceflight. In a similar study of long-duration spaceflight in a single astronaut aboard Mir for 100 days (Category III), Monk and colleagues reported that the participant's oral temperature rhythm appeared to remain entrained to the imposed 24-hour schedule during the first two-thirds of the mission, but a drift in his circadian rhythm timing was apparent during the last third of spaceflight (Monk et al. 2001). Sleep duration was also reduced during the last third of the mission and performance on cognitive tests revealed an increase in speed, but a decrease in accuracy. These findings suggest that circadian misalignment may be responsible for some proportion of sleep loss and performance impairment during spaceflight.

Non-24 hour operations during spaceflight have also been associated with circadian misalignment among astronauts. Monk and colleagues examined the circadian rhythms of four astronauts during a Shuttle mission (Category III), where the scheduled timing of sleep was advanced (shifter earlier), by 25 minutes a day for a two-week mission (Monk et al. 1998). Using body temperature, cortisol and dim light melatonin onset (DLMO) measures, they found that the astronauts were able to shift their circadian rhythms, but there were individual differences in the phase angle of entrainment (i.e. the timing of the circadian nadir relative to sleep), where some participants had relatively advanced circadian phases and others had relatively delayed circadian phases. In a similar study of five astronauts aboard two Space Shuttle missions (Category III), Dijk and colleagues reported that the circadian rhythm of cortisol did not shift in conjunction with an imposed 20 minute daily advance shift in scheduled sleep timing, leading to progressive circadian desynchrony with each day in flight (Dijk et al. 2001). In a recent Category III evaluation of circadian rhythms during spaceflight, Flynn-Evans and colleagues applied a mathematical model to estimate the timing of the circadian nadir among 21 astronauts aboard the International Space Station; crewmembers were studied an average of 155 days each, 3,248 days total (Flynn-Evans et al. 2015). In this study it was reported that the estimated circadian phase occurred outside the sleep episode 19% of the time during spaceflight. This resulted in the loss of one-hour of total sleep on misaligned compared to aligned sleep episodes, along with a higher prevalence of sleep medication use during misaligned sleep episodes.

There are several possible reasons for the occurrence of circadian misalignment during spaceflight. Stable circadian entrainment to an imposed schedule requires the presence of light of sufficient intensity, wavelength and duration, timed to facilitate entrainment and a schedule that is within the limits of entrainment for an individual. In low-Earth orbit, the period of the solar light-dark cycle is 90 minutes, which is far too short for circadian entrainment in humans. In the

absence of supplemental exposure to light of sufficient intensity during wake episodes and darkness during sleep episodes, the 90-minute light dark cycle would be expected to elicit circadian misalignment. Exposure to light has been reported during scheduled sleep episodes due to lack of free time during scheduled wake episodes for looking out windows (Hooke et al. 1986). Conversely, there may be situations where lighting conditions during wake episodes are insufficient to maintain entrainment. Some modules on ISS and on Space Shuttle do not have windows and are illuminated by artificial lighting that may be insufficient to maintain stable circadian entrainment. Each of these issues would be a concern during deep space missions, where episodes of constant light or constant darkness may be experienced and where internal light intensity may be restricted due to energy consumption. It is also important to note that circadian entrainment to light occurs through ocular light exposure. There have been several documented cases of intra-ocular pressure leading to concerns about visual impairment during spaceflight (Mader et al. 2011). Given that eye diseases associated with progressive deterioration of vision have been associated with circadian rhythm disorders and non-24-hour sleep wake disorder (Flynn-Evans et al. 2014), it is important to evaluate whether the circadian misalignment observed during spaceflight relates to ambient lighting conditions or changes within the eye that prevent appropriate circadian entrainment.

In addition to the importance of light in maintaining circadian entrainment, astronauts are often required to maintain wakefulness at adverse circadian phases due to mission demands. Launch windows are limited to narrow bands of time each day to ensure that the vehicles achieve a suitable orbit for a given mission. If that launch window occurs during the biological night, the astronauts need to awaken several hours prior to the appointed launch time. In the weeks prior to flight, astronauts typically adopt an advancing or delaying sleep schedule in order to be awake at launch time (Monk et al. 2004). Additionally, in order to prepare for events, US astronauts have been historically scheduled to sleep at times on a non-24 hour schedule that would be expected to impose circadian misalignment. For example, Nicholson evaluated Apollo sleep schedules and found that they were insufficient to allow for circadian entrainment (Nicholson 1972). Shuttle astronauts were frequently required to shift sleep timing each day in order to allow for wakefulness at an appropriate window for landing. Astronauts on long-duration missions have typically adopted a 24-hour schedule, but would be required to “slam-shift,” whereby they suddenly are required to sleep at a time many hours before or after their nominal bedtime in order to have scheduled wakefulness coincide with mission events. These abrupt shifts in the imposed sleep-wake schedule can also induce circadian misalignment.

4. Occurrence of Work Overload During Spaceflight

Category III evidence reveals work overload during some spaceflight missions, including those of the Skylab and Apollo Programs. The workload during the second Skylab mission steadily increased over eight weeks, while crewmembers of the third Skylab mission reported that they quickly ran into difficulty due to work overload. The fast-paced schedule and workload of the mission caused the crewmembers to consistently feel behind on tasks, which was associated with an overall reduction in morale. At the start of the 45th day of their 59-day mission, the crewmembers of Skylab 3 refused to perform scheduled tasks. Mission Control personnel later acknowledged that the schedule had been such that it had not given the crewmembers adequate time in which to adjust to their environment (Cooper 1996). Category III evidence from

the Apollo Program also reveals that some of the Apollo crews reported intense sleepiness and mental fatigue while they were performing lunar EVAs (Scheuring et al. 2007). Shuttle missions to ISS involved faced-paced work schedules as crews perform complex, critical tasks. Of the 22 EVAs that were conducted during 2007, nine of these dangerous, and critical, endeavors lasted seven or more hours.

Astronauts surveyed about workload reported mission factors that challenged sleep including night operations, slam shifting and “schedule creep” that led to workload tasks being shifted into times that were intended to be “off the clock” (Whitmire 2013). The more demanding the scheduled workload was perceived to be, the less easily they reported being able to fall asleep and stay asleep. Some reported not being ready for sleep at scheduled bedtime due to work scheduling and lack of time to “wind down”. For those astronauts interviewed, about the same number didn’t feel that scheduled workload impacted sleep as did feel that sleep quality and quantity were reduced.

Similarly, work was the most frequent journal entry category by ISS astronauts and was most commonly broken down into the subcategories of: high workload, low workload, “tedious/frustrating,” “work is good,” and schedule (Stuster 2010). The journals entries revealed that scheduling issues were typically due to insufficient time allocated for tasks. Comments from the astronaut journals provide insight into how individuals responded to work overload during missions:

- “Today was a hard day. Small things are getting to me. I am tired. I think that the ground is scheduling less time for tasks than before”
- “...lack of ‘padding’ in the schedule means that there is little time to accomplish small tasks, or to recover from mistakes”
- “Several of the procedures, as usual, just took much longer than timelined.”
- “I’m ready for the weekend. The past couple of days of reduced sleep and eating opportunities have added a little strain. I felt it especially yesterday. Today, the fatigue and hunger are present but not the strain.”
- “That made for about an 18-hour working day. Our working day started at midnight, by the way, just to make sure we were extra tired.”
- “I feel that the workload is going up; these last few weeks seem to have been pretty taxing. I’m very tired.”

5. Occurrence of reduced sleep quality arising from sleep loss, circadian desynchronization, and work overload during spaceflight

The question of whether sleep quality is disrupted during spaceflight deserves further study. The combination of sleep loss, circadian desynchronization, and work overload appears to impact objective sleep quality as measured using polysomnography, although with inconsistent changes in sleep architecture between individuals and studies. In contrast, subjective reports of sleep quality measured through interviews, sleep quality scales and questionnaires have been mixed, with many studies finding that astronauts do not perceive a reduction in sleep quality during spaceflight.

During the Skylab Missions, Frost and colleagues studied three astronauts at multiple time points over 28, 59, and 84-day missions, where astronauts maintained a 24-hour schedule (Category III, (Frost et al. 1976)). They found changes in sleep quality, as defined by sleep architecture, relative to baseline, including increased Stage 3 (slow wave sleep), variable Stage 4 (slow wave sleep) and increased rapid eye movement (REM) sleep. They also found that the number of awakenings remained stable or decreased during spaceflight relative to baseline, however, this may relate to the reduced sleep opportunity that they observed during spaceflight. Of note, they reported individual variation in response to the spaceflight environment over time. They reported that the participant who completed the 28-day mission experienced a significant decrease in total sleep time over the course of the mission, but that this was as a result of self-selected shorter sleep episodes. In contrast, the participant who completed the 84-day mission reportedly experienced sleep difficulty during the first half of the flight, with longer sleep latency and short sleep duration, but better sleep outcomes during the second half of the mission.

Four studies of objective sleep quality were conducted on Mir, where operations were maintained on a 24-hour schedule. These evaluations revealed that astronauts experienced reduced REM latency and increased slow wave sleep (SWS) during the second sleep cycle. One astronaut had significant problems with a long latency and poor sleep efficiency leading the authors to describe those problems as “space insomnia” (Gundel et al. 1997). Similarly, Stickgold conducted a polysomnography study of five NASA-Mir astronauts who provided an average of 24 in-flight nights of sleep recording (Stickgold 1999). In this study, in-flight REM sleep time was reduced by more than 50% compared to pre-flight and in-flight total sleep time was reduced by 27% compared to pre-flight even though in-flight time in bed was longer. As a result, sleep efficiency was significantly reduced in-flight to an average of 63%, which is consistent with clinically-defined poor sleep quality. In an EEG study of eight astronauts aboard Mir, slow wave sleep was reportedly reduced compared to pre-flight (Category III, (Moldofsky et al. 2000)). In contrast to the report by Frost, late in the mission study participants experienced more awake time, movement arousals and more transitions to stage 1 sleep compared to pre-flight. In a fourth study conducted aboard Mir, Stoilova and colleagues evaluated astronauts completing flights ranging from 9 to 241 days aboard Mir. They found that sleep latency shortened relative to baseline and that the time from sleep onset to slow wave sleep onset lengthened from the beginning to the end of the missions (Stoilova et al. 2000).

Objective sleep quality was studied on two Shuttle flights (Category II). Monk studied four astronauts at two time points during a 17-day mission using PSG and found no differences between sleep early flight and late flight though all astronauts had decreased time in bed (TIB) and slow wave sleep in-flight (Monk et al. 1998). Among five participants studied during two short-duration Shuttle flights, Dijk and colleagues found that the final third of sleep episodes showed changes in sleep with more wake time and reduced slow wave sleep (Dijk et al. 2001). A form of ‘REM rebound’ occurred with a “prominent” increase during post-flight sleep. It is important to note that the imposed schedule during these studies involved daily shifts in sleep timing, in contrast to the Skylab and Mir studies, which maintained 24-hour operations.

Subjective sleep quality ratings collected regarding sleep in space have been mixed. In studies where sleep quality ratings were collected in conjunction with other sleep measures, sleep quality has been consistently rated as poorer than ground-based sleep quality. Dijk reported that

Shuttle astronauts rated sleep quality and being physically rested as significantly worse for in-flight sleep relative to ground-based sleep. Similarly, Barger and colleagues found that sleep quality was rated significantly worse during spaceflight as collected in daily sleep logs. In contrast, in a sleep log study conducted by Dinges and colleagues, sleep quality ratings were generally rated as ‘good’ (Dinges et al. 2013). Similarly, in a post-flight interview and survey by Whitmire, about half of the respondents (52%) agreed that sleep quality improved during spaceflight, while only 6% disagreed that their sleep quality improved (Whitmire 2013); given the retrospective nature of this assessment however, these findings may be limited.

A unique analysis of ISS astronaut journals revealed evidence of decreased sleep quality through passive, personal reporting (Stuster 2010); Category III). In this analysis, Stuster found that astronauts reported being tired more often during the first quarter of ISS missions relative to later in the missions. Interestingly, astronauts reported more naps during the third and fourth quarters supporting the notion that adaptive strategies may be learned and employed. This finding suggests that sleep quality may improve with time in space or it may indicate that astronauts habituate to their subjective perception of poor sleep quality. Journal entries by astronauts reveal the impact of reduced sleep quality on performance outcomes:

- “Very tired. Woke up at 2 am and couldn’t get back to sleep. Finally fell asleep and overslept”
- “The time shift is starting to make the end of the day tough. We are pretty tired right now having shifted about 6 hours over the weekend”
- “I need to get more sleep tonight than the past few. I can feel the fatigue accumulating and it will be important to be rested for the undocking in a few days.”

In addition, the astronaut journals reveal a trend towards negative comments throughout the course of a mission (Figure 2).

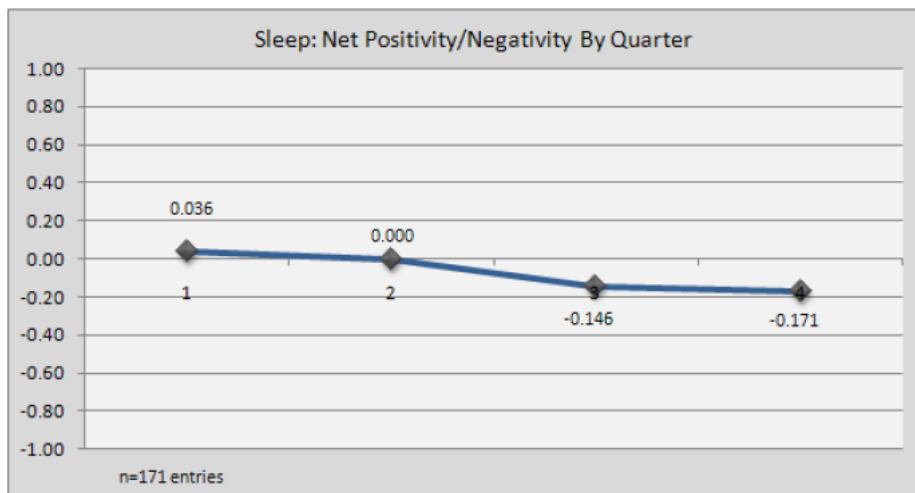


Figure 2. Net positivity and negativity in sleep journal entries by quarter of mission. Reproduced from Stuster 2010.

6. Occurrence of reduced alertness and performance arising from sleep loss, circadian desynchronization, and work overload during spaceflight

Ground-based evidence strongly indicates that sleep loss, circadian desynchronization, and work overload lead to performance decrements. There have been few studies of cognitive performance during spaceflight and even fewer that included sleep, circadian rhythms, and workload measures. In addition, the studies completed to date have evaluated few study participants over varying times of day on varying mission durations. Finally, it is difficult to compare the results of different studies due to the lack of standard measures of cognitive function. Table 2 summarizes the results from studies of performance during spaceflight.

Table 2. Spaceflight Cognitive Performance Studies

Study	Year	Mission	No.	Measurement type	Effect	Type of Effect	Mission Days
Schifflett et al.	1996	STS-65, STS-78	7	PAWS (battery of performance tests); subjective assessments of cumulative fatigue	Yes	Decrements in memory-search performance, correlated with self-assessment fatigue	14 (STS-65) 15 (STS-78)
Manzey and Lorenz	1998	<i>Mir</i>	1	Accuracy and response time: four tasks from AGARD-STRES (GRT, MST, UTT, DT); mood and workload assessments	Yes	Pre-launch decrements associated with lowered mood scores; decrements in tracking performance varied in flight, associated w/adaptation (i.e., to space, and back to Earth)	438
Manzey et al.	1998	<i>Mir</i>	1	Accuracy and response time: four tasks from AGARD-STRES (GRT, MS, UTT, DT)	Yes	Fine manual control decrements (UTT) due to adaptation; potential decrement in tracking/memory-search during DT	8
Monk et al.	1998	STS-78	4	VAS alertness rating	No	Higher ratings early in the flight	17
Newman and Lathan	1999	STS-42	4	Memory recall task	No		4
Dijk et al.	2001	STS-90, STS-95	5 (STS-90) 1 (STS-95)	PVT (calculation, recall memory, VAS, KSS)	PVT- <i>n.s.</i>	Most lapses in-flight; least lapses post-flight	16 (STS-90) 10 (STS-95)

Dijk et al.	2001	STS-90, STS-95	5 (STS-90) 1 (STS-95)	Self-assessment of fatigue	Yes	Fatigue levels worst in-flight; best post- flight	16 (STS-90) 10 (STS-95)
Kelly et al.	2005	STS-89	4	DSST, NR	NR- Yes	Increased in-flight; DSST with small changes	10

PAWS = Performance Assessment Workstation. AGARD = Advisory Group for Aerospace Research and Development (NATO). STRES = Simulated Training Requirements Effectiveness Report. GRT = Grammatical Reasoning Test. MST = Memory Search Task. UTT = Unstable Tracking Task. DT = Dual Task. VAS = Visual Analog Scale. PVT = Psychomotor Vigilance Task. KSS = Karolinska Sleepiness Scale. DSST = Digit Symbol Substitution Test. NR = Number Recognition.

The studies evaluating performance during spaceflight have been mixed, but this may relate to the fact that each study only included a small number of participants. Benke evaluated the response time and accuracy of one cosmonaut before, during and after a 6-day mission on Mir and found no significant decrements in performance (Benke et al. 1993) Category III). A separate case study conducted by Manzey and colleagues suggests that fatigue-related performance decrements may occur for certain types of tasks (Manzey et al. 1998) Category III). In this study, a single astronaut completed mood, fatigue, and workload rating scales, along with a grammatical reasoning task, memory search task, unstable tracking task, and a dual task that consisted of unstable tracking with concurrent memory search, before, during, and after an eight-day mission on Mir. In this study, there was no difference in speed and accuracy of short-term memory retrieval and no impairment in logical reasoning relative to ground-based measures. The participant did experience a reduction in fine manual control movements during the unstable tracking task and greater interference effects during the dual-task and memory search. These performance impairments correlated with the astronaut's subjective ratings of fatigue. In another study conducted on Mir, four astronauts studied during a 17-day mission rated their alertness degraded from measurements early in-flight to later in the mission (Monk et al. 1998), although no performance testing was conducted on that mission.

Newman and Lathan conducted a Category II experiment on cosmonauts during spaceflight and did not find impairments in a memory-search performance task, although tracking disruptions were apparent (Newman and Lathan 1999). In contrast, a performance monitoring study by Schiflett et al. included daily assessments of the different mental functions of three astronauts during a 13-day shuttle mission (Schiflett et al. 1996). Tracking performance, time-sharing efficiency, and memory-search performance were all found to be impaired in space. The researchers hypothesized that the impairment in memory-search performance in two of the three astronauts was not related to microgravity but, rather, was a side effect of decreased alertness and fatigue.

In the most comprehensive study of sleep, circadian rhythms and performance conducted, Dijk and colleagues studied five astronauts during two Shuttle flights and found a non-significant trend toward worse performance in-flight relative to before or after flight (Dijk et al. 2001). A detailed analysis of the time course of changes involving neurobehavioral measures, which was based on two measures that were derived from the psychomotor vigilance task (PVT) and the probed recall memory test, suggested that most of the study participants exhibited a decline in performance during the last week before launch, a further decline in-flight, and a slow recovery post-flight.

The declining performance during flight and improvement post-flight correlated with REM sleep.

Four astronauts on a 10-day mission reported significantly higher in-flight subjective fatigue ratings compared to post-flight. Their performance on the digit symbol substitution task (DSST) and number recognition tasks were slightly altered during flight (Kelly et al. 2005).

Recently, Whitmire conducted a survey and interview study and found that for those astronauts who reported worsening quality of sleep over the course of their shuttle mission, there was a positive correlation with reports of increased fatigue as the mission progressed. Despite this correlation, over half of the astronauts (57%) that participated in an interview did not perceive any impact from fatigue during their mission. A few acknowledged mistakes in attention and short-term memory as being due to fatigue and a minority of individuals felt that interactions between crew and ground personnel were noticeably different when fatigued (Whitmire 2013). The comments that astronauts made regarding fatigue reveal individual differences in perception and response to fatigue-related performance decrements:

- “I was able to maintain the same level of performance, but that came at a much higher concentration level.”
- “Fatigue had the effect that I’d ask somebody to watch me.”
- “When you’re fatigued...it’s more important to not make a mistake...kind of slow down and do it very consciously.”

Collectively, these data reveal some associations between reduced performance and fatigue, however, given the limited number of participants completing performance studies along with the diversity of measures used to assess cognitive performance, it is difficult to evaluate how sleep loss, fatigue, circadian desynchronization, and work overload in flight translate into performance decrements. Furthermore, where performance impairment has been observed, it is unclear how such measures relate to operational performance and errors. Evaluation of cognitive performance using the PVT, combined with workload ratings and sleep data, is currently underway.

6. Sex differences in response to conditions of sleep loss, circadian desynchronization, and work overload during spaceflight

Sex differences have not been systematically studied during spaceflight. A recent review investigating published and unpublished research related to sex and gender differences in behavioral adaptation to human spaceflight revealed very few investigations of sex differences during spaceflight (Goel et al. 2014). This examination included a total of 201 (30 females and 171 males) astronauts and cosmonauts from 1988-2013. Representation from the US astronauts corps included 26 females and 103 males. The lack of studies on sex differences during spaceflight likely relates to the small number of female astronauts available for study. Preliminary data communicated from D. F. Dinges to Goel for inclusion in the review stated that several measures including PVT, self-reported sleep duration, sleep quality, workload, stress, and tiredness that were collected in-flight and postflight on 18 astronauts (4F) showed no sex-based differences on any of the measures. Given the lack of information on sex differences related to

sleep during spaceflight, it is important that data collected from multiple studies includes standardized measures, so that sex-differences may be systematically evaluated in the future.

7. Countermeasures

a. Pharmacological Countermeasures

Sleep medication use by astronauts is the most prevalent fatigue countermeasure used during spaceflight. Shuttle astronauts who participated in a post-flight debriefing reported more sleep medication use on dual-shift than on single-shift missions (50% vs 19%; (Santy et al. 1988), Category III). Barger et al. found that about three-quarters of both Shuttle and ISS astronauts reported using sleep medications during their missions, including on 52% of nights aboard the Shuttle (Barger et al. 2014), Category II), although sleep medication use was associated with a faster sleep latency, it was not associated with a longer sleep duration.

Consistent with the findings of Barger et al., the majority of shuttle astronauts responding to a survey (71%) indicated that sleep medications were used to help with falling asleep. For those that reported using medications, zolpidem (65%), zaleplon (28%), and continuous release zolpidem (22%) were most reported (Whitmire 2013), Category III). About a quarter of the respondents indicated that they used sleep medications to get back to sleep after a mid-sleep waking, with those whose sleep was more easily disturbed more likely to do so.

There is little data on the use of wake promoting medications during spaceflight. In a post-flight interview, Whitmire and colleagues found that 75% of the astronauts interviewed reported use of alertness medications during their mission. Those astronauts that reported use of stimulants in the form of caffeine pills or modafinil also reported being less able to fall asleep (Whitmire 2013).

A Category I trial was conducted during STS-90 and STS-95 in order to evaluate the efficacy of melatonin as a countermeasure compared to placebo. In this study of five astronauts, melatonin improved sleep latency compared to placebo, but there were no differences in other sleep parameters (Dijk et al. 2001).

A recent analysis of medication records from 24 ISS astronauts from 20 missions lasting 30 days or more reveals that the most common medications used during spaceflight were for sleep, pain, congestion, or allergy. Medication use was generally consistent with that prescribed to the adult population, with the exception of sleep medications, which were about ten times more prevalent in spaceflight. Many medication uses were linked to schedule changes (Wotring 2015), Category III).

b. Light

Brainard and colleagues conducted a series of studies to evaluate the LED-based Solid State Light Assemblies (SSLAs) for deployment during spaceflight (Brainard GC 2013). They found that the lighting generated from the SSLAs is sufficient to allow for adequate visual performance, color discrimination, and melatonin suppression. The SSLAs are scheduled for

launch in 2016 and will replace ISS fluorescent lights. These lights have been designed with 3 settings: 1) white light for high visual acuity; 2) blue-enriched white light for high circadian/alertness; 3) blue-minimized white light for low circadian/alertness (pre-sleep), leading to a Dynamic Lighting Schedule (DLS). Despite the extensive ground-based work to develop and optimize the SSLAs for spaceflight, it will be important to evaluate the effectiveness of the light as a countermeasure on ISS in order to design lighting schemes for deep space missions. Accordingly, a flight study is scheduled to begin on the ISS once the lights are deployed in 2016.

c. Schedule

Currently flight surgeons work with other operational personnel to modify flight schedules to allow for adequate sleep and time off on a case-by-case basis (Scheuring et al. 2015). A scheduling dashboard is under development to track behavioral health and mission stressors and to enable early stage detection and mitigation. Performance models based on sleep-wake history can inform scheduling decisions related to both critical tasks and countermeasure implementation. Given the prevalence of schedule-induced circadian desynchrony experienced during spaceflight, objective evaluation of scheduling countermeasures deployed during spaceflight is advised.

B. Ground-based evidence

1. Sleep loss

a. Measuring the impact of sleep loss using the psychomotor vigilance task

Ground-based laboratory and field studies have repeatedly confirmed the deleterious effects of sleep loss on performance and health. Sleep deprivation results in an overall slowing of responses, an increase in lapses and in errors of commission, and enhances time-on-task effects. Extended wakefulness affects a number of neurobehavioral systems that then influence one another in synergistic or antagonistic ways. There is a general consensus confirming that vigilance is the component of cognition that is most consistently and significantly affected by periods without sleep. The psychomotor vigilance task (PVT) has emerged as the dominant means of evaluation of sleep deprivation. It has been used in hundreds of studies, and known to be sensitive and reliable in revealing the occurrence of sleepiness arising from sleep loss and circadian desynchrony, with demonstrated validity.

The standard laboratory version of the PVT is 10 or 20 minutes long and requires an individual to press a button on a response box after a stimulus is presented on a screen. This gold-standard approach to administering the PVT is often impractical for use in an operational setting, such as spaceflight. As such, several new versions of the PVT have been developed to improve feasibility for use in the field. In order to evaluate different stimulus presentations, Jung and colleagues compared an auditory version of the PVT to the standard visual PVT among 40 participants (14F) over 40 hours of total sleep deprivation (Jung 2011). They found that both versions of the PVT showed significant reductions associated with time awake. Auditory vigilance was found to be faster (reciprocal mean reaction time (RT) and 10% slowest RT) than visual vigilance during sleep deprivation, with visual PVT performance showing more

variability. Honn and colleagues evaluated the platform used for data collection by comparing a five-minute touch screen PVT to a 10-minute laptop version over 38 hours of total sleep deprivation (Honn et al. 2015). They found a larger effect size using the laptop relative to the PDA, but found that overall the touch-screen version provided results comparable to laptop PVT. These findings suggest that the PVT may be modified to suit mission needs and still yield reliable estimates of performance impairment.

In an effort to reduce the duration of the PVT, Basner and colleagues developed a three-minute version of the PVT (PVT-B; (Basner et al. 2011). Decreasing the inter-stimulus interval from 2-10 seconds to 1-4 seconds resulted in longer reaction times, which increased the sensitivity of the shorter task. In a comparison of the effect sizes of the PVT-B with the standard 10-minute PVT in a laboratory sleep deprivation protocol, Basner reported that the PVT-B was able to discriminate alert from sleep-deprived individuals, but this effect was attenuated relative to the 10-minute version of the test (Basner et al. 2011). In a similar effort to improve the efficiency of the PVT, Basner and Dinges developed an adaptive duration version of the PVT (PVT-A) in order to account for individual differences in response. This version of the PVT uses a decision threshold to categorize a respondent as a high/medium/low performer. The PVT-A adapts to an individual respondent and stops sampling once sufficient data are gathered. In a study of 31 individuals (18F) under total sleep deprivation and 43 individuals (16F) under partial sleep deprivation, the authors found reliable agreement between the PVT-A and the 10-minute PVT. The average duration of the PVT-A was 6.5 minutes, which indicates that some individuals may not have shown signs of impairment until several minutes into the test. These findings support the notion that a longer version of the PVT is preferable, but that the PVT-A may be sufficient to reliably capture sleep loss-related impairment, with a shorter overall test duration (Basner and Dinges 2012).

b. Laboratory evaluations describing the impact of sleep loss on human alertness, performance and wellness

Although sleep loss has long been recognized as a factor contributing to performance impairment, two separate, elegant studies conducted by Van Dongen et al. and Belenky et al. clearly demonstrate the magnitude of performance impairment experienced by individuals under conditions of total and systematic sleep restriction (Figures 3 and 4). In these studies, participants were restricted to three, five, seven and nine hours in bed for seven days (Belenky et al. 2003) and four, six or eight hours in bed for two weeks, plus no sleep for three days (Van Dongen et al. 2003). The results of these studies showed that sleep restriction of 5-6 hours a night, similar to that experienced by astronauts, results in impaired performance within a week.

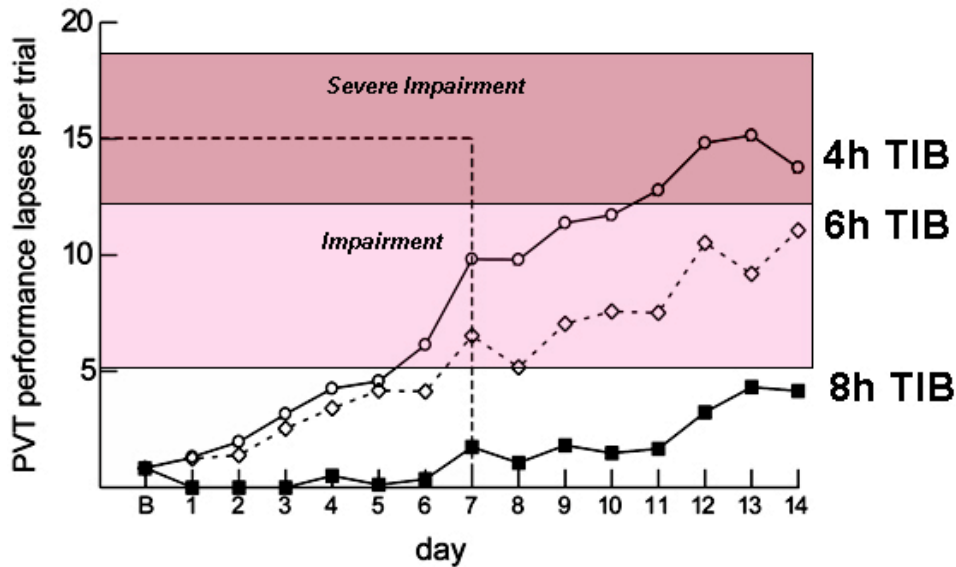


Figure 3. Performance lapses for time in bed (TIB) over 14 days of sleep restriction (Van Dongen et al., 2003).

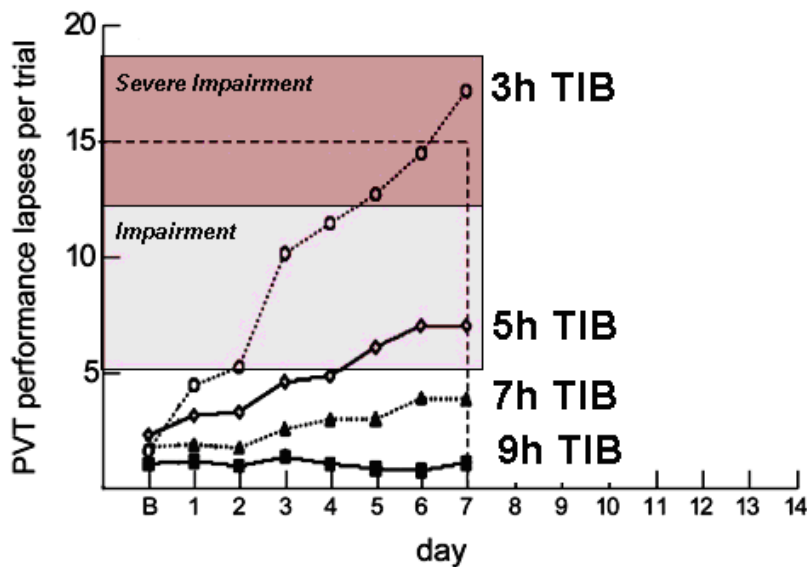


Figure 4. PVT performance lapses for TIB over 7 days sleep restriction (Belenky et al, 2003)

Building upon the seminal work of Belenky and Van Dongen, several other researchers have conducted laboratory studies to further describe how different patterns of sleep loss affect human physiology and performance. Cohen exposed nine individuals to both chronic sleep restriction and extended wakefulness, followed by 10-hour sleep opportunities and another exposure to chronic sleep restriction and extended wakefulness (Cohen et al. 2010); Category II). Despite the recurrent acute and chronic sleep loss, 10-hour sleep opportunities consistently restored vigilance performance for several hours of wakefulness. Importantly, chronic sleep loss increased the rate of deterioration in performance across wakefulness, particularly during the circadian “night” even after the 10-hour sleep opportunity. The deterioration in performance

during the biological night brought on by acute sleep loss was significantly greater than the impairment induced by acute sleep loss in rested individuals. This experiment shows that individuals cannot “repay” sleep loss in a single extended sleep episode. Functionally, this means that a chronically sleep-restricted individual could develop a false sense of recovery from prior sleep debt as a result of performing well for the first few hours of a waking day. However, during subsequent bouts of extended wakefulness, the cumulative effect of chronic sleep loss may cause performance to deteriorate much more rapidly, particularly during the late circadian night.

Chee and colleagues provide insight into the mechanism underlying lapses related to sleep loss. They investigated brain activation during lapses of the PVT under rested and sleep-deprived conditions (Chee et al. 2008), Category I). They scanned 17 subjects using functional magnetic resonance imaging and found that lapses (response time > 500 ms) occurred under both conditions, but sleep deprivation attenuated brain activation relative to rested conditions. Despite this, participants were able to produce some fast responses during sleep deprivation. During these responses, neural activation appeared similar to the activation observed under rested conditions. These findings suggest that the variability observed in PVT response times during sleep deprivation arise from an inability to voluntarily sustain attention.

The findings of Chee and colleagues have direct application to operational activities where sustained attention is required over long durations of time. In a Category I laboratory study, Basner and colleagues demonstrated how the PVT may be used as a proxy for operational performance on a mundane task. They evaluated 36 individuals (20F) using a simulated luggage screening task and 3-minute PVT over 34 hours of sleep deprivation (Basner and Rubinstein 2011). They found that performance deteriorated during night work, over the period of sleep deprivation and the 3-min PVT effectively predicted performance on the simulated task. These findings suggest that the PVT may be useful as a tool for determining fitness for duty in situations where individuals are required to complete a task requiring sustained attention.

Although reaction time and lapses as measured by the PVT are highly sensitive to sleep loss, other domains of cognitive function are also impaired. Lim and Dinges conducted a Category I meta-analysis of PVT effect sizes compared to other cognitive tests in studies that included 24-48 hours of sleep deprivation (Lim and Dinges 2010). They found that the largest effects of sleep deprivation were revealed through tests of vigilance or simple attention. However, sleep deprivation also elicited a significant effect in reducing performance for outcomes in the cognitive domains of complex attention and working memory. Interestingly, they found no impairment in accuracy measures. These findings may help explain why astronauts are able to perform accurately while sleep deprived, although reportedly at a slower processing speed.

Training may account for the lack of operational performance errors due to sleep loss reported by astronauts. Galvan reported on performance effects related to fatigue for a simulated telerobotic task (n=16, 7F; (Galvan 2012). In this Category I laboratory study, participants maintained a six-hour nightly sleep schedule in an effort to mimic astronaut habitual sleep duration. The participants were evaluated on a telerobotics task during a simulated “slam shift.” Despite sleep restriction, slam shifts, and a long test period, subjects maintained performance on the primary robotics task. The participants experienced consistent decrements in performance on

a secondary task, suggesting that secondary task performance appears to be more sensitive related to fatigue due to sleep restriction.

In addition to conferring performance impairment, sleep deprivation has also been shown to elicit other negative health consequences. Minkel and colleagues completed a Category I, three-night laboratory experiment where they evaluated 26 subjects (12F) during a night of sleep deprivation preceded and followed by stable sleep (Minkel et al. 2014). In addition to the PVT, they used the Trier Social Stress Test (TSST) to introduce psychosocial stress and elicit stress responses. They found that sleep deprivation was associated with both elevated resting cortisol release and with an exaggerated cortisol response to TSST, which was indicative of elevated HPA axis responses in healthy adults. The authors speculate that individual differences in the stress response may represent a risk factor for adverse health effects such as obesity.

Sleep deprivation has also been shown to impair judgment of human facial emotions, which has important implications for astronaut social interactions during confined, long-duration spaceflight. In a Category I laboratory study, van der Helm and colleagues randomized 37 study participants (21F) to 30 hours sleep deprivation or control (normal sleep; (van der Helm et al. 2010). They measured facial recognition affect by exposing participants to happy, sad and angry faces ranging from neutral to strong in emotion strength. They found that under total sleep deprivation, participants were less able to recognize angry and happy facial expressions. These findings are of particular concern for long-duration spaceflight, where team members will need to assess each other's well-being. It is unclear whether experience with an individual would modify the results.

c. Individual differences in response to sleep loss

Accumulating evidence suggests that there are trait-like individual differences in response to sleep loss. Van Dongen and colleagues conducted a Category I laboratory evaluation, where 21 volunteers were subjected to 36 hours of sleep deprivation on three separate occasions and were randomized to spend either 12 hours (twice) or 6 hours in bed for the week prior to the laboratory study (Van Dongen et al. 2004). In each condition, participants sustained similar impairment on a word detection task and on the PVT during the sleep deprivation relative to their prior level of impairment. Interestingly, the poorest performers on the word detection task were not the worst performers measured by PVT. These findings suggest that interindividual variation in response to sleep loss is stable and trait-like, but dependent on the type of task used for evaluation.

In a Category I laboratory study, Rupp and colleagues further evaluated individual differences in response to total and partial sleep loss (Rupp et al. 2012). In a randomized cross-over trial, they studied 19 subjects (8F) under 63 hours of total sleep deprivation and sleep restriction of seven nights with three hours of time in bed, separated by 2-4 weeks to allow for recovery. They found that participants who showed poorer performance on the PVT and mood ratings under conditions of total sleep deprivation also had greater vulnerability to sleep restriction. Of note, they did not find such trait-like variability in self-reports of sleepiness or the maintenance of wakefulness task.

Several studies have been conducted in an attempt to identify genetic polymorphisms associated with vulnerability or resilience to sleep loss. It has been shown that some genetic polymorphisms are associated with vulnerability to sleep loss. The most well described such polymorphism in humans is the PER3 polymorphism. The PER3 gene contains a variable number tandem repeat (VNTR) polymorphism. This polymorphism is characterized by a homozygous four (PER3^{4/4}) or five (PER3^{5/5}) repeat of 54-nucleotide coding-region segment (those heterozygous are PER3^{4/5}). There is evidence to suggest that the PER3^{5/5} variant is associated with susceptibility to fatigue-related cognitive deficits. This vulnerability may relate to an individual's response to sleep loss or to diurnal preference.

Several studies examining total sleep deprivation have demonstrated that inter-individual differences to sleep loss, sleep architecture, waking response, and executive function vary based on genotype (Groeger et al. 2008; Vandewalle et al. 2009; Viola et al. 2007), with the PER3^{5/5} genotype being associated with poorer performance. These studies suggest that the performance decrements observed in those carrying the PER3^{5/5} are due to increased sleep propensity and sleep pressure in response to sleep deprivation (Viola et al. 2007) and a longer habitual sleep need (Archer et al. 2008). It has been suggested that this difference is due to the PER3^{4/4} variant being associated with activation of the parietal and temporal brain regions in response to sleep loss (Vandewalle et al. 2009). The PER3 polymorphism has also been shown to be linked to an individual's diurnal preference. The PER3^{5/5} variant is associated with subjective morningness (Archer et al. 2003; Pereira et al. 2005), and an earlier DLMO and body temperature nadir (Duffy et al. 1999), while the PER3^{4/4} variant has been linked to delayed sleep phase syndrome (Archer et al. 2003) and later circadian phase (Duffy et al. 1999).

Although these findings support clear differences in performance associated with the PER3 polymorphism, such differences were not found under conditions of chronic nocturnal sleep restriction (Goel et al. 2009a). The negative finding in this study infers that there may be an interaction between the accumulation of sleep debt and circadian phase.

Recently, Goel and colleagues have conducted experiments investigating other potential biomarkers for individual variability in sleep homeostat, sleepiness and effects in functioning due to sleep loss. The COMT Val158Met polymorphism may be a genetic marker for predicting individual differences in sleep homeostasis and physiology, but not in cognitive and executive function responses while DQB1*0602, a polymorphism that is linked to narcolepsy, has been found to predict interindividual differences in sleep homeostasis and physiologic sleep under conditions of chronic partial sleep deprivation (Goel 2011; Goel 2010), Category II).

2. Sleep Inertia

Sleep inertia is a state of impaired performance, grogginess and disorientation upon first awakening from sleep (Jewett et al. 1999). Sleep inertia is generally felt for a brief period of time (20-30 min) though will linger longer and be more pronounced when influenced by other factors, such as the stage of sleep one awakens from -- more so when from deeper, slow wave sleep, the extent of any existing sleep debt and circadian time of day (Scheer et al. 2008). Ironically, sleep inertia can temporarily obscure the recuperative effects of a sleep or nap period (Ruggiero and Redeker 2014).

In a practical, Category II laboratory evaluation of sleep inertia, Signal et al. provided 20, 40 and 60-minute nighttime nap opportunities ending at 0200 to 24 individuals prior to a 20 hour episode of extended wakefulness (Signal et al. 2012). In this Category II laboratory study, performance on a Working Memory Task (WMT) was impaired immediately post-nap, with the largest effects after longer naps. These findings confirm conventional fatigue risk management recommendations that suggest that shorter nap durations are better for reducing the impact of sleep inertia.

Emergency situations that necessitate forced awakenings create a further challenge to managing sleep inertia. Studies of forced awakenings have elicited mixed results. Ribak and colleagues analyzed Israeli Air Force accidents over a 12-year period and found that the highest rate of accidents was for the first hour in the morning after awakening from sleep period (Ribak et al. 1983), Category III). There was also a similar pattern (to a lesser degree) in the afternoon that was attributed to late shift pilots with later wake times. Similarly, Kubo and colleagues studied 12 individuals on a simulated night shift to evaluate the impact of sleep inertia following a 60-minute nap at 0400 or no nap (Kubo et al. 2010), Category I). They found that performance was significantly worse following a 60-min nap at 0400 compared to the no-nap condition.

In contrast, Gregory and colleagues surveyed medical helicopter pilots in order to evaluate the impact of napping on shift and found that approximately half felt that sleep inertia upon waking from a nap never compromised operational safety (Gregory et al. 2010). Similarly, Signal and colleagues studied 21 ultra long-range airline pilots who slept an average of 3.3 hours during a 7-hour rest opportunity and found minimal evidence of sleep inertia, however, they also reported that participants experienced very little slow wave sleep during inflight sleep, which may moderate the impact of sleep inertia (Signal et al. 2013).

3. Circadian Desynchronization

The circadian pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, regulates many aspects of biological function in addition to the sleep drive. Numerous laboratory and field studies have been conducted in order to identify the causes and consequences of circadian desynchronization. The period of the human circadian rhythm is approximately 24.2 (Czeisler et al. 1999). The circadian rhythm is reset by exposure to light through the intrinsically photosensitive retinal ganglion cell layer of the eye, which is distinct from the system used for human visual responses to light (Czeisler et al. 1995). The light signal is in turn transmitted down the retinohypothalamic tract to the SCN, which is the location of the central circadian pacemaker (Czeisler and Gooley 2007). Upon receipt of the light signal, the circadian rhythm will be reset. Regular timing of light exposure on Earth leads to entrainment to the 24-hour day. In the absence of photic cues, the circadian pacemaker will revert to its endogenous period, as is the case for totally blind individuals (Flynn-Evans et al. 2014). For circadian resetting, the intensity, spectra, duration, and timing of light determine the magnitude and direction of phase shifting and potency of acute alerting (Lockley 2005). Under carefully controlled lighting conditions, the circadian rhythm is capable of being reset to a non-24-hour period. When an imposed light-dark cycle is too rapid or too long for circadian entrainment, circadian desynchronization occurs, such that the internal biological function, including the drive

for sleep is misaligned relative to the imposed schedule (Czeisler and Gooley 2007). There have been several Category I and Category II laboratory investigations that have further elucidated the impact of light and abrupt schedule changes on human circadian physiology.

Wright and colleagues randomized 12 individuals to a 24 or 24.6-hour day length and studied three additional individuals on a 23.5 hour day length under dim light of less than two lux during wakefulness (Wright et al. 2001), Category II). They found that five of six individuals were able to entrain to the 24-hour day length in the presence of the dim light, but none of the individuals in the 24.6 or 23.5 hour schedule conditions were able to synchronize with the imposed dim light-dark cycle. These findings highlight the importance of maintaining adequate light exposure to facilitate circadian entrainment.

A laboratory study by Gronfier and colleagues demonstrated that entrainment to an hour longer than one's endogenous circadian period is possible for most individuals in the presence of adequate light exposure (Gronfier et al. 2007). In this Category II study, 12 individuals were evaluated to determine their circadian period. They were then scheduled to remain on a day-length that was one hour longer than their endogenous circadian period and randomized to ambient light of 25 lux, 100 lux or 25 lux followed by 100 lux with two 9500 lux bright light pulses scheduled before bedtime. They found that 25 lux was insufficient for circadian entrainment for all individuals, 100 lux led to entrainment, but there were broad individual differences in the timing of circadian phase relative to sleep timing in that condition. In the bright light pulse condition, the individual variation in phase angle of entrainment was reduced and all individuals experienced a stable phase shift to the one-hour longer period.

The impact of light on the human circadian system follows a phase response curve (PRC), such that light timed in the biological evening elicits a phase delay (later shift) and light timed in the biological morning elicits a phase advance (earlier shift) (Czeisler et al. 1989; Honma and Honma 1988; Jewett et al. 1994; Khalsa et al. 2003; Minors et al. 1991; Van Cauter et al. 1994). Recently, two new phase response curves to light have been completed, furthering understanding of how the timing, duration, and wavelength of a light pulse interact to elicit changes in circadian timing. St. Hilaire and colleagues constructed a phase response curve to a one-hour pulse of ~10,000 lux of full spectrum bright light, using data from 34 young, healthy men and women (St Hilaire et al. 2012). They found that the one-hour light pulse elicited phase shifts in a consistent manner with a prior 6.7 hour light pulse, but that the shorter duration light pulse conferred 50% of the phase delay observed in the 6.7 hour PRC and 22% of the phase advance. A second PRC constructed by Rüger and colleagues used a 6.5 hour pulse of short-wavelength light (480 nm), which produced 75% of the phase shift of 10,000 lux of white light, but required only 4% of the energy (Rüger et al. 2013). These findings suggest that shorter light pulses and/or narrow bandwidth light pulses, which may be more acceptable to astronauts, might be more efficient in producing phase shifts when required.

Accumulating evidence suggests that the intrinsically photosensitive retinal ganglion cells that receive the circadian light signal become desensitized by continuous light exposure (Wong et al. 2005). This has implications for how the timing and pattern of light exposure influence circadian phase shifting. In a Category I study evaluating the impact of prior light history in modifying the phase shifting effect of light exposure, Chang et al. evaluated 13 healthy

young adults during two separate exposures to full spectrum, 450 lux light, and two placebo light exposures of 1 lux, timed during the biological night (Chang et al. 2011). These light exposure sessions were preceded by three days of exposure to 1 lux of light or three days of 90 lux of light, with each participant receiving both conditions in a random order. This study demonstrated that phase delays of the circadian rhythm (i.e. shifting circadian phase later) were 38 minutes later, representing a 62% increase in efficacy, when exposure to 90 lux of light followed the pre-condition of three days in 1 lux of light compared to three days of exposure to 90 lux of light. These findings suggest that the phase shifting effect of light on the circadian rhythm may be enhanced by preceding light exposure sessions with exposure to dim light. It remains unclear, how long dim light is required prior to bright light exposure in order to elicit a stronger effect.

In an effort to evaluate the impact of lighting on circadian phase under naturalistic conditions, Chang and colleagues conducted a laboratory-based crossover study where 12 healthy, young participants were randomized to read for one-hour before bed using a traditional book and bedside lamp for one week preceded or followed by an hour of reading using a light-emitting eReader (Category I). They found that exposure to light from e-readers, such as iPads, during the one hour before bed resulted in an average one-hour phase shift in circadian timing, relative to placebo (reading a book with a bedside lamp) (Chang et al. 2015). In addition, using an e-reader before bed increased alertness and sleep latency. These findings highlight the importance of providing sleep hygiene training to astronauts along with access to activities that do not involve supplemental light exposure before sleep.

Although the response of the human circadian system to light is generally predictable, there is a great deal of variability in the phase angle of entrainment achieved between individuals, particularly under dim light conditions. In a Category II laboratory study of 14 men conducted by Dijk and colleagues, the sleep schedule was shifted by 10 hours over five days under either moderate light of 100-150 lux or bright light of ~10,000 lux of 5-8 hours, timed relative to wake time by a mathematical model designed to optimize the timing of light exposure (Dijk et al. 2012). All participants in the bright light group experienced a phase advance (earlier circadian phase) of all circadian phase markers compared to those in the moderate light group who did not shift. Interestingly, individuals with stronger melatonin suppression were more alert and performed better throughout an extended wakefulness episode compared with those who had weak melatonin suppression, regardless of study condition. In a separate Category II laboratory study conducted by Sletten and colleagues, poorer performance, decreased alertness, and more slow eye movements were apparent in individuals who had a later DLMO, when sleeping on a fixed sleep schedule (i.e. the participants who woke at an earlier circadian phase performed worse) (Sletten et al. 2015). These findings suggest that individual differences in circadian phase and the phase angle of entrainment can affect alertness and performance even under a fixed sleep wake schedule. This is of particular importance for deep space missions, where it may not be possible to generate exposure to light of sufficient intensity to facilitate a stable phase angle of entrainment for all individuals.

Circadian misalignment arising from inappropriate exposure to light or abrupt changes in the timing of sleep and wake lead to several health consequences in addition to the immediate impact on sleep, alertness and cognitive function. Circadian misalignment and shiftwork have been linked to increased risk of breast cancer (Schernhammer et al. 2001) and elevated prostate

specific antigen (Flynn-Evans et al. 2013) and increased risk of metabolic syndrome (Sohail et al. 2015). Recently, short-term studies of circadian desynchronization have revealed changes in hormone profiles that are medical precursors to disease states. Buxton and colleagues evaluated metabolic outcomes among 21 participants (11 young, 10 older) on a three week forced desynchrony study (Buxton et al. 2012). Sleep restriction combined with circadian disruption for up to three weeks reduced metabolic rate and caused a relative reduction in insulin secretion to a standardized meal. The effects on metabolism were age-independent with both young and older participants exhibiting increases in postprandial glucose and decreases in postprandial insulin.

Similarly, Nguyen and Wright evaluated leptin levels (a hormone associated with satiety) among 14 individuals randomized to a 24 or 24.6-hour day for 25 days (Nguyen and Wright 2010). In this study half of participants developed desynchronized circadian rhythms, which resulted in reduced leptin levels. Prolonged reduction of leptin levels would be expected to increase appetite. These findings have important implications for long-duration spaceflight, where there is the potential for extended bouts of circadian desynchrony, which could lead to substantial endocrine disruption.

4. Work Overload

Work overload can generally be considered as a product of time on task, task complexity, and task intensity. Factors related to work overload that can impair performance include time on task, task sequence, time of day, number of tasks performed, and the extent of partial or total sleep loss. Not easily measured, most studies that evaluate work overload primarily consider time on task or work period duration measures. While fatigue resulting from time on task can be effectively relieved by taking breaks within a work period, fatigue related to time awake can only be relieved by sleep (McDonald et al. 2011).

Work underload can also lead to fatigue. Underload situations are those with low levels of task-related arousal, such as overreliance on automation, monotonous or routine tasks, and active but less engaging tasks. Such circumstances can unmask underlying physiological symptoms of sleep loss and circadian desynchronization, and can especially be exacerbated by time awake, existing sleep debt, and timing during the circadian nadir (Hutchins 2013). Rosekind emphasized “the need to not permit fatigued operators to over-rely on automation and fail to vigilantly track it” (Rosekind 2014).

Thus, both “active” and “passive” tasks can interact with other physiological factors to contribute to fatigue and degraded performance. A study of a simulated industrial task found that drowsiness was affected more by slower paced work, such as monitoring, than faster paced work. Another study found that “hectic” and physically demanding work predicted increased self-reporting of difficulties with sleep and tiredness (Williamson 2013).

A recent Category III study of ultra long-range commercial aviation operations conducted by van den Berg and colleagues showed that cabin crew (n=55, 30F) operating flights between South Africa and the US reported high workload on the NASA-TLX scale that was linearly associated with higher subjective sleepiness and fatigue ratings and more PVT lapses (van den Berg 2015). In this study, workload ratings were not influenced by amount of in-flight sleep or

by hours awake at top of descent, suggesting that workload contributes to fatigue independently of recent sleep history.

In a laboratory study that utilized a 20-minute PVT to evaluate sustained mental workload, Lim and colleagues found that subjects showed significant time-on-task effects with slower reaction times over the course of the task (Lim et al. 2010). Self-reports of mental fatigue following the experimental task were significantly worse than pre-task. In a separate Category I laboratory study, Dinges and colleagues evaluated 63 individuals (29F) over four conditions of moderate or high workload and four or eight hour sleep per night over a five-day period (Dinges et al. 2013). They found that high workload increased subjective fatigue and sleepiness ratings and delayed sleep onset, but response times on the PVT, maintenance of wakefulness task (MWT) and executive function were not affected. In addition, high workload was associated with less wake after sleep onset and more slow wave energy. In contrast, sleep restriction produced significant increases in PVT lapses, subjective ratings, and decreased PVT speed and MWT latency. There were no interactions between workload and sleep. These findings may explain some of the reported astronaut experiences in space, given that high cognitive workload was shown to affect subjective perceptions of sleep and delayed sleep onset.

5. Ground-based operational evidence describing reduced performance under conditions of sleep loss, circadian desynchronization, and work overload

a. Aviation, medicine and military populations

Studies of population groups that are analogous to astronauts (e.g., military, medical, and aviation personnel) provide compelling evidence that working long shifts for extended periods of time contributes to sleep loss, circadian desynchronization, and work overload. Studies in these groups provide evidence to help characterize the extent of performance decrements, accidents, health problems, and other detrimental consequences that may be anticipated under similar working conditions during spaceflight.

Several Category III surveys have been conducted among occupational cohorts in order to characterize working conditions, fatigue, and resulting consequences. A collection of studies conducted by the NASA Fatigue Countermeasures Laboratory suggest that airline pilots self-report sleeping somewhat longer than astronauts on average, but frequently report experiencing fatigue as a by-product of their workload and schedules. A NASA survey of 1404 long-haul commercial airline pilots found that they averaged about 7.6 hours of sleep per night while at home between trips. The majority rated themselves as ‘good’ or ‘very good’ sleepers, though over half reported they had difficulty sleeping in an onboard rest facility, or bunk, ‘often’ or a ‘majority of the time,’ highlighting the importance of sleep habitability in facilitating quality sleep (Rosekind et al. 2000b). Another NASA survey of 1488 corporate/executive aviation pilots conducted by Rosekind and colleagues found that they averaged about 7.3 hours of sleep per night while at home. The majority rated themselves as ‘good’ or ‘very good’ sleepers, though 61% reported fatigue as a common occurrence in flight operations. Factors that contributed to the workday in which they’d been most fatigued included long duty day, early morning departure, multiple flight legs, and night flights (Rosekind et al. 2000a). Similarly a survey of 456 airline pilots conducted by Reis et al. found that medium/short-haul pilots rated fatigue as more of an

issue, in terms of total and mental fatigue, than did long-haul pilots (Reis et al. 2013). In a study of 332 pilots, Wu and colleagues examined sleep during off-duty periods at home. The average sleep achieved by these pilots was comparable to males in the general population and similar to findings from other studies, but their subjective reporting of total sleep time of 7.6 hours was about an hour more than actigraphy-measured sleep (6.8 hours; (Wu 2015).

Category III survey studies in other cohorts provide further insight into the sleep habits and consequences experienced by individuals in high workload environments. In a survey of 697 emergency medical services (EMS) helicopter pilots, 41% reported that their self-reported sleep need was 6-7 hours, yet 28% reported nodding off during a flight (Gregory et al. 2010). In addition, 84% reported that fatigue had affected their flight performance. These findings do not appear to be related to shiftwork alone, as a separate survey of EMS pilots (n= 395), found that all respondents self-assessed some level of fatigue regardless of whether they were working days or nights (Nix et al. 2013). Similarly, in a survey of 547 ground-based EMS workers, Patterson and colleagues found that 55% of respondents were classified as fatigued while at work according to the Chalder Fatigue Questionnaire. About 89% reported “safety compromising behaviors” and fatigued respondents had greater risks of injury, medical error, and safety compromising behaviors (Patterson et al. 2012). Collectively, these survey studies provide important lessons for spaceflight operations in that they demonstrate that fatigue is apparent as a problem in populations with similar workload, challenging schedules, and stress. These studies also highlight the utility of using survey data in order to monitor and evaluate the health of an operational system.

Several Category II and Category III studies have been conducted using objective measures to evaluate sleep, circadian rhythms and workload among other occupational cohorts that are analogous to astronauts. Gander and colleagues conducted a Category II study of 237 pilots flying long-range and ultra-long range (> 12 hour flights) operations and determined that flight departure timing had a strong influence on subsequent fatigue ratings including ratings at top of descent and during landings that occurred at adverse circadian phases. Departure timing also influenced the amount of in-flight sleep that pilots were able to obtain (Gander et al. 2014). These findings demonstrate that time of day (as an estimate of circadian phase) is an important consideration for the timing of critical operations. In a subsequent Category III study among 70 pilots, the same group found that ultra-long range pilots slept an average of 38 minutes longer compared to long-range pilots during flight (Gander et al. 2013). This resulted in lower ratings of sleepiness ratings and improved reaction times at the end of the ultra-long range flights suggesting that the additional sleep during the longer flights helped mitigate the associated fatigue.

In medicine, the combination of work overload and chronic sleep restriction has been shown to lead to decreased performance. In a study of 34 medical residents (23F) working extended shifts over a 3-week rotation that included alternating 24 and 30-hr shifts with 8-hr shifts, Anderson and colleagues found significant reductions in performance due to the extended shifts (Anderson et al. 2012). Residents exhibited impaired performance over the course of each individual extended shift due to acute sleep loss, while a cumulative deterioration of performance occurred with successive extended shifts due to chronic sleep deficiency. Similarly, Gordon and colleagues conducted an investigation evaluating the performance of 17 medical interns on a

high-fidelity patient simulator after a 16-hour night shift or after a 24-30 hour extended duty shift (Gordon et al. 2010). Performance was significantly better when interns worked a 16-hour overnight shift as compared with 24-30-hour shifts. On the extended shift, 75% of interns did not perform at an acceptable level, double the rate for their shorter night shift. Individual differences were also noted as some sleep-deprived individuals performed much worse than others, some maintained performance, and a few actually improved their performance (Gordon et al. 2010).

Given the nature of military operations, combined with the fact that a large proportion of the astronaut population is derived from the military, studies involving these populations are particularly relevant to spaceflight. The majority of studies involving military personnel demonstrate that sleep loss is prevalent and similar to that experienced by astronauts. A recent RAND report led by Troxel summarized the scope of sleep issues faced by members of all branches of the military (Troxel et al. 2015). This report included results from a survey comprised of 1,957 service members that demonstrated that military personnel experience reduced sleep quantity, consistent with that experienced by astronauts, with 62% of respondents reporting an average of less than six hours of sleep per night. Respondents also had a high prevalence of poor sleep quality, with nearly half having a Pittsburgh Sleep Quality Index (PSQI) score indicative of a sleep disorder (> 5). In addition, about 18% reported use of sleep medication during past month.

Surveys in other military groups have yielded similar results. Mysliwiec and colleagues studied 725 military personnel (49F) and found that self-reported sleep duration averaged 5.7 hours per night, with 42% reporting obtaining less than five hours a night on average. This study also revealed a strong association between insomnia and post-traumatic stress disorder and pain symptoms, highlighting the complex relationship between sleep loss and symptoms of other conditions (Mysliwiec et al. 2013). Similarly, a sample of 375 veterans found that sleep problems were common post-deployment, with 45% reporting sleep latency averaging longer than 30 minutes, 21% reporting average sleep duration less than 4.5 hours and with approximately 89% classified as 'poor sleepers' according to the PSQI (Plumb et al. 2014).

A survey of 49 Army officers, suggests that fatigue risk management training is an important component to mitigating risk among Army personnel. Miller and colleagues found that close to 80% of Army officers had not received a sleep management plan during their most recent deployment and 55% reported fatigue as an issue in their unit (Miller et al. 2011). During elevated workload operations, officers averaged about four hours of sleep per night, with 82% reporting feeling sleep-deprived. Among officers who did receive fatigue management training, 66% felt their unit did a good job managing sleep, as opposed to only 25% of those without a plan.

Studies of specific cohorts of military personnel have confirmed the findings of survey studies and suggest that rank and workload may be associated with sleep duration. Pleban and colleagues found that candidates at the US Army Ranger School averaged 3.2 hours of sleep during a 58-day period (Pleban 1990). In contrast, Belenky et al. found that during a 14-day operation at the National Training Center, personnel at squad and crew level averaged 7-8 hours of sleep per night, while battalion and brigade commanders averaged just over four hours per night (Belenky 1997). In this study, the higher the rank the less sleep was recorded. These

findings highlight the need for evaluation of workload at all ranks in order to ensure that all individuals have ample sleep opportunity.

Objective measures of sleep loss, circadian desynchrony, and work overload in the military confirm the deleterious consequences of working under such conditions. A Category III case study of the actigraphy-derived sleep patterns of one Navy officer during a six-month deployment period was evaluated by Shattuck and colleagues (Shattuck and Matsangas 2015a). On average, the officer obtained 5.2 hours of sleep per day with approximately six hours of time in bed. The officer obtained eight hours of sleep only 2% of the time and experienced less than four hours of sleep 17% of the time. Similar to what has been observed in astronauts, sleep was further reduced below five hours a night for a week following a critical event. The authors used a model called the Fatigue Avoidance Scheduling Tool (FAST) to estimate the officer's predicted effectiveness based on his actual sleep patterns and found that he was predicted to be below 70% effectiveness during 15% of his waking time. Shattuck and colleagues conducted a larger Category II study of 69 active crewmembers on a Navy destroyer over 11 days using actigraphy, the Epworth Sleepiness Scale (ESS) and PVT (Shattuck and Matsangas 2015b). They found that crew with normal ESS scores averaged 6.9 hours total sleep time, which was about 26 minutes longer than crew with high ESS scores. Importantly, crew with high ESS scores had 60% slower reaction times and 60% more lapses and false starts compared to crew with normal ESS scores. These findings suggest that there may be some utility in monitoring astronauts using subjective screening tools at regular intervals throughout a mission when objective measures are not possible.

Recently, Shattuck and colleagues evaluated Navy work schedules in order to determine the impact of schedule design on sleep and performance. In this Category II field study, four different watch schedules were analyzed between sailors on different surface vessels including five hours on, ten hours off (5/10), three hours on, nine hours off (3/9), six hours on, six hours off (6/6), and six hours on, 18 hours off (6/18) resulting in a backwards shift rotation. Crew on 5/10 had most daily sleep, averaging 6.9 hours, but the worst PVT performance. Sleep on 5/10 was at irregular, circadian-misaligned times and was of poor quality. The best PVT performance occurred during the 3/9 schedule, where sleep averaged 6.4 hours, which resulted in reaction times that were 13% faster and errors were reduced by a third. Results from the study highlight the importance of designing schedules that not only allow for ample sleep opportunity, but also schedules that allow for appropriate timing of sleep relative to circadian phase (Shattuck 2015). These findings are particularly relevant for planning watch schedules for future deep space missions.

b. Spaceflight analog and simulation studies

Although studies of military personnel provide important insights into the causes and consequences of sleep loss among individuals working under high workload, the stressors impacting servicemembers are quite different than the stressors experienced by astronauts. As such, analog missions to Antarctica, evaluation of mission controllers and simulated spaceflight missions provide the most relevant parallel to spaceflight operations.

Table 3. Summary of Ground-based Sleep Studies and Category of Evidence

Source	Average Hours of Sleep	Missions	Mission Duration (days)	Subjects (N)	Measurement Tool	Category of Evidence
Barger et al., 2014	5.6*	105-day controllers	105	19	Actigraphy	II
Barger et al., 2014	6.9*	105-day crew	105	6	Actigraphy	II
Basner et al., 2013	7.4	520-day crew	520	6	Actigraphy	II
Barger et al., 2012	6.2	PML controllers	78	15	Actigraphy	II
Grófa et al., 2011	7.3**	FMARS	37	7	Sleep logs	II
Groemer et al., 2010	6.0	AustroMars	14	2	Actigraphy	II

* prior to extended shift; ** 'late' Mars period

Several studies have been conducted in Antarctica, where the isolation and workload is similar to that experienced in spaceflight. These studies reveal prevalent circadian desynchrony and associated sleep loss. Palinkas and colleagues studied 91 men and women at 3 different Antarctica research stations (Category III). In this study exposure to total darkness, which differed by station latitude, was significantly associated with total sleep time, the timing of sleep onset and sleep quality (Palinkas et al. 2000). In a separate study, six members of an expedition team were studied during a winter stay at an Antarctica research station. Polysomnography recordings yielded significant changes to sleep during dark winter months especially with reduced slow wave sleep, while REM and stages 1 & 2 increased. Total sleep time decreased compared to baseline as did sleep efficiency, while wake time after sleep onset increased (Bhattacharyya et al. 2008). These findings confirm the need for a robust light-dark cycle and associated schedule in order to promote and maintain circadian entrainment during long-duration spaceflight.

Evidence arising from ground-based personnel working supporting spaceflight and robotic Mars missions show strikingly similar results to data collected in spaceflight. Ground personnel are a critical component of space operations and can be physiologically challenged by the nature of constant mission activities, particularly when operations require non-24 hour work schedules. In a Category II study of 30 ground personnel who were required to adjust to a Mars Sol (24.65 hours, a circadian shift of 39 minutes per day) in order to support Mars Exploration Rovers (MER) operations, Deroshia and colleagues reported that about half of the participants showed adaptation to Mars Sol while the rest failed to entrain (Deroshia et al. 2008). Overall, time in bed was reduced for all mission personnel while working the MER schedule compared to baseline. A majority of MER personnel reported increased fatigue, irritability, sleepiness, and decreased concentration and energy during their study period (Deroshia et al. 2008). In addition,

one reportedly fatigued individual was injured by walking into a wall and another reported falling asleep in the car at the onramp to the freeway (Bass et al. 2004). These findings highlight the real-world consequences of sleep loss and circadian desynchrony.

Similar to MER operations, ground personnel supporting the Phoenix Mars Lander mission were required to work on a Mars Sol for 78 days (Table 3). Barger and colleagues conducted a Category III study and found that although most participants were able to adjust to the Mars day, there was a significant impact on sleep, with 15 participants averaging 6.2 hours per Mars day, with half of sleep episodes less than six hours and only 23% of sleep episodes lasting for seven hours or more. This shortened sleep and circadian misalignment resulted in significant consequences. Controllers' self-reported levels of fatigue and sleepiness significantly increased when work was scheduled at an inappropriate circadian phase. Extended wakefulness of 21 hours or more was associated with a significant decline in performance and alertness, highlighting the negative consequences when sleep loss, circadian desynchrony, and work overload coincide (Barger et al. 2012).

Simulated astronaut missions to Mars have yielded similar findings. AustroMars was a simulation of a Mars surface crew expedition with six analog astronauts participating in a two-week mission. Groemer et al. collected actigraphy from two participants who averaged 6.3 and 5.7 hours sleep with 1 hour less sleep during week 2 compared to week 1 (Groemer 2010). Gríofa evaluated seven subjects living on a Martian Sol for 37 days at the Flashline Mars Arctic Research Station using sleep diaries (Gríofa et al. 2011). Unlike other studies, the participants in this analog slept longer during the Mars Sol compared to before the simulation, but sleep duration decreased about 35 minutes on average from early to late during the simulation.

Longer duration Mars simulations have revealed more complex problems. Both ground personnel (mission controllers) and crewmembers were studied in a 105-day simulated spaceflight mission. In this study, six male crewmembers worked an extended 24-hr shift every sixth day but otherwise were regularly scheduled for sleep from 2400 to 0800 (Barger 2014). In this Category II study, crewmembers averaged about seven hours of sleep for the two workdays prior to the extended shift, 1.9 hours during the 24-hr period that included the night shift, and 10.2 hours for the day following the extended shift. In the majority of situations (86%), crewmembers napped one or more times for an average duration of 1.8 hours. The extent of napping remained consistent over the course of the mission. Significant performance impairments related to extended shifts were present in all personnel studied in the 105-day simulation despite the use of countermeasures (naps, light, caffeine, education). Cognitive function of crewmembers significantly worsened during the extended work shift. Subjective reporting of sleepiness, alertness, energy, mood and other factors all were significantly worse during the extended work shift. Cognitive function of mission controllers also significantly worsened during the extended work shift. Negative changes in mood during extended shifts can have implications for impaired communications between crewmembers and controllers.

In the longest and most rigorous high-fidelity simulation of a long-duration Mars mission, Basner and colleagues studied six male participants for 520 days of confined isolation (Basner et al. 2013). Participants worked a five days on, two days off schedule with a typical workday from 0800 to 1930. Crew sleep episodes were shortest during the first 40 days of the

mission, averaging 6.8 hours. Overall, sleep episodes averaged 7.4 hours, and sleep increased with time into the study. The study investigators postulate that this may have reflected reaction to the confinement, monotony, and low light conditions. There was an also decreased level of waking activity as the study progressed as measured by actigraphy. The differences in sleep patterns between participants were striking. Four participants maintained a 24-hr sleep/wake cycle while one subject had a split-sleep pattern, with more diurnal sleep during the second half of study. One participant was free-running with a circadian period of about 25 hours. Changes in sleep timing meant some crewmembers were sleeping while others were awake (and vice versa) which could pose an added challenge for crew coordination in long-duration missions. Despite the variation in sleep timing and circadian rhythms between participants, the majority of participants maintained performance levels throughout the study. One participant who had low waking activity levels, the least amount of sleep, and frequent ratings of poor sleep quality experienced the high rates of PVT performance errors, consistent with partial sleep deprivation (Basner et al. 2013).

c. Sex differences in response to sleep loss, circadian desynchronization and work overload

There is limited data on sex-based differences in sleep and circadian rhythm in isolated and confined extreme environments. Several home-based survey and field studies on sex differences have been conducted with mixed results. Category III studies investigating the self-reported sleep habits of healthy men and women in their home setting consistently find that women go to bed and fall asleep earlier than men and self-report longer sleep (Jean-Louis et al. 1999; Reyner et al. 1995). Despite this, women have been shown to have poorer sleep quality and on average report feeling more tired shortly upon awakening. On average, women are more likely to rate themselves as morning type than men, but older women are more likely to have a longer sleep latency compared to older men (Randler 2007). In a Category II study conducted by Walsleben et al., polysomnographically measured sleep revealed that women over 40 had longer sleep times, lower arousal and few awakenings, more slow wave sleep, and less Stage 1 and 2 sleep compared to men (Walsleben et al. 2004).

Recent laboratory data indicate sex differences exist in the phase angle of entrainment (Cain et al. 2010) and circadian period (Duffy et al. 2011) between women and men. In a Category II study conducted by Cain et al., young healthy women were found to have a significantly higher melatonin amplitude and lower core body temperature compared to men. The timing of the circadian phases was earlier in women despite the two groups having identical habitual sleep-wake time. These findings suggest that women have a different phase angle of entrainment, leading to waking at a later biological time. These findings could explain the 6-min shorter intrinsic circadian periods Duffy et al. observed in women compared to men (Duffy et al. 2011). In this study, a significantly greater proportion of women were found to have intrinsic circadian periods shorter than 24 hours. One constraint of these studies is that they did not assess the women's menstrual phases, which has been shown to influence the intrinsic circadian period and melatonin amplitude (Shecter 2010).

Survey studies have revealed several general differences between male and female shiftworkers. Female shift workers have been shown to have a lower BMI, more health problems and sleep disorders compared to male shift workers (Admi et al. 2008; Marquie and Foret 1999;

Rouch et al. 2005). They also report more frequent difficulties falling asleep and higher hypnotic use compared to men (Marquie and Foret 1999). Similarly, women reported higher levels of fatigue as expressed by lack of energy, physical exertion, physical discomfort, and sleepiness during shiftwork, suggesting that women may have a more difficult time adapting to shiftwork relative to men (Ahsberg et al. 2000).

Sex differences have not been observed in operational environments. In a Category II study, Caldwell et al. examined the effects of sleepiness and fatigue on simulator flight performance, mood and recovery sleep in male and female helicopter pilots during 40-hours of sustained wakefulness (Caldwell and LeDuc 1998). There were no sex differences for any of the polysomnographic variables except for movement time, with men moving more during sleep than women. Men were significantly tenser than women and women were significantly more vigorous than men but there were no effects between sex and sleep on any flight maneuvers. The results of this study are supported by those of Chelette et al., who investigated the effects of sleep deprivation on performance of active duty Air Force personnel in a 1-G simulator and found no sex differences (Chelette et al. 1998). These results suggest that both men and women are equally capable and prepared for enduring sleep deprivation in the aviation context. These findings may suggest that individuals who are better able to adapt to demanding schedules self-select into such occupations, thereby eliminating sex differences. Alternatively, it may be that the underlying sex differences observed in laboratory and survey studies are present, but intense training eliminates difference between men and women.

There may be sex differences in sleep and circadian rhythms related to environmental exposures. At altitude, the reduced oxygen level of the blood induces breathing variability, with periods of deep and rapid breathing alternating with central apnea. This breathing pattern is called high-altitude periodic breathing (PB) and it may lead to sleep disturbances with frequent awakenings (Lombardi et al. 2013). Lombardi and colleagues evaluated respiratory patterns during sleep at sea level and in conditions of acute and prolonged exposure at high (3400m) and very high (5400m) altitude hypobaric hypoxia in a group of healthy subjects. Their results revealed significant sex differences. At high altitude (acute exposure, first night) the cardio-respiratory evaluation showed a higher number of central sleep apneas and hypoapneas in males compared to females (high AHI (apnea-hypoapnea index), high ODI (oxygen desaturation index)). At very high altitude (acute exposure, first night) AHI and ODI increased in both males and females, but significantly higher in males. After prolonged exposure (10 days) there was no significant change in sex differences at 5400m altitude.

It appears that women are more able to detect impairment caused by fatigue and consequently become more cautious in taking risks than men. For example, in a Category II report, Baulk et al. (2006) found no sex differences in subjective sleepiness or driving performance measures over a period of extended wakefulness; however, sex differences were found in PVT performance with females having slower reaction times than males (Baulk et al. 2006). At 24-26 hours of sustained wakefulness women rated their driving worse than males. This suggests that when sleep deprived, women appear to be more perceptive of impairment caused by fatigue than men. In line with this, an investigation of highway accidents found that men had a significantly higher risk of accidents late at night compared to women (Akerstedt and Kecklund 2001). Another study investigating the effects of sleep deprivation on risk taking and

altruistic behavior as a function of subjects' sex found that females showed a significant decrease in riskier choices compared to men after sleep loss (Ferrara et al. 2015).

As noted in NASA's recent report on Sex and Gender, the impact of sex differences in response to sleep loss, circadian desynchrony, and work overload deserves further study (Goel et al. 2014). More research is required in order to confirm the results of the few studies that have demonstrated sex-based differences in these areas. In addition, there is no evidence to date to indicate whether sex differences are apparent in response to fatigue countermeasures.

6. Countermeasures

a. Pharmacologic countermeasures

There are several pharmacologic countermeasures that may be suitable to improve alertness and performance or to enhance sleep duration and timing during spaceflight.

Caffeine is the most widely used wake-promoting countermeasure. Although the majority of caffeine use is self-selected, several controlled studies have shown that caffeine is an effective countermeasure when used strategically. Wyatt and colleagues studied 16 men in a Category I laboratory trial where participants were randomized to receive an hourly low-dose of caffeine or placebo during a forced desynchrony protocol including 28.57 hours awake, followed by a 14.28 hour sleep opportunity over 25 days (Wyatt et al. 2004). This schedule resulted in circadian desynchronization, extended wakefulness and associated sleep disruption. The authors found that caffeine improved alertness, cognitive throughput, and performance on the PVT. In a separate Category I laboratory trial, Van Dongen and colleagues randomized 28 men to three nights of total sleep deprivation with placebo, with caffeine after 66 hours of wakefulness, with naps and placebo or with naps and caffeine after 66 hours of wakefulness (Van Dongen et al. 2001). In this setting of extreme sleep deprivation, caffeine did not reduce nap initiation or duration, but did reduce the impact of sleep inertia, by conferring improved performance after the nap episodes. These findings were replicated in a Category I trial by Newman and colleagues who randomized 15 individuals, awakened twice during a nocturnal sleep episode, to receive either caffeinated gum or placebo (Newman et al. 2013). In this trial, the caffeinated gum condition reduced the impact of sleep inertia more quickly than placebo. Collectively these studies support the use of caffeine to enhance performance, particularly for emergent situations where extended wakefulness or where a rapid transition from sleep to wake is required.

Other stimulants may be useful countermeasures during situations where extended wakefulness and sustained attention is required. Researchers at the Walter Reed Army Institute of Research have conducted several studies comparing the effectiveness of caffeine, modafinil, and dextroamphetamine on alertness and performance during extended wakefulness. Wesensten and colleagues conducted a Category I laboratory trial where 48 participants were subjected to 85 hours of sleep deprivation and randomized to receive a single dose of caffeine (600 mg), modafinil (400 mg), dextroamphetamine (20 mg), or placebo after 64 hours of wakefulness (Wesensten et al. 2005). In this study, all three stimulants improved PVT performance following drug administration for 2-4 hours and were similar in effectiveness. Killgore and colleagues conducted a Category I laboratory trial where 54 participants (25F) were subjected to 44 hours of

sleep deprivation and randomized to receive a single dose of caffeine (600 mg), modafinil (400 mg), dextroamphetamine (20 mg), or placebo. All of the stimulant groups improved PVT reaction time and lapse rate. In this case caffeine had the shortest latency to improvement, but was associated with the most negative side-effects. Dextroamphetamine had the longest latency to improvement and caused disrupted recovery sleep (initiated at hour 61 of the study). Modafinil improved PVT performance and was not associated with any side effects (Killgore 2008). All three countermeasures elicited improvements in performance on executive function tests compared to placebo, however, each medication tested affected performance in a different way. More work is required to evaluate the exact impact of stimulants on executive functioning before such agents are deployed in a spaceflight environment (Killgore et al. 2009).

Given that hypnotics have been developed for the treatment of insomnia, comparatively few studies have been conducted evaluating the effectiveness of hypnotics in healthy populations. Hart and colleagues conducted a Category I trial evaluating the impact of placebo or 5 or 10 mg of zolpidem on sleep, mood, and performance during a simulated shiftwork protocol consisting of three day shifts and three night shifts (Hart et al. 2003). They found that zolpidem improved sleep quality, but decreased mood the following day. In the field, Van Camp conducted a study evaluating the effectiveness of zolpidem on enhancing sleep duration and quality during rapid, unpredictable shift changes among remotely piloted aircraft crewmembers (Van Camp 2009). In this study, 43 active duty crewmembers were provided with three 10 mg tablets of zolpidem and were instructed to take the medication during a sleep episode preceding a day off in order to evaluate the efficacy of the drug. In this study, 63% of crewmembers took the medication, of whom 70% reported that they experienced improved sleep quality free of side effects. These findings suggest that use of hypnotics such as zolpidem may be warranted for improving sleep quality and quantity when eight hours are available for sleep, under the supervision of a physician trained to evaluate subsequent performance and side-effects.

Unlike other sleep-inducing hypnotics, melatonin is a chronobiotic that is used to shift the circadian rhythm in order to shift the timing of sleep. Numerous laboratory and field studies have been conducted to evaluate the efficacy of melatonin in improving sleep during jet-lag and under conditions of circadian desynchrony. In a Category I laboratory study, Sharkey and colleagues randomized 21 individuals participating in a simulated night shift study to either 1.8 mg of melatonin or placebo for two daytime sleep episodes following a simulated night shift. They found that melatonin improved daytime sleep duration on the first day following a night shift, but not on the second day (Sharkey et al. 2001). In a similar Category I study conducted by Wyatt et al., 36 participants (15F) were randomized to receive pharmaceutical grade melatonin (0.3 mg or 5 mg) or placebo before bed during a forced desynchrony protocol involving 20 hour days including 6.67 hours of sleep (Wyatt et al. 2006). Both doses of melatonin modestly improved sleep efficiency during circadian misaligned sleep episodes relative to placebo, supporting the use of melatonin during episodes of circadian misalignment.

A recent trial conducted by Burke and colleagues suggests that the combination of melatonin administration and light can enhance an advance phase shift (Burke et al. 2013). In this Category I laboratory trial, 36 participants (18F) were randomized to receive either dim light and placebo, dim light and 5 mg melatonin, bright light and placebo or bright light and 5 mg melatonin, with drug administration timed 5.75 hours prior to habitual bedtime and bright light

timed one hour prior to habitual wake time. The combined effect of melatonin and bright light elicited the largest phase shift. These findings may be useful in facilitating astronaut phase shifts; accordingly, NASA's Clinical Practice Guidelines for Managing Circadian Desynchrony include recommendations that incorporate such practices.

Melatonin has also been used as a therapy to entrain the circadian rhythms of blind individuals with non-24 hour sleep-wake disorder (Lockley et al. 2000). Given that circadian misalignment has been observed during spaceflight, combined with the fact that one individual participating in the Mars 520-day experiment developed a free-running circadian rhythm, melatonin may be an appropriate countermeasure for preventing circadian desynchrony during long-duration spaceflight missions.

B. Light

Light may be used as a countermeasure in two ways. First, light may be used to shift circadian phase or to facilitate stable entrainment. Second, light may be used to enhance alertness and cognitive performance through acute alerting effects (Lockley et al. 2006). There have been several novel light exposure regimes developed in recent years to improve the efficacy of light treatment, while also reducing the duration and intensity of light required to produce results.

A study by Thompson and colleagues examined the impact of dawn simulation on the dissipation of sleep inertia (Category III). They found increased melatonin suppression and improved subjective sleep quality following a dawn simulation (Thompson et al. 2014). A similar study by Grandner and colleagues demonstrated that a light mask timed to deliver light through closed eyelids approximately two hours prior to habitual waketime was sufficient to cause a circadian phase advance (Grandner et al. 2013).

Zeitler and colleagues conducted a rigorous Category II study examining the impact millisecond flashes of light administered during sleep had on circadian phase shifting and sleep architecture (Zeitler et al. 2014). They found that light flashes of 2 milliseconds given every 30 seconds were sufficient to cause a phase shift of approximately 30 minutes. The authors did not find that the light caused any significant difference in sleep stage or power density, but they did find that the brain waves registered an extra-retinal potential timed with each light flash, supporting the notion that extremely brief light flashes are capable of being registered by the brain and have an impact on circadian timing. Millisecond flashes of light may be a more feasible way for astronauts to experience light exposure during spaceflight compared to longer duration exposures, particularly given the reduced energy consumption required by short pulses of light relative to continuous light exposure.

The human circadian pacemaker is most sensitive to short-wavelength light in the 460-480 nm range (Brainard et al. 2008; Lockley et al. 2006), making it possible to reduce the intensity of light exposure in favor of narrow bandwidth blue light. In a randomized, within subjects study of eight young, healthy men and women (Category I), West and colleagues compared the effectiveness of exposure to different irradiances of narrow bandwidth blue light (485-465 nm) and broad-spectrum white 4,000 K fluorescent light (40 $\mu\text{W}/\text{cm}^2$) at night in suppressing melatonin (West et al. 2011). They found that blue irradiances above 20 $\mu\text{W}/\text{cm}^2$

significantly suppressed melatonin in a dose-response manner, with higher irradiances eliciting greater suppression. They also reported that blue light of approximately $10 \mu\text{W}/\text{cm}^2$ produced a mean percentage reduction in melatonin relative to 4,000 K light, although neither of these exposures significantly suppressed melatonin. Given that melatonin suppression is associated with improved alertness and performance, this study demonstrates that lower intensity blue light may have better feasibility relative to broad spectrum bright light.

Although light in the blue spectrum is associated with the human circadian system, there may be some benefit to providing brief exposures to green light in order to improve alertness and phase shifting. Recent research has revealed that the human visual system has peak sensitivity to green light of approximately 555 nm (Gooley et al. 2012; Zaidi et al. 2007). Gooley and colleagues demonstrated that both blue and green wavelength light are capable of eliciting melatonin suppression, but the effect of green light is temporary and blue light is required for sustained suppression (Gooley et al. 2010). These findings suggest that it may be possible to use short-duration pulses of green light or sustained duration pulses of blue light, or a combination of both in order to optimize light-induced circadian phase shifting.

In addition to the phase shifting effects elicited by light at different times of day, light confers acute alerting effects during the day and night. In a Category II laboratory trial, Rahman and colleagues randomized 16 volunteers to a daytime exposure to 460 nm light or 555 nm of light compared to 16 participants who were randomized to a nocturnal light exposure of the same wavelengths (Rahman et al. 2014). The authors found that daytime and nighttime exposure to 460 nm light improved reaction time and lapses compared to exposure to 555 nm light. These findings support the use of blue wavelength light for acute alerting and provide a non-pharmaceutical alternative for enhancing performance during periods of extended or circadian misaligned work.

In the field, some individuals working on the Phoenix Mars Lander project were provided with blue light boxes in order to facilitate a circadian phase shift to the Mars Sol (Barger et al. 2012). Although compliance with the blue light protocol was sporadic, 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 the program. In addition, the majority of those who received the blue light boxes were able to successfully entrain to the Mars Sol. These findings provide practical support for the inclusion of lighting countermeasures in mission operations throughout NASA.

C. Scheduling countermeasures

Numerous studies have evaluated the utility of napping on subsequent alertness and performance in laboratory and field settings. Split sleep opportunities may be useful as a countermeasure during periods of heavy workflow or in anticipation of a slam shift. Mollicone and colleagues conducted a 14-day Category II laboratory study of 90 individuals (38F) with a split sleep protocol that allowed nocturnal anchor sleep periods of varying durations plus diurnal nap opportunities over 10 days. The authors found that both objective and subjective performance degraded with decreased total sleep opportunity, but that the split-sleep did not

negatively affect performance relative to a single consolidated bout of sleep (Mollicone et al. 2008). In a follow up report, the authors describe that split sleep was associated with reduced performance in the morning following the reduced nighttime sleep opportunity, but was enhanced following the diurnal nap (Mollicone et al. 2010).

Similar findings were reported by Jackson and colleagues who randomized 53 male volunteers to either a 10 hour nighttime sleep opportunity, a split sleep opportunity of five hours at night, and five hours during the day and a 10 hour daytime sleep opportunity (Jackson et al. 2014), Category II). They found that polysomnography-derived sleep duration was similar in the nocturnal and split sleep opportunities, but was approximately two hours shorter during the ten-hour daytime sleep opportunity. Together these findings support the notion that strategically timed naps may be useful in mitigating the impact of shortened sleep episodes. It is important to note, however, that in the Mars 520-day simulation study, one participant was a habitual napper (Basner et al. 2013). This nap pattern reduced the individual's interaction with other crewmembers by approximately 20%. In addition, self-selected napping can lead to altered patterns of light-dark exposure, potentially leading to a free-running circadian rhythm as observed in another crewmember participating in the Mars 520-day simulation. These observations emphasize the need to carefully schedule and monitor naps during long-duration missions to prevent circadian desynchronization.

There may be some utility in providing astronauts with opportunities for sleep extension before and/or after heavy workflow. In a Category II experiment conducted by Banks and colleagues, 159 participants (78F) were subjected to four hours of sleep restriction for five nights, followed by recovery sleep opportunities ranging from 0-10 hours. Objective and subjective neurobehavioral functions improved in a dose-response manner with increased recovery sleep. A single night of recovery proved insufficient to restore daytime functioning to baseline levels, suggesting that longer recovery sleep opportunity and/or multiple extended sleep opportunities are required for restoration of cognitive function (Banks et al. 2010).

There may also be some ability for humans to preemptively extend sleep prior to anticipated sleep restriction. Rupp and colleagues conducted a Category II study of 24 individuals (13F) comparing performance on the PVT and an addition task during a week sleep restriction including three hours time in bed, preceded by either a week of 10 hours of sleep opportunity or a week of habitual sleep of approximately 7.1 hours (Rupp et al. 2010). Sleep extension prior to sleep restriction led to mixed results. The sleep extension improved cognitive throughput, which continued into recovery sleep. In contrast, reaction time did not improve during sleep restriction following sleep extension. It is possible that the 10-hour of sleep opportunity acted as recovery sleep following modest, self-selected sleep restriction. In either case, there appears to be a beneficial effect associated with sleep extension prior to sleep restriction.

i. Fatigue risk management programs in aviation and in the military

Schedule-related fatigue is prevalent in aviation and the military. The aviation industry is at the forefront of implementing fatigue risk management systems (FRMS) in an effort to evaluate and manage schedules and workload. Commercial passenger carriers are required to

have FRMS programs in place as part of duty hour regulations developed by the FAA. FRMS programs include providing fatigue risk management education to personnel and evidence-based scheduling (Williamson 2013). As a result of this requirement, airlines are continuously evaluating the impact of rosters on crew alertness and performance. In one such study, an alertness management program was implemented at a US airline including education and an innovative scheduling intervention that allowed flight crew the opportunity for sleep at more ‘sleep-friendly’ times during trans-continental operations. A Category I study comprised of data from 29 pilots found that they averaged about six hours of total sleep time during a baseline period and about 5.3 hours of sleep while operating a standard schedule, but slept significantly more (6.5 hours) during the innovative schedule. PVT performance was significantly better during the innovative schedule, supporting the cognitive benefits that can come from fatigue risk management interventions (Rosekind et al. 2006).

Similar fatigue risk management tools have been developed by military personnel. A novel subjective peer-to-peer fatigue rating system was developed by Gaydos and colleagues and implemented during a deployed military helicopter operation. In this study, each pilot provided an anonymous weekly rating of fatigue for every other pilot in unit. The authors report that crew were generally satisfied with the program and thought it helped keep the issue of fatigue visible to command personnel (Gaydos et al. 2013). This type of anonymous rating system may be useful in an astronaut population, where individuals may feel uncomfortable disclosing their own fatigue.

In 2009, the Army incorporated a sleep deprivation chapter into its doctrinal Field Manual that provides guidance on the development of “unit sleep plans.” The information included in this manual provides army personnel with information on how to optimize sleep period timing and duration, napping, and understanding individual differences in sleep need. Other guidance includes information on how to enhance the sleep environment during operations and information on the use of stimulants, prescription sleep medications, food and alcohol. Of note, the manual also includes information on prioritizing sleep need by task demands on personnel, with sleep being prioritized among leaders in critical decision-making roles (Krueger 2012).

Similarly, in 2011, NASA and the International Partners began the development of Clinical Practice Guidelines for Managing Circadian Desynchrony in Spaceflight Operations (CPG), and NASA completed a more specific version of the document in 2013. The CPG is primarily focused on guiding flight surgeons with standardized recommendations for helping astronauts manage fatigue during the pre-mission phase, owing to heavy training schedules and transmeridian travel that is particularly consuming in the latter phases of ISS mission training. Much of the principles defined, however, are applicable to others in the NASA workforce, including overnight shift workers in Mission Control, and can also help guide in-mission countermeasure recommendations for astronauts.

V. COMPUTER-BASED MODELING AND SIMULATION

Biomathematical models hold promise as a technological tool that can be used in concert with other tools and strategies to manage fatigue risks in an operational setting. There are

numerous biomathematical models that have been developed to predict performance impairment arising from acute and chronic sleep loss, circadian desynchronization, and sleep inertia. Given the complexity of the underlying causes of fatigue, along with individual differences in performance in response to fatigue, each model differs in the modeling approach, development and refinement and predictive utility.

Through a competitive grant process, NASA has funded the development and refinement of a biomathematical models developed at Harvard (Jewett and Kronauer 1999). Harvard has developed and validated a mathematical model of the human circadian pacemaker and neurobehavioral performance and alertness that includes the three key processes of circadian rhythms, sleep/wake homeostasis and sleep inertia. The model was developed based on laboratory studies evaluating responses to an addition task and a subjective alertness assessment. It has been extended to also include PVT and DSST outputs, with each output having its own set of equations, unlike the other models that have one output for all performance metrics. The model incorporates data from many different sleep and wake conditions to estimate sleep homeostasis and sleep inertia. The model also provides outputs for circadian phase by incorporating the effect of light on the circadian system in equations. Circadian Performance Simulation Software (CPSS) was developed based on this model and has been used by NASA to design light countermeasures for astronaut pre-launch schedules (Dean et al. 2009).

A strength of the Harvard model is that it is continually being refined as laboratory and field studies reveal new information about sleep-wake dynamics, circadian rhythms, and countermeasures. For example, Philips and colleagues used a simplified model including the homeostatic drive for sleep and the circadian drive for wake in order to predict sleep architecture changes arising from a variable schedule. They found that they were able to generate predictions for state-specific rebounds following total sleep deprivation and REM sleep deprivation (Phillips et al. 2013). Philips et al. also evaluated the ability of the model to predict individual phenotypes and found that individual differences in activity could be captured by the inclusion of the influence of lighting and circadian output information. In addition, Phillips and colleagues have also worked on incorporating a physiologically-based model that is able to account for many aspects of sleep within self-selected schedules (Phillips et al. 2011). The addition of these components has yielded a model that predicts that sleep episodes will be shortest when they are initiated near the circadian nadir. These model predictions are consistent with laboratory findings.

The Harvard model has also been extended to include the influence of some countermeasures. Breslow and colleagues have been able to successfully predict the pharmacokinetics and results of a melatonin administration PRC using modeling. This melatonin model may provide a basis for predicting and optimizing melatonin use in real-world settings. However, it is important to note that the authors found that interindividual variability in response to countermeasures is difficult to predict, making it difficult to tailor model predictions for individuals with different sensitivities to melatonin (Breslow et al. 2013).

Recently researchers at Washington State University have developed a model to predict fatigue (McCauley et al. 2009). This model is based on the two-process model of sleep with an extension of coupled, non-homogeneous first-order ordinary differential equations in order to

account for the changes associated with chronic sleep restriction. This model was validated against lapses of attention on the PVT during chronic sleep restriction protocols and was able to explain 72.2% of the variance in grouped average data. The McCauley model has also been updated to better explain the decay in performance within a single episode of extended wakefulness in order to account for whether the preceding sleep episode was aligned or misaligned with circadian phase (McCauley et al. 2013). The incorporation of Bayesian statistics in this model allows for the individualization of performance predictions, based on previous PVT performance under a specified sleep-wake schedule.

A weakness of the Harvard models and the McCauley model is the lack of a user-friendly interface for enabling operational personnel to easily utilize the models. As such, NASA has funded the development of a dashboard for integrating the Harvard and McCauley model predictions into a graphical user interface that will allow flight surgeons and mission planning teams to quickly evaluate how schedule and lighting changes may influence predictions of performance. The McCauley model, as incorporated in the Dashboard software, includes the effects of caffeine in its predictive algorithms. The dashboard has the potential to incorporate predictions from other models and may be updated to reflect refinements to model predictions. Unlike with commercial off the shelf interfaces currently on the market (described below), this interface is tailored specifically for NASA use and is also being developed to integrate sensor and performance data, which may aid in operational decision making during NASA missions.

There are other several candidate models that deserve consideration for future inclusion in the NASA dashboard. Building on the work of McCauley et al., Rajdev and colleagues developed the unified mathematical model to address and “unify” effects of both total and chronic sleep restriction (Rajdev et al. 2013). The researchers used the classic two-process model proposed by Borbely and incorporated a “fading memory” component, wherein sleep debt is modeled so that chronic sleep restriction is reflected in model predictions and extended sleep bouts are modeled to include sleep “banking.” The authors validated the model predictions using three studies that included systematic chronic sleep restriction and total sleep deprivation. They found that the unified model provided more accurate and consistent predictions compared to the Borbely and McCauley models (Rajdev et al. 2013). The same group has used the two-process model to compare dose-dependent effects of caffeine based on data from two laboratory studies. At group level, performance predictions for a range of doses (50-300 mg) yielded up to 90% improvement over the two-process model. For individual-specific models, average improvement was up to 23% better (Ramakrishnan et al. 2014). The Unified Model has also recently been updated to evaluate individual differences in response to total and chronic sleep restriction. In a study of 15 individuals, Ramakrishnan and colleagues evaluated total sleep deprivation of 64 hours and chronic sleep restriction of three hours a night for seven nights and found that the Unified Model captured individual trait-like characteristics for both sleep-loss conditions, with predictions that were 50% better for individuals than the group-average model (Ramakrishnan et al. 2015). These findings demonstrate that the Unified Model holds promise for improving predictions for individuals under conditions of acute and chronic sleep loss.

Although NASA is developing tools for use in spaceflight operations, several other models are currently in use in other industries. The Sleep, Activity, Fatigue and Task Effectiveness (SAFTE) model is a widely used fatigue model that was originally developed for

the US Army and Air Force. This model has been incorporated into a commercial off-the-shelf user interface that allows operational personnel to evaluate schedules against model predictions (Fatigue Avoidance Scheduling Tool, FAST). The SAFTE model was developed based on a laboratory study using the PVT and predicts a metric described as cognitive effectiveness. The model provides a number of performance metrics including percent change in cognitive speed, lapse likelihood, and reaction time along with sleep-wake metrics, including sleep reservoir and circadian phase. The outputs all provide measurements of both duty time and critical time below an adjustable fatigue risk criterion line (2014; Hursh et al. 2004a; Hursh et al. 2004b).

A strength of the SAFTE model is that it has been evaluated in an operational environment. In a Category III case-control study, the 30-day schedules of railroad crews were retrospectively evaluated prior to 400 human factors and 1000 non-human factors accidents. The authors found a linear relationship between model estimates and risk of human factors accidents ($r=-0.93$), while no relationship was found for non-human factors accidents. In addition, time of day variation was observed with human factors accidents ($r=0.71$) but not for non-human factors accidents. Accidents were relatively more likely from 0000-0300 and 1200-1500 and less likely from 0900-1200 and 1500-1800. In this study, circadian desynchrony accounted for half of the variation in timing of human factors accidents. Risk of human factors accidents increased with effectiveness scores below 90 and progressively increased when effectiveness was further reduced (Hursh et al. 2006). In contrast, a recent evaluation of the SAFTE FAST model that was conducted by Hartzler and colleagues revealed that it may not provide accurate predictions for individuals under conditions of extreme sleep loss (Hartzler et al. 2015). In this study, FAST was used to analyze data from a study that involved restricting 24 individuals to four hours of nightly sleep for four days. The authors found that FAST rarely predicted more than 5% of variation in performance, but with the addition of other factors this improved to about 35%. When they evaluated the predictors that yielded the greatest improvement in predictions, they found that the addition of the profile of mood states and performance on a flight simulator added the most value to the model predictions. Although this analysis was conducted using the FAST model, it is important to note that very few of the current models would be likely to predict between-individual variation in performance in this scenario. In most cases, fatigue models are based on average data and are not designed to discriminate between individuals.

Similar to the SAFTE model, The System for Aircrew Fatigue Evaluation (SAFE) is a biomathematical model that is widely used in aviation operations. SAFE was commissioned by the UK Civil Aviation Authority (CAA) as a regulatory tool assist with the assessment of likely fatigue in airline rosters. The underlying fatigue model was created from studies commissioned by the UK Ministry of Defence in 1980 and the UK CAA funded subsequent research for its application and use with aircrew. SAFE describes and predicts the likely fatigue and sleep patterns experienced by pilots for a given schedule of duties. SAFE produces Samn-Perelli fatigue scores throughout the duty period, which is a subjective rating of fatigue. A forecasted fatigue score is generated every 15 minutes and predicts likely sleep patterns (2014). A Category III comparison was made between data collected from in-flight pilot fatigue studies with predictions from SAFE. The results of this study demonstrated that correlations were stronger between subjective fatigue measures than for objective reaction time. In addition, the model showed good agreement with objective measures for some duty schedules, but had poor agreement for other duty schedules. These findings demonstrate the difficulty in producing a

single model to predict all possible fatigue-related issues that may be encountered in an operational environment (Powell et al. 2014).

In addition to the models described above, there are several other commercial off the shelf and academic models that have been developed. For a description of some of these other models see CASA 2014, (Mallis et al. 2004; Van Dongen 2004).

In summary, biomathematical models hold promise for aiding in schedule design and in helping to guide flight surgeons and operational personnel on optimal timing of light and pharmacological countermeasure treatment. The International Air Transport Association (IATA) provided the following guidance to its members, which is relevant to the use of models in a spaceflight environment “To use models properly requires some understanding of what they can and cannot predict. An important question to ask about any model is whether it has been validated against fatigue data from operations similar to those an operator conducts. And while some modeling programs such as SAFE and SAFTE are used in aviation, those models still lack peer-reviewed validation.” Despite the large number of models that have been developed, it is important to note that none have been validated in a spaceflight environment and most are based on the average performance of average individuals, under carefully controlled laboratory conditions. As such, no existing model should be expected to adequately predict risk in the real-world. At the present time, the models hold promise for guiding general schedule design, but are too broad for determining absolute risk in a spaceflight setting.

VI. RISK IN CONTEXT OF EXPLORATION MISSION OPERATIONAL SCENARIOS

As detailed in this report, space flight evidence shows that astronauts experience sleep loss, circadian desynchronization and work overload during spaceflight. Ground-based evidence demonstrates that these conditions lead to reduced performance, increased risk of injuries and accidents and short and long-term health consequences.

Presently, NASA’s plans for future exploration missions consist of shorter duration missions (less than 30 days) to the moon and/or an asteroid, as well as longer duration missions (up to 2.5 years) to Mars, as outlined in the Mars Design Reference Architecture (DRM) 5.0 (Drake 2009).

It is anticipated that short-duration missions will be fast-paced “sprints” that are similar in nature to shuttle missions. While schedule shifting should not be prevalent, throughout the entire duration, crews will likely be required to shift while they are conducting critical-mission tasks; and consistent with historical spaceflight, the overall mission tempo is likely to be high and strenuous. While future systems will likely be heavily automated, and automation has been associated with an overall increase in safety, over reliance on automation may introduce new risks, such as fluctuations from low workload (i.e., passive monitoring) to high workload demands that may arise in the case of an anomaly and/or emergency situation. This concern is exponential under conditions of sleep loss and/or circadian desynchrony. Furthermore, the vehicle that is expected to carry crewmembers on these journeys, while more spacious than the Apollo capsules, requires crew share a common area for sleeping. Efforts are underway to provide evidence-based recommendations for relevant aspects of the vehicle, such as the lighting system, however, given that common sleep areas introduce sleep inhibitors such as noise, sleep is

likely to remain a challenge for some individuals. Performance decrements therefore remain a plausible risk during short-duration exploration missions.

Mars. Mars missions confer different phases of risk. The initial transit to Mars is anticipated to be similar to the ISS long-duration experience, although crewmembers will be confined to a smaller habitable environment and access to sunlight could be constant, self-selected and intermittent or infrequent depending on the design and trajectory of the spacecraft. Given that crewmembers participating in the Mars 520-day simulation showed signs of torpor and two of six crewmembers had significantly disrupted sleep schedules, it is anticipated that a Mars transit will have the potential to confer significant issues associated with sleep loss and circadian desynchrony. Although it is not anticipated that this transit will require slam shifting and high-tempo schedules necessitated by dockings and critical mission activities, it is likely that the astronauts will need to rotate through a shiftwork watch schedule. There is also a potential risk for work underload to increase the likelihood of circadian desynchrony, torpor and sleep loss. In addition, although work overload is a concern for operations occurring in low-Earth orbit, high workload scenarios allow for repetitive interaction with mission equipment, which may reinforce mission training. In a Mars transit scenario where crewmembers are not regularly exposed to vehicle systems, there is increased risk of cognitive failure due to sleep loss and circadian desynchronization during emergency situations.

In preparation for landing and on the surface of Mars, work overload may emerge as a concern as crewmembers work to establish a habitable base and conduct experiments. In addition to a likely change in the pace of activities during Mars surface operations, circadian desynchrony is likely to develop as a problem as the Mars Sol is approximately 40 minutes longer than the Earth Sol. Although several studies have demonstrated that most individuals are capable of entraining to a Mars Sol, such entrainment requires appropriately timed light of sufficient intensity, duration and wavelength. Such lighting schemes will likely require supplemental lighting due to the Mars atmosphere. Sunlight on Mars is about one-half of the brightness of that on Earth, and the Martian sky does not appear blue, but pink due to suspended dust (Ockert-Bell et al. 1997), which means that the dominant long wavelength on Mars may be insufficient for human circadian entrainment through stimulation of melanopsin containing retinal ganglion cells. These factors make it very likely that the conditions associated with a Mars transit and surface operations will lead to performance errors arising from sleep loss, circadian desynchrony and work overload.

Implications for future space flight. The behavioral consequences of performance errors due to sleep loss, circadian desynchronization, extended work shifts, fatigue, and work overload on ISS are currently being evaluated. Cognitive decrements that are caused by fatigue, inadequate light exposure, circadian dynamics, and work/sleep schedules, will more profoundly affect crews who are on a long-term lunar or Mars mission, where fewer resources will be available to mitigate these factors. The risk factors may become compounded by the fact that asteroid and Mars missions bring additional hazards and communication delays relative to missions to low-Earth orbit.

Currently, NASA STD-3001, Volume 1 provides standards regarding a normal, uninterrupted sleep period; standards for circadian shifting caused by schedule demands; and limits for the

amount of work that can be performed within one day and one week. The current standards, however, do not provide specific limits for performance thresholds. BHP anticipates developing normative databases for space flight using tools and measures that have been initially tested and verified in laboratories and high-fidelity analogs such as NEEMO [NASA Extreme Environment Mission Operations] and, subsequently, space flight. In mission analogs, astronauts can establish individual and group baselines as well as normative data for an environment that can be compared with space flight.

Flight designers and flight surgeons are concerned that crewmembers, and especially ground control personnel, may not be obtaining the minimum recommended rest periods: actual sleep/work time is not the same as the time that is planned. Evidence shows that, overall, sleep is shorter and interrupted in flight. During critical mission phases, schedule shifting and workload demands are strenuous for both ground and flight teams. It is important to ensure that the current NASA STD-3001, Volume 1 standards are enforced to protect work/rest schedules for both ground and flight crews, particularly during high-tempo operations. If crews are shifted or have to perform during this allotted sleep time, recovery time needs to be allowed and individualized countermeasures need to be readily available.

VII. GAPS

Based on the present and prior reviews, BHP has identified several gaps that need to be addressed in order to characterize and effectively manage performance impairment due to sleep loss, circadian desynchronization and work overload during spaceflight.

Sleep Gap 1: We need to identify a set of validated and minimally obtrusive tools to monitor and measure sleep-wake activity, and associated performance changes for spaceflight.

Sleep Gap 2: We need to understand the contribution of sleep loss, circadian desynchronization, extended wakefulness and work overload, on individual and team behavioral health and performance (including operational performance), for spaceflight.

Sleep Gap 4: We need to identify indicators of individual vulnerabilities and resiliencies to sleep loss and circadian rhythm disruption, to aid with individualized countermeasure regimens, for autonomous, long duration and/or distance exploration missions.

Sleep Gap 5: We need to identify environmental specifications and operational regimens for using light to prevent and mitigate health and performance decrements due to sleep, circadian, and neurobehavioral disruption, for flight, surface and ground crews, during all phases of spaceflight operations.

Sleep Gap 6: We need to identify how individual crewmembers can most effectively and safely use medications to promote sleep, alertness, and circadian entrainment, as needed during all phases of spaceflight operations.

Sleep Gap 8: We need to develop individualized scheduling tools that predict the effects of sleep-wake cycles, light and other countermeasures on performance, and can be used to identify optimal (and vulnerable) performance periods during spaceflight.

Sleep Gap 9: We need to identify an integrated, individualized suite of countermeasures and protocols for implementing these countermeasures to prevent and/or treat chronic partial sleep loss, work overload, and/or circadian shifting, in spaceflight.

Sleep Gap 10: We need to identify the spaceflight environmental and mission factors that contribute to sleep decrements and circadian misalignment, and their acceptable levels of risk.

VIII. CONCLUSION

Spaceflight evidence demonstrates that astronauts experience sleep loss, circadian desynchrony, and work overload consistent to a degree that is associated with significant performance impairment in ground-based studies. As NASA transitions from low-Earth orbit to lunar and Mars missions, flight and ground crews will continue to face challenges that are associated with acquiring adequate sleep, circadian desynchronization, fatigue, and workload demands.

As spaceflight performance data are limited, BHP research aims to further characterize performance in the space flight environment using standardized, validated tools that detect cognitive deficits that are related to fatigue. BHP research efforts will further describe the nature of sleep in space over long-duration missions, and tasks are under way to determine which factors enhance or infringe on sleep and disrupt circadian rhythms in space. The spaceflight environment is reported to be noisy, poorly lit, and, for some, uncomfortable. Shifting schedules and heavy workloads can pose additional challenges.

Astronauts have proven to be resourceful in mitigating sleep loss, circadian desynchronization, and work overload. Sleep medication, sleep hygiene, and self-selected scheduling countermeasures, such as naps, are commonly employed by astronauts. BHP is evaluating the effectiveness of existing countermeasures and developing new strategies to further improve spaceflight sleeping conditions. For example, the pharmacokinetics of sleep medications may be different in space relative to on Earth. Non-sleep medications may be required in flight, and the potential interactions between these and the sleep medications that are prescribed in space flight have yet to be determined. Similarly, additional research will aid in the use of artificial lighting as a countermeasure for increasing acute alertness as well as facilitating the alignment of circadian rhythms. The long-term safety and efficacy of light as a non-pharmaceutical aid for alertness, circadian shifting, and sleep will inform requirements for the lunar and Mars crew habitats as well as recommendations to the crews, flight controllers, and flight medical operations.

Continued research efforts are necessary to address the psychological and physiological health of individuals during and following space flight missions. The sleep and circadian systems affect immunology, hormone production gastrointestinal function, and cardiovascular health; sleep

disruption can also serve as a contributing factor for the risk of behavioral conditions (Chapter 1) as well as for the risk that is related to poor team cohesion and psychosocial adaptation (Chapter 2). Similarly, countermeasures that are developed to aid the sleep and circadian system can also serve to enhance other aspects of health. Addressing the sleep and circadian system thus further addresses other risks within BHP as well as enhances other discipline research areas that are related to the human system and health outcomes from living and working in the space flight environment.

IX. REFERENCES

- (2014) Biomathematical Fatigue Models Guidance Document. In: Pacific DdA (ed). Civil Aviation Safety Authority (CASA)
- Admi H, Tzischinsky O, Epstein R, Herer P, Lavie P (2008) Shift work in nursing: is it really a risk factor for nurses' health and patients' safety? *Nurs Econ* 26(4):250-7
- Ahsberg E, Kecklund G, Akerstedt T, Gamberale F (2000) Shiftwork and different dimensions of fatigue *International Journal of Industrial Ergonomics* 26(4):457-465
- Akerstedt T, Gillberg M (1979) Effects of sleep deprivation on memory and sleep latencies in connection with repeated awakenings from sleep. *Psychophysiology* 16(1):49-52
- Akerstedt T, Kecklund G (2001) Age, gender and early morning highway accidents. *Journal of sleep research* 10(2):105-10
- Anderson C, Sullivan JP, Flynn-Evans EE, Cade BE, Czeisler CA, Lockley SW (2012) Deterioration of neurobehavioral performance in resident physicians during repeated exposure to extended duration work shifts. *Sleep* 35(8):1137-46 doi:10.5665/sleep.2004
- Archer SN, et al. (2003) A length polymorphism in the circadian clock gene *Per3* is linked to delayed sleep phase syndrome and extreme diurnal preference. *Sleep* 26(4):413-5
- Archer SN, Viola AU, Kyriakopoulou V, von Schantz M, Dijk DJ (2008) Inter-individual differences in habitual sleep timing and entrained phase of endogenous circadian rhythms of *BMAL1*, *PER2* and *PER3* mRNA in human leukocytes. *Sleep* 31(5):608-17
- Banks S, Van Dongen HP, Maislin G, Dinges DF (2010) Neurobehavioral dynamics following chronic sleep restriction: dose-response effects of one night for recovery. *Sleep* 33(8):1013-26
- Barger LK, et al. (2014) Prevalence of sleep deficiency and use of hypnotic drugs in astronauts before, during, and after spaceflight: an observational study. *The Lancet Neurology* 13(9):904-12 doi:10.1016/S1474-4422(14)70122-X
- Barger LK, et al. (2012) Learning to live on a Mars day: fatigue countermeasures during the Phoenix Mars Lander mission. *Sleep* 35(10):1423-35 doi:10.5665/sleep.2128
- Barger LK, Wright, K. P., Burke, T. M., Chinoy, E. D., Ronda, J. M., Lockley, S. W., Czeisler, C. A. (2014) Sleep and cognitive function of crewmembers and mission controllers working 24-h shifts during a simulated 105-day spaceflight mission. *Acta Astronautica* 93:230-242
- Basner M, Dinges DF (2009) Dubious bargain: trading sleep for Leno and Letterman. *Sleep* 32(6):747-52
- Basner M, Dinges DF (2012) An adaptive-duration version of the PVT accurately tracks changes in psychomotor vigilance induced by sleep restriction. *Sleep* 35(2):193-202 doi:10.5665/sleep.1620
- Basner M, et al. (2013) Mars 520-d mission simulation reveals protracted crew hypokinesia and alterations of sleep duration and timing. *Proceedings of the National Academy of Sciences of the United States of America* 110(7):2635-40 doi:10.1073/pnas.1212646110

- Basner M, Mollicone D, Dinges DF (2011) Validity and Sensitivity of a Brief Psychomotor Vigilance Test (PVT-B) to Total and Partial Sleep Deprivation. *Acta Astronaut* 69(11-12):949-959 doi:10.1016/j.actaastro.2011.07.015
- Basner M, Rubinstein J (2011) Fitness for duty: a 3-minute version of the Psychomotor Vigilance Test predicts fatigue-related declines in luggage-screening performance. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine* 53(10):1146-54 doi:10.1097/JOM.0b013e31822b8356
- Bass DS, Wales RC, Shalin VL (2004) Choosing Mars time: analysis of the Mars Exploration Rover experience. Paper presented at the Institute of Electrical and Electronic Engineers Aerospace Conference
- Baulk S, Biggs S, van den Heuel C, Reid K, Dawson D (2006) Managing Driver Fatigue: Quantifying real world performance impairment. vol ATSB Research and Analysis Report, Centre for Sleep Research, University of South Australia
- Belenky G (1997) Sleep, Sleep Deprivation, and Human Performance in Continuous Operations. Paper presented at the Joint Services Conference on Professional Ethics - JSCOPE '97,
- Belenky G, et al. (2003) Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: a sleep dose-response study. *Journal of sleep research* 12(1):1-12
- Benke T, Koserenko O, Watson NV, Gerstenbrand F (1993) Space and cognition: the measurement of behavioral functions during a 6-day space mission. *Aviation, space, and environmental medicine* 64(5):376-9
- Bhattacharyya M, Pal MS, Sharma YK, Majumdar D (2008) Changes in sleep patterns during prolonged stays in Antarctica. *Int J Biometeorol* 52(8):869-79 doi:10.1007/s00484-008-0183-2
- Brainard GC CW, Ayers M, Kemp J, Warfield B, Maida J, Bowen C, Bernecker C, Lockley SW, Hanifin JP (2013) Solid-state lighting for the International Space Station: tests of visual performance and melatonin regulation. *Acta Astronautica* 92(1):21-8 doi: <http://dx.doi.org/10.1016/j.actaastro.2012.04.019>
- Brainard GC, et al. (2008) Sensitivity of the human circadian system to short-wavelength (420-nm) light. *Journal of biological rhythms* 23(5):379-86 doi:10.1177/0748730408323089
- Breslow ER, Phillips AJ, Huang JM, St Hilaire MA, Klerman EB (2013) A mathematical model of the circadian phase-shifting effects of exogenous melatonin. *Journal of biological rhythms* 28(1):79-89 doi:10.1177/0748730412468081
- Burke TM, et al. (2013) Combination of light and melatonin time cues for phase advancing the human circadian clock. *Sleep* 36(11):1617-24 doi:10.5665/sleep.3110
- Buxton OM, et al. (2012) Adverse metabolic consequences in humans of prolonged sleep restriction combined with circadian disruption. *Science translational medicine* 4(129):129ra43 doi:10.1126/scitranslmed.3003200
- Cain SW, et al. (2010) Sex differences in phase angle of entrainment and melatonin amplitude in humans. *Journal of biological rhythms* 25(4):288-96

- Caldwell JA, Jr., LeDuc PA (1998) Gender influences on performance, mood and recovery sleep in fatigued aviators. *Ergonomics* 41(12):1757-70
doi:10.1080/001401398185956
- Chang AM, Aeschbach D, Duffy JF, Czeisler CA (2015) Evening use of light-emitting eReaders negatively affects sleep, circadian timing, and next-morning alertness. *Proceedings of the National Academy of Sciences of the United States of America* 112(4):1232-7 doi:10.1073/pnas.1418490112
- Chang AM, Scheer FA, Czeisler CA (2011) The human circadian system adapts to prior photic history. *The Journal of physiology* 589(Pt 5):1095-102
doi:10.1113/jphysiol.2010.201194
- Chee MW, et al. (2008) Lapsing during sleep deprivation is associated with distributed changes in brain activation. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 28(21):5519-28 doi:10.1523/JNEUROSCI.0733-08.2008
- Chelette TL, Albery WB, Esken RL, Tripp LD (1998) Female exposure to high G: performance of simulated flight after 24 hours of sleep deprivation. *Aviation, space, and environmental medicine* 69(9):862-8
- Cohen DA, et al. (2010) Uncovering residual effects of chronic sleep loss on human performance. *Science translational medicine* 2(14):14ra3
doi:10.1126/scitranslmed.3000458
- Cooper HS, Jr. (1996) The loneliness of the long-duration astronaut. *Air & space Smithsonian* 11(2):37-45
- Czeisler CA, et al. (1999) Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 284(5423):2177-81
- Czeisler CA, Gooley JJ (2007) Sleep and circadian rhythms in humans. *Cold Spring Harbor symposia on quantitative biology* 72:579-97 doi:10.1101/sqb.2007.72.064
- Czeisler CA, et al. (1989) Bright light induction of strong (type 0) resetting of the human circadian pacemaker. *Science* 244(4910):1328-33
- Czeisler CA, et al. (1995) Suppression of melatonin secretion in some blind patients by exposure to bright light. *The New England journal of medicine* 332(1):6-11
doi:10.1056/NEJM199501053320102
- Dawson D, Reid K (1997) Fatigue, alcohol and performance impairment. *Nature* 388(6639):235 doi:10.1038/40775
- Dean DA, 2nd, Forger DB, Klerman EB (2009) Taking the lag out of jet lag through model-based schedule design. *PLoS computational biology* 5(6):e1000418
doi:10.1371/journal.pcbi.1000418
- Deroshia CW, Colletti LC, Mallis MM (2008) The Effects of the Mars Exploration Rovers (MER) Work Schedule Regime on Locomotor Activity Circadian Rhythms, Sleep and Fatigue. NASA, Moffett Field, CA
- Dijk DJ, Czeisler CA (1994) Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neuroscience letters* 166(1):63-8
- Dijk DJ, Czeisler CA (1995) Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 15(5 Pt 1):3526-38

- Dijk DJ, Duffy JF, Silva EJ, Shanahan TL, Boivin DB, Czeisler CA (2012) Amplitude reduction and phase shifts of melatonin, cortisol and other circadian rhythms after a gradual advance of sleep and light exposure in humans. *PloS one* 7(2):e30037 doi:10.1371/journal.pone.0030037
- Dijk DJ, et al. (2001) Sleep, performance, circadian rhythms, and light-dark cycles during two space shuttle flights. *American journal of physiology Regulatory, integrative and comparative physiology* 281(5):R1647-64
- Dinges DF, Basner M, D.J. M, Goel N, Braun M (2013) ISS Missions: Elevated workload and reduced sleep duration. Paper presented at the NASA Human Research Program Investigators' Workshop, Galveston, TX,
- Drake BG, editor (2009) *Human Exploration of Mars Design Reference Architecture 5.0*. NASA Johnson Space Center, Houston, Texas
- Duffy JF, et al. (2011) Sex difference in the near-24-hour intrinsic period of the human circadian timing system. *Proceedings of the National Academy of Sciences of the United States of America* 108 Suppl 3:15602-8 doi:10.1073/pnas.1010666108
- Duffy JF, Dijk DJ, Hall EF, Czeisler CA (1999) Relationship of endogenous circadian melatonin and temperature rhythms to self-reported preference for morning or evening activity in young and older people. *Journal of investigative medicine : the official publication of the American Federation for Clinical Research* 47(3):141-50
- Ferrara M, Bottasso A, Tempesta D, Carrieri M, De Gennaro L, Ponti G (2015) Gender differences in sleep deprivation effects on risk and inequality aversion: evidence from an economic experiment. *PloS one* 10(3):e0120029 doi:10.1371/journal.pone.0120029
- Flynn-Evans E, Barger LK, Kubey A, Sullivan JP, Czeisler CA Sleep and Circadian Rhythms among 21 Astronauts during Long-duration Missions on the International Space Station. In: *NASA Human Research Program Investigators' Workshop, Galveston, TX, 2015*.
- Flynn-Evans EE, Mucci L, Stevens RG, Lockley SW (2013) Shiftwork and prostate-specific antigen in the National Health and Nutrition Examination Survey. *Journal of the National Cancer Institute* 105(17):1292-7 doi:10.1093/jnci/djt169
- Flynn-Evans EE, Tabandeh H, Skene DJ, Lockley SW (2014) Circadian Rhythm Disorders and Melatonin Production in 127 Blind Women with and without Light Perception. *Journal of biological rhythms* 29(3):215-224 doi:10.1177/0748730414536852
- Frost JD, Jr., Shumate WH, Salmay JG, Booher CR (1976) Sleep monitoring: the second manned Skylab mission. *Aviation, space, and environmental medicine* 47(4):372-82
- Galvan R (2012) *Effects of Fatigue on Simulated Space Telerobotics Performance : A Preliminary Study Analysis.*, MIT
- Gander PH, et al. (2014) Pilot fatigue: relationships with departure and arrival times, flight duration, and direction. *Aviation, space, and environmental medicine* 85(8):833-40 doi:10.3357/ASEM.3963.2014
- Gander PH, Signal TL, van den Berg MJ, Mulrine HM, Jay SM, Jim Mangie C (2013) In-flight sleep, pilot fatigue and Psychomotor Vigilance Task performance on ultra-long range versus long range flights. *Journal of sleep research* 22(6):697-706 doi:10.1111/jsr.12071

- Gaydos SJ, Curry IP, Bushby AJR (2013) Fatigue Assessment: Subjective Peer-to-Peer Fatigue Scoring. *Aviation, space, and environmental medicine* 84:1105-8
- Goel N, et al. (2014) Effects of sex and gender on adaptation to space: behavioral health. *J Womens Health (Larchmt)* 23(11):975-86 doi:10.1089/jwh.2014.4911
- Goel N, Banks S, Mignot E, Dinges DF (2009a) PER3 polymorphism predicts cumulative sleep homeostatic but not neurobehavioral changes to chronic partial sleep deprivation. *PloS one* 4(6):e5874 doi:10.1371/journal.pone.0005874
- Goel N, Banks, S., Lin, L., Mignot, E., & Dinges, D. F. (2011) Catechol-O-Methyltransferase Val158Met polymorphism associates with individual differences in sleep physiologic responses to chronic sleep loss. *PloS one* 6(12)
- Goel N, Banks, S., Mignot, E., & Dinges, D. F. (2010) DQB1*0602 predicts interindividual differences in physiologic sleep, sleepiness, and fatigue. *Neurology* 75(17):1509–1519
- Goel N, Basner M, Rao H, Dinges DF (2013) Circadian rhythms, sleep deprivation, and human performance. *Progress in molecular biology and translational science* 119:155-90 doi:10.1016/B978-0-12-396971-2.00007-5
- Goel N, Rao H, Durmer JS, Dinges DF (2009b) Neurocognitive consequences of sleep deprivation. *Seminars in neurology* 29(4):320-39 doi:10.1055/s-0029-1237117
- Gooley JJ, et al. (2012) Melanopsin and rod-cone photoreceptors play different roles in mediating pupillary light responses during exposure to continuous light in humans. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 32(41):14242-53 doi:10.1523/JNEUROSCI.1321-12.2012
- Gooley JJ, Rajaratnam SM, Brainard GC, Kronauer RE, Czeisler CA, Lockley SW (2010) Spectral responses of the human circadian system depend on the irradiance and duration of exposure to light. *Science translational medicine* 2(31):31ra33 doi:10.1126/scitranslmed.3000741
- Gordon JA, et al. (2010) Does simulator-based clinical performance correlate with actual hospital behavior? The effect of extended work hours on patient care provided by medical interns. *Academic medicine : journal of the Association of American Medical Colleges* 85(10):1583-8 doi:10.1097/ACM.0b013e3181f073f0
- Grandner MA, Kripke DF, Elliott J, Cole R (2013) Short wavelength light administered just prior to waking: a pilot study. *Biol Rhythm Res* 44(1):13-32 doi:10.1080/09291016.2011.632578
- Gregory KB, Winn W, Johnson K, Rosekind MR (2010) Pilot fatigue survey: exploring fatigue factors in air medical operations. *Air medical journal* 29(6):309-19 doi:10.1016/j.amj.2010.07.002
- Griofa MO, Blue RS, Cohen KD, O'Keefe DT (2011) Sleep stability and cognitive function in an Arctic Martian analogue. *Aviation, space, and environmental medicine* 82(4):434-41
- Groeger JA, Viola AU, Lo JC, von Schantz M, Archer SN, Dijk DJ (2008) Early morning executive functioning during sleep deprivation is compromised by a PERIOD3 polymorphism. *Sleep* 31(8):1159-67
- Groemer G, Gruber, V., Bishop, S., Peham, D., Wolf, L., Högl, B (2010) Human performance data in a high workload environment during the simulated Mars expedition. *Acta Astronautica* 66(5-6):780-787

- Gronfier C, Wright KP, Jr., Kronauer RE, Czeisler CA (2007) Entrainment of the human circadian pacemaker to longer-than-24-h days. *Proceedings of the National Academy of Sciences of the United States of America* 104(21):9081-6 doi:10.1073/pnas.0702835104
- Gundel A, Nalishiti V, Reucher E, Vejvoda M, Zulley J (1993) Sleep and circadian rhythm during a short space mission. *The Clinical investigator* 71(9):718-24
- Gundel A, Polyakov VV, Zulley J (1997) The alteration of human sleep and circadian rhythms during spaceflight. *Journal of sleep research* 6(1):1-8
- Hacker BC, Grimwood JM (1977) *On the Shoulders of Titans: A History of Project Gemini*. Washington DC, p 584-92
- Hart CL, Ward AS, Haney M, Foltin RW (2003) Zolpidem-related effects on performance and mood during simulated night-shift work. *Experimental and clinical psychopharmacology* 11(4):259-68 doi:10.1037/1064-1297.11.4.259
- Hartzler BM, Chandler DF, Sill CB (2015) Identification of measures and moderators to improve prediction of impairments due to chronic sleep loss. Paper presented at the Aerospace Medical Association Meeting,
- Hirshkowitz M, et al (2015) National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health* 1:40-43
- Honma K, Honma S (1988) Circadian rhythm: its appearance and disappearance in association with a bright light pulse. *Experientia* 44(11-12):981-3
- Honn KA, Riedy SM, Grant DA (2015) Validation of a portable, touch-screen psychomotor vigilance test. *Aerospace medicine and human performance* 86(5):428-34 doi:10.3357/AMHP.4165.2015
- Hooke LR, Radtke M, Garshnek V, Teeter R, Rowe JE (1986) NASA Contractor Report 3822(08) USSR Space Life Sciences Digest. vol 7, Washington D. C.
- Hursh SR, Balkin TJ, Miller JC, Eddy DR (2004a) The Fatigue Avoidance Scheduling Tool: Modeling to Minimize the Effects of Fatigue on Cognitive Performance. Paper presented at the Digital Human Modeling for Design and Engineering Symposium, Rochester, MI,
- Hursh SR, Raslear TG, Kaye AS, Fanzone JF (2006) Validation and Calibration of a Fatigue Assessment Tool for Railroad Work Schedules - Summary Report. In: Transportation Do (ed).
- Hursh SR, et al. (2004b) Fatigue models for applied research in warfighting. *Aviation, space, and environmental medicine* 75(3 Suppl):A44-53; discussion A54-60
- Hutchins SD, Laux, L., Wickens, C. D., & Sebok, A. The Effect of Continuous Wakefulness on Complex Cognitive Task Performance: A Quantitative Synthesis of Research. In: *Human Factors and Ergonomics Society Annual Meeting, 2013*. vol 57(1). p 793–797
- Jackson ML, Banks S, Belenky G (2014) Investigation of the effectiveness of a split sleep schedule in sustaining sleep and maintaining performance. *Chronobiology international* 31(10):1218-30 doi:10.3109/07420528.2014.957305
- Jean-Louis G, Mendlowicz MV, Von Gizycki H, Zizi F, Nunes J (1999) Assessment of physical activity and sleep by actigraphy: examination of gender differences. *J Womens Health Gend Based Med* 8(8):1113-7

- Jewett ME, Kronauer RE (1999) Interactive mathematical models of subjective alertness and cognitive throughput in humans. *Journal of biological rhythms* 14(6):588-97
- Jewett ME, Kronauer RE, Czeisler CA (1994) Phase-amplitude resetting of the human circadian pacemaker via bright light: a further analysis. *Journal of biological rhythms* 9(3-4):295-314
- Jewett ME, Wyatt JK, Ritz-De Cecco A, Khalsa SB, Dijk DJ, Czeisler CA (1999) Time course of sleep inertia dissipation in human performance and alertness. *Journal of sleep research* 8(1):1-8
- Johnson MP, Duffy JF, Dijk DJ, Ronda JM, Dyal CM, Czeisler CA (1992) Short-term memory, alertness and performance: a reappraisal of their relationship to body temperature. *Journal of sleep research* 1(1):24-9
- Jung CM, Ronda, J. M., Czeisler, C., & Wright, K. P. (2011) Comparison of sustained attention assessed by auditory and visual psychomotor vigilance tasks prior to and during sleep deprivation. *Journal of sleep research* 20(2):348–355
- Kelly TH, Hienz RD, Zarcone TJ, Wurster RM, Brady JV (2005) Crewmember performance before, during, and after spaceflight. *Journal of the experimental analysis of behavior* 84(2):227-41 doi:10.1901/jeab.2005.77-04
- Khalsa SB, Jewett ME, Cajochen C, Czeisler CA (2003) A phase response curve to single bright light pulses in human subjects. *The Journal of physiology* 549(Pt 3):945-52 doi:10.1113/jphysiol.2003.040477
- Killgore W, Rupp, T., Grugle, N., Reichardt, R., Lipizzi, E., Balkin, T. (2008) Effects of dextroamphetamine, caffeine and modafinil on psychomotor vigilance test performance after 44 h of continuous wakefulness. *J Sleep Res* 17:309–321 doi:doi: 10.1111/j.1365-2869.2008.00654.x
- Killgore WDS, Kahn-Greene ET, Grugle NL, Killgore DB, Balkin TJ (2009) Sustaining Executive Functions During Sleep Deprivation: A Comparison of Caffeine, Dextroamphetamine, and Modafinil. *Sleep* 32(2):205-216
- Klerman EB, Dijk DJ (2005) Interindividual variation in sleep duration and its association with sleep debt in young adults. *Sleep* 28(10):1253-9
- Klerman EB, Gershengorn HB, Duffy JF, Kronauer RE (2002) Comparisons of the variability of three markers of the human circadian pacemaker. *Journal of biological rhythms* 17(2):181-93
- Krueger G (2012) Soldier Fatigue and Performance Effectiveness: Yesterday, Today and Tomorrow. In: Matthews G DP, Neubauer C, Hancock P (ed) *The Handbook of Operator Fatigue* Ashgate, Surrey, England
- Krueger PM, Friedman EM (2009) Sleep duration in the United States: a cross-sectional population-based study. *American journal of epidemiology* 169(9):1052-63 doi:10.1093/aje/kwp023
- Kubo T, et al. (2010) How do the timing and length of a night-shift nap affect sleep inertia? *Chronobiology international* 27(5):1031-44 doi:10.3109/07420528.2010.489502
- Lim J, Dinges DF (2010) A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. *Psychological bulletin* 136(3):375-89 doi:10.1037/a0018883

- Lim J, Wu WC, Wang J, Detre JA, Dinges DF, Rao H (2010) Imaging brain fatigue from sustained mental workload: an ASL perfusion study of the time-on-task effect. *Neuroimage* 49(4):3426-35 doi:10.1016/j.neuroimage.2009.11.020
- Lockley SW (2005) Timed melatonin treatment for delayed sleep phase syndrome: the importance of knowing circadian phase. *Sleep* 28(10):1214-6
- Lockley SW, Evans EE, Scheer FA, Brainard GC, Czeisler CA, Aeschbach D (2006) Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. *Sleep* 29(2):161-8
- Lockley SW, Skene DJ, James K, Thapan K, Wright J, Arendt J (2000) Melatonin administration can entrain the free-running circadian system of blind subjects. *J Endocrinol* 164(1):R1-6
- Lombardi C, et al. (2013) High-altitude hypoxia and periodic breathing during sleep: gender-related differences. *Journal of sleep research* 22(3):322-30 doi:10.1111/jsr.12012
- Luckhaupt SE, Tak S, Calvert GM (2010) The prevalence of short sleep duration by industry and occupation in the National Health Interview Survey. *Sleep* 33(2):149-59
- Mader TH, et al. (2011) Optic disc edema, globe flattening, choroidal folds, and hyperopic shifts observed in astronauts after long-duration space flight. *Ophthalmology* 118(10):2058-69 doi:10.1016/j.ophtha.2011.06.021
- Mallis MM, Mejdal S, Nguyen TT, Dinges DF (2004) Summary of the key features of seven biomathematical models of human fatigue and performance. *Aviation, space, and environmental medicine* 75(3 Suppl):A4-14
- Manzey D, Lorenz B, Poljakov V (1998) Mental performance in extreme environments: results from a performance monitoring study during a 438-day spaceflight. *Ergonomics* 41(4):537-59 doi:10.1080/001401398186991
- Marquie JC, Foret J (1999) Sleep, age, and shiftwork experience. *Journal of sleep research* 8(4):297-304
- McCauley P, Kalachev LV, Mollicone DJ, Banks S, Dinges DF, Van Dongen HP (2013) Dynamic circadian modulation in a biomathematical model for the effects of sleep and sleep loss on waking neurobehavioral performance. *Sleep* 36(12):1987-97 doi:10.5665/sleep.3246
- McCauley P, Kalachev LV, Smith AD, Belenky G, Dinges DF, Van Dongen HP (2009) A new mathematical model for the homeostatic effects of sleep loss on neurobehavioral performance. *Journal of theoretical biology* 256(2):227-39 doi:10.1016/j.jtbi.2008.09.012
- McDonald J, Patel D, Belenky B (2011) Sleep and Performance Monitoring in the Workplace: The Basis for Fatigue Risk Management. In: Kryger M RT, Dement W (ed) *Principles and Practices of Sleep Medicine*. vol 5th ed.,
- Miller NL, Shattuck LG, Matsangas P (2011) Sleep and fatigue issues in continuous operations: a survey of U.S. Army officers. *Behavioral sleep medicine* 9(1):53-65 doi:10.1080/15402002.2011.533994
- Minkel J, et al. (2014) Sleep deprivation potentiates HPA axis stress reactivity in healthy adults. *Health Psychol* 33(11):1430-4 doi:10.1037/a0034219
- Minors DS, Waterhouse JM, Wirz-Justice A (1991) A human phase-response curve to light. *Neuroscience letters* 133(1):36-40

- Moldofsky H, et al. (2000) Long term effects of microgravity on human sleep, cytokine, and endocrines. *Gravitat Space Biol Bull* 14:41
- Mollicone DJ, Van Dongen HP, Rogers NL, Banks S, Dinges DF (2010) Time of day effects on neurobehavioral performance during chronic sleep restriction. *Aviation, space, and environmental medicine* 81(8):735-44
- Mollicone DJ, Van Dongen HP, Rogers NL, Dinges DF (2008) Response Surface Mapping of Neurobehavioral Performance: Testing the Feasibility of Split Sleep Schedules for Space Operations. *Acta Astronaut* 63(7-10):833-840
doi:10.1016/j.actaastro.2007.12.005
- Monk TH, Buysse DJ, Billy BD, DeGrazia JM (2004) Using nine 2-h delays to achieve a 6-h advance disrupts sleep, alertness, and circadian rhythm. *Aviation, space, and environmental medicine* 75(12):1049-57
- Monk TH, Buysse DJ, Billy BD, Kennedy KS, Willrich LM (1998) Sleep and circadian rhythms in four orbiting astronauts. *Journal of biological rhythms* 13(3):188-201
- Monk TH, Kennedy KS, Rose LR, Linenger JM (2001) Decreased human circadian pacemaker influence after 100 days in space: a case study. *Psychosomatic medicine* 63(6):881-5
- Mysliwiec V, McGraw L, Pierce R, Smith P, Trapp B, Roth BJ (2013) Sleep disorders and associated medical comorbidities in active duty military personnel. *Sleep* 36(2):167-74 doi:10.5665/sleep.2364
- Newman DJ, Lathan CE (1999) Memory processes and motor control in extreme environments. *IEEE Trans Syst Man Cybern C Appl Rev* 29(3):387-94
- Newman RA, Kamimori GH, Wesensten NJ, Picchioni D, Balkin TJ (2013) Caffeine gum minimizes sleep inertia. *Percept Mot Skills* 116(1):280-93
doi:10.2466/29.22.25.PMS.116.1.280-293
- Nguyen J, Wright KP, Jr. (2010) Influence of weeks of circadian misalignment on leptin levels. *Nat Sci Sleep* 2:9-18
- Nicholson AN (1972) Sleep patterns in the aerospace environment. *Proceedings of the Royal Society of Medicine* 65(2):192-4
- Nix S, Gossett K, Shepherd AD (2013) An investigation of pilot fatigue in helicopter emergency medical services. *Air medical journal* 32(5):275-9
doi:10.1016/j.amj.2013.04.001
- Ockert-Bell ME, Bell JF, 3rd, Pollack JB, McKay CP, Forget F (1997) Absorption and scattering properties of the Martian dust in the solar wavelengths. *Journal of geophysical research* 102(E4):9039-50
- Palinkas LA, Houseal M, Miller C (2000) Sleep and mood during a winter in Antarctica. *International journal of circumpolar health* 59(1):63-73
- Patterson PD, et al. (2012) Association between poor sleep, fatigue, and safety outcomes in emergency medical services providers. *Prehosp Emerg Care* 16(1):86-97 doi:10.3109/10903127.2011.616261
- Pereira DS, et al. (2005) Association of the length polymorphism in the human Per3 gene with the delayed sleep-phase syndrome: does latitude have an influence upon it? *Sleep* 28(1):29-32
- Phillips AJ, Czeisler CA, Klerman EB (2011) Revisiting spontaneous internal desynchrony using a quantitative model of sleep physiology. *Journal of biological rhythms* 26(5):441-53 doi:10.1177/0748730411414163

- Phillips AJ, Robinson PA, Klerman EB (2013) Arousal state feedback as a potential physiological generator of the ultradian REM/NREM sleep cycle. *Journal of theoretical biology* 319:75-87 doi:10.1016/j.jtbi.2012.11.029
- Pleban RJ, Valentine, P.J., Penetar, D.M., Redmond, D.P., and Belenky, G. (1990) Characterization of sleep and body composition changes during ranger training. *Military Psychology* 2:145-156
- Plumb TR, Peachey JT, Zelman DC (2014) Sleep disturbance is common among servicemembers and veterans of Operations Enduring Freedom and Iraqi Freedom. *Psychological services* 11(2):209-19 doi:10.1037/a0034958
- Powell DM, Spencer MB, Petrie KJ (2014) Comparison of in-flight measures with predictions of a bio-mathematical fatigue model. *Aviation, space, and environmental medicine* 85(12):1177-84 doi:10.3357/ASEM.3806.2014
- Rahman SA, Flynn-Evans EE, Aeschbach D, Brainard GC, Czeisler CA, Lockley SW (2014) Diurnal spectral sensitivity of the acute alerting effects of light. *Sleep* 37(2):271-81 doi:10.5665/sleep.3396
- Rajdev P, et al. (2013) A unified mathematical model to quantify performance impairment for both chronic sleep restriction and total sleep deprivation. *Journal of theoretical biology* 331:66-77 doi:10.1016/j.jtbi.2013.04.013
- Ramakrishnan S, Laxminarayan S, Wesensten NJ, Kamimori GH, Balkin TJ, Reifman J (2014) Dose-dependent model of caffeine effects on human vigilance during total sleep deprivation. *Journal of theoretical biology* 358:11-24 doi:10.1016/j.jtbi.2014.05.017
- Ramakrishnan S, et al. (2015) Can a mathematical model predict an individual's trait-like response to both total and partial sleep loss? *Journal of sleep research* 24(3):262-9 doi:10.1111/jsr.12272
- Randler C (2007) Gender differences in morningness–eveningness assessed by self-report questionnaires: A meta-analysis. *Personality and Individual Differences* 43(7):1667–1675 doi:doi:10.1016/j.paid.2007.05.004
- Reis C, Mestre C, Canhao H (2013) Prevalence of fatigue in a group of airline pilots. *Aviation, space, and environmental medicine* 84(8):828-33
- Reyner LA, Horne JA, Reyner A (1995) Gender- and age-related differences in sleep determined by home-recorded sleep logs and actimetry from 400 adults. *Sleep* 18(2):127-34
- Ribak J, et al. (1983) Diurnal rhythmicity and Air Force flight accidents due to pilot error. *Aviation, space, and environmental medicine* 54(12 Pt 1):1096-9
- Rosekind MR Sleep in an Operational Environment: What can go wrong? (presentation remarks). In: NSBRI NASA Sleep Workshop, Houston, TX, September 2014 2014.
- Rosekind MR, Co EL, Gregory KB, Miller DL (2000a) Crew Factors in Flight Operations XIII: A Survey of Fatigue Factors in Corporate/Executive Aviation Operations NASA, Moffett Field, CA
- Rosekind MR, Gregory KB, Co EL, Miller DL, Dinges DF (2000b) Crew factors in flight operations XII: A survey of sleep quantity and quality in on-board crew rest facilities. NASA, Moffett Field, CA

- Rosekind MR, Gregory KB, Mallis MM (2006) Alertness management in aviation operations: enhancing performance and sleep. *Aviation, space, and environmental medicine* 77(12):1256-65
- Rosekind MR, Gregory KB, Mallis MM, Brandt SL, Seal B, Lerner D (2010) The cost of poor sleep: workplace productivity loss and associated costs. *Journal of occupational and environmental medicine / American College of Occupational and Environmental Medicine* 52(1):91-8 doi:10.1097/JOM.0b013e3181c78c30
- Rouch I, Wild P, Ansiau D, Marquie JC (2005) Shiftwork experience, age and cognitive performance. *Ergonomics* 48(10):1282-93 doi:10.1080/00140130500241670
- Ruger M, et al. (2013) Human phase response curve to a single 6.5 h pulse of short-wavelength light. *The Journal of physiology* 591(Pt 1):353-63 doi:10.1113/jphysiol.2012.239046
- Ruggiero JS, Redeker NS (2014) Effects of napping on sleepiness and sleep-related performance deficits in night-shift workers: a systematic review. *Biol Res Nurs* 16(2):134-42 doi:10.1177/1099800413476571
- Rupp TL, Wesensten NJ, Balkin TJ (2010) Sleep history affects task acquisition during subsequent sleep restriction and recovery. *Journal of sleep research* 19(2):289-97 doi:10.1111/j.1365-2869.2009.00800.x
- Rupp TL, Wesensten NJ, Balkin TJ (2012) Trait-like vulnerability to total and partial sleep loss. *Sleep* 35(8):1163-72 doi:10.5665/sleep.2010
- Santhi N, Horowitz TS, Duffy JF, Czeisler CA (2007) Acute sleep deprivation and circadian misalignment associated with transition onto the first night of work impairs visual selective attention. *PloS one* 2(11):e1233 doi:10.1371/journal.pone.0001233
- Santy PA, Kapanka H, Davis JR, Stewart DF (1988) Analysis of sleep on Shuttle missions. *Aviation, space, and environmental medicine* 59(11 Pt 1):1094-7
- Scheer FA, Shea TJ, Hilton MF, Shea SA (2008) An endogenous circadian rhythm in sleep inertia results in greatest cognitive impairment upon awakening during the biological night. *Journal of biological rhythms* 23(4):353-61 doi:10.1177/0748730408318081
- Schernhammer ES, et al. (2001) Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *Journal of the National Cancer Institute* 93(20):1563-8
- Scheuring R, et al. (2007) The Apollo Medical Operations Project: Recommendations to Improve Crew Health and Performance for Future Exploration Missions and Lunar Surface Operations. vol NASA/TM-2007-214755, S-1005. Johnson Space Center, Houston, TX
- Scheuring RA, R.C. M, Johnston SL (2015) Fatigue in U.S. Astronauts Onboard the International Space Station: Environmental Factors, Operational Impacts, and Implementation of Countermeasures. Paper presented at the Aerospace Medical Association Annual Scientific Meeting, Lake Buena Vista, FL, May 2015
- Schifflett SG, Eddy DR, Schlegel RE, Shehab RL (1996) Microgravity effects on standardized cognitive performance measures. NTI, Incorporated
- Sebok A, Wickens, C., & Sargent, R. Using Meta-Analyses Results and Data Gathering to Support Human Performance Model Development. In: *Human Factors and Ergonomics Society Annual Meeting, 2013*. vol 57(1). p 783-787

- Sharkey KM, Fogg LF, Eastman CI (2001) Effects of melatonin administration on daytime sleep after simulated night shift work. *Journal of sleep research* 10(3):181-92
- Shattuck NL, Matsangas P (2015a) A 6-month assessment of sleep during naval deployment: a case study of a commanding officer. *Aerospace medicine and human performance* 86(5):481-5 doi:10.3357/AMHP.4140.2015
- Shattuck NL, Matsangas P (2015b) Psychomotor vigilance performance predicted by Epworth Sleepiness Scale scores in an operational setting with the United States Navy. *Journal of sleep research* 24(2):174-80 doi:10.1111/jsr.12243
- Shattuck NL, Matsangas, P. (2015) A comparison of sleep and performance of U.S. Navy sailors on four different shiftwork schedules. Paper presented at the Sleep, Shecter A, Boivin, D. (2010) Sleep, Hormones, and Circadian Rhythms throughout the Menstrual Cycle in Healthy Women and Women with Premenstrual Dysphoric Disorder. *International Journal of Endocrinology* 2010:Article ID 259345 doi:10.1155/2010/259345
- Signal TL, Gander PH, van den Berg MJ, Graeber RC (2013) In-flight sleep of flight crew during a 7-hour rest break: implications for research and flight safety. *Sleep* 36(1):109-15 doi:10.5665/sleep.2312
- Signal TL, van den Berg MJ, Mulrine HM, Gander PH (2012) Duration of sleep inertia after napping during simulated night work and in extended operations. *Chronobiology international* 29(6):769-79 doi:10.3109/07420528.2012.686547
- Sletten TL, Segal AY, Flynn-Evans EE, Lockley SW, Rajaratnam SM (2015) Inter-Individual Differences in Neurobehavioural Impairment following Sleep Restriction Are Associated with Circadian Rhythm Phase. *PloS one* 10(6):e0128273 doi:10.1371/journal.pone.0128273
- Sohail S, Yu L, Bennett DA, Buchman AS, Lim AS (2015) Irregular 24-hour activity rhythms and the metabolic syndrome in older adults. *Chronobiology international* 32(6):802-13 doi:10.3109/07420528.2015.1041597
- St Hilaire MA, Gooley JJ, Khalsa SB, Kronauer RE, Czeisler CA, Lockley SW (2012) Human phase response curve to a 1 h pulse of bright white light. *The Journal of physiology* 590(Pt 13):3035-45 doi:10.1113/jphysiol.2012.227892
- Stickgold R, Hobson, J.A. (1999) REM sleep and sleep efficiency are reduced during space flight.
- Stoilova I, Zdravev T, Yanev T (2000) Evaluation of sleep in space flight. *Comptes rendus de l'Academie Bulgare des sciences : sciences mathematiques et naturelles* 53(6):59-62
- Stuster J (2010) Behavioral Issues Associated with Long- Duration Space Expeditions : Review and Analysis of Astronaut Journals Experiment. vol JSC-CN-21128,
- Thompson A, Jones H, Gregson W, Atkinson G (2014) Effects of dawn simulation on markers of sleep inertia and post-waking performance in humans. *Eur J Appl Physiol* 114(5):1049-56 doi:10.1007/s00421-014-2831-z
- Troxel W, et al. (2015) Sleep in the military: Promoting healthy sleep among U.S. servicemembers. RAND Corporation, Santa Monica, CA
- Van Camp R (2009) Zolpidem in fatigue management for surge operations of remotely piloted aircraft. *Aviat Space Environ Med* 80(6):553-5

- Van Cauter E, et al. (1994) Demonstration of rapid light-induced advances and delays of the human circadian clock using hormonal phase markers. *The American journal of physiology* 266(6 Pt 1):E953-63
- van den Berg MJ, Signal, T., Gander, P.H. (2015) Greater subjective workload is associated with higher cabin crew fatigue on ULR flights. Paper presented at the Sleep,
- van der Helm E, Gujar N, Walker MP (2010) Sleep deprivation impairs the accurate recognition of human emotions. *Sleep* 33(3):335-342
- Van Dongen HP (2004) Comparison of mathematical model predictions to experimental data of fatigue and performance. *Aviation, space, and environmental medicine* 75(3 Suppl):A15-36
- Van Dongen HP, Maislin G, Mullington JM, Dinges DF (2003) The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 26(2):117-26
- Van Dongen HP, Price NJ, Mullington JM, Szuba MP, Kapoor SC, Dinges DF (2001) Caffeine eliminates psychomotor vigilance deficits from sleep inertia. *Sleep* 24(7):813-9
- Van Dongen HPA, Baynard MD, Maislin G, Dinges DF (2004) Systematic interindividual differences in neurobehavioral impairment from sleep loss: Evidence of trait-like differential vulnerability. *Sleep* 27(3):423-33
- Vandewalle G, et al. (2009) Functional magnetic resonance imaging-assessed brain responses during an executive task depend on interaction of sleep homeostasis, circadian phase, and PER3 genotype. *The Journal of neuroscience : the official journal of the Society for Neuroscience* 29(25):7948-56
doi:10.1523/JNEUROSCI.0229-09.2009
- Viola AU, et al. (2007) PER3 polymorphism predicts sleep structure and waking performance. *Current biology : CB* 17(7):613-8 doi:10.1016/j.cub.2007.01.073
- Walsleben JA, et al. (2004) Sleep and reported daytime sleepiness in normal subjects: the Sleep Heart Health Study. *Sleep* 27(2):293-8
- Watson NF, et al. (2015) Recommended Amount of Sleep for a Healthy Adult: A Joint Consensus Statement of the American Academy of Sleep Medicine and Sleep Research Society. *Sleep* 38(6):843-4 doi:10.5665/sleep.4716
- Wehr TA, et al. (1993) Conservation of photoperiod-responsive mechanisms in humans. *The American journal of physiology* 265(4 Pt 2):R846-57
- Wesensten NJ, Killgore WD, Balkin TJ (2005) Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. *Journal of sleep research* 14(3):255-66 doi:10.1111/j.1365-2869.2005.00468.x
- West KE, et al. (2011) Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. *Journal of applied physiology* 110(3):619-26 doi:10.1152/jappphysiol.01413.2009
- Whitmire A, Slack, K., Locke, J., Keeton, K. (2013) Sleep Quality Questionnaire Short-Duration Flyers. vol NASA/TM-2013-217378. Johnson Space Center, Houston, TX
- Wilkinson R (1969) Some factors influencing the effect of environmental stressors upon performance. *Psychological bulletin* 72(4):260-72

- Williamson A, Friswell, R. (2013) Fatigue in the workplace: causes and consequences. *Fatigue: Biomedicine, Health & Behavior* 1:1-2:81-98
doi:10.1080/21641846.2012.744581
- Wong KY, Dunn FA, Berson DM (2005) Photoreceptor adaptation in intrinsically photosensitive retinal ganglion cells. *Neuron* 48(6):1001-10
doi:10.1016/j.neuron.2005.11.016
- Wotring VE (2015) Medication use by U.S. crewmembers on the International Space Station. *FASEB J* doi:10.1096/fj.14-264838
- Wright KP, Jr., Hughes RJ, Kronauer RE, Dijk DJ, Czeisler CA (2001) Intrinsic near-24-h pacemaker period determines limits of circadian entrainment to a weak synchronizer in humans. *Proceedings of the National Academy of Sciences of the United States of America* 98(24):14027-32 doi:10.1073/pnas.201530198
- Wu LJ, van den Berg, M.J., Gander, P.H. (2015) Actigraphy and self-reported baseline sleep duration in commercial airline pilots. Paper presented at the Sleep,
- Wyatt JK, Cajochen C, Ritz-De Cecco A, Czeisler CA, Dijk DJ (2004) Low-dose repeated caffeine administration for circadian-phase-dependent performance degradation during extended wakefulness. *Sleep* 27(3):374-81
- Wyatt JK, Dijk DJ, Ritz-de Cecco A, Ronda JM, Czeisler CA (2006) Sleep-facilitating effect of exogenous melatonin in healthy young men and women is circadian-phase dependent. *Sleep* 29(5):609-18
- Zaidi FH, et al. (2007) Short-wavelength light sensitivity of circadian, pupillary, and visual awareness in humans lacking an outer retina. *Current biology : CB* 17(24):2122-8 doi:10.1016/j.cub.2007.11.034
- Zeitler JM, Fisicaro RA, Ruby NF, Heller HC (2014) Millisecond flashes of light phase delay the human circadian clock during sleep. *Journal of biological rhythms* 29(5):370-6 doi:10.1177/0748730414546532

X. TEAM

Erin Flynn-Evans PhD, MPH leads the Fatigue Countermeasures Laboratory at NASA Ames Research Center. Dr. Flynn-Evans is a circadian physiologist and epidemiologist with broad experience in the field of sleep and circadian physiology. Her research involves laboratory and field research, with a focus on evaluating the causes of consequences of fatigue in spaceflight and aviation. She has also investigated the long-term health consequences of persistent circadian misalignment and has been at the forefront of investigating the associations between shiftwork, sleep loss and cancer development.

Kevin Gregory, BS is an independent consultant and statistician with over 30 years of experience conducting sleep research. Mr. Gregory began his career as a research associate in the Fatigue Countermeasures Laboratory at NASA Ames Research Center, where he was instrumental in developing the first fatigue risk management programs for airlines. Subsequent to his work at NASA, Mr. Gregory was the Vice President at the fatigue consulting firm Alertness Solutions.

Lucia Arsintescu, MA has worked as a Senior Research Associate in the Fatigue Countermeasures Laboratory at NASA Ames Research Center for over 10 years.

Alexandra Whitmire, PhD

Lauren Leveton, PhD

The authors wish to thank Dr. Kelly Slack and Ms. Kristine Ohnesorge for providing assistance with coordination of manuscript acquisition and planning and Mr. Zachary Caddick for manuscript review and comments. The authors would also like to acknowledge the contributions that were made by our BHP community, including flight surgeons and medical operations, researchers from the National Science Biomedical Research Institute, our external investigators, and many others. Their time and work in this risk area are critical for understanding and communicating what is known and unknown regarding the risks of, and their mitigation for, human space flight, particularly as NASA plans exploration missions to the moon and Mars. Such knowledge will enable the space agency to meet these future challenges and succeed.

XI. LIST OF ACRONYMS

FMCSA	<i>Federal Motor Carrier Safety Administration</i>
FAA	Federal Aviation Administration
HRP	Human Research Program
BHP	Behavioral Health and Performance
NASA	<i>National Aeronautics and Space Administration</i>
NASA STD	<i>NASA Standards and Technical Document</i>
IRP	Integrated Research Plan
ExMC	Exploration Medical Capabilities
HHC	Human Health and Countermeasures
SHFH	Space Human Factors & and Habitability Element
JSC	Johnson Space Center
STS	Space Transportation System
ISS	International Space Station
PSG	Polysomnography
DLMO	Dim Light Melatonin Onset
EVA	Extravehicular Activity
REM	Rapid Eye Movement
SWS	Slow Wave Sleep
EEG	Electroencephalography
PAWS	Performance Assessment Workstation
AGARD	Advisory Group for Aerospace Research and Development (NATO)
STRES	Simulated Training Requirements Effectiveness Report
GRT	Grammatical Reasoning Test
MST	Memory Search Task
UTT	Unstable Tracking Task
DT	Dual Task
VAS	Visual Analog Scale
PVT	Psychomotor Vigilance Task
KSS	Karolinska Sleepiness Scale
DSST	Digit Symbol Substitution Test
NR	Number Recognition
LED	Light Emitting Diode
SSLAs	Solid State Light Assemblies
DLS	Dynamic Lighting Schedule
PDA	Personal Digital Assistant
TIB	Time in Bed
TSST	Trier Social Stress Test
HPA	Hypothalamic–Pituitary–Adrenal
PER3	PERIOD3
VNTR	Variable Number Tandem Repeat
COMT	Catechol-O-Methyl Transferase
WMT	Working Memory Task
PRC	Phase Response Curve
NASA-TLX	NASA Task Load Index

MWT	Maintenance of Wakefulness Test
TM	Technical Memorandum
EMS	Emergency Medical Services
PSQI	Pittsburgh Sleep Quality Index
FAST	Fatigue Avoidance Scheduling Tool
ESS	Epworth Sleepiness Scale
NREM	Non-Rapid Eye Movement
MER	Mars Exploration Rover
BMI	Body Mass Index
AHI	Apnea Hypoapnea Index
ODI	Oxygen Desaturation Index
FRMS	Fatigue Risk Management Systems
CPSS	Circadian Performance Simulation Software
SAFTE	Sleep, Activity, Fatigue and Task Effectiveness
FAST	Fatigue Avoidance Scheduling Tool
SAFE	System for Aircrew Fatigue Evaluation
CAA	Civil Aviation Authority
CASA	Civil Aviation Safety Authority
IATA	International Air Transport Association

APPENDIX A: MEASUREMENT OF SLEEP, CIRCADIAN PHASE AND WORKLOAD

Sleep

Polysomnography(PSG) and Electroencephalogram (EEG) The gold standard for assessing sleep stage, duration, timing and quality is through PSG and EEG. The EEG is collected through electrodes placed at designated locations on the scalp and face as indicated by the International 10-20 system. The EEG records brain activity during sleep, which can be analyzed to determine sleep stage, and the precise timing of sleep onset and offset, along with the frequency, number and duration of waking during a sleep episode. The EEG may also be analyzed to evaluate the power density of brain waves in order to provide information about sleep homeostasis. PSG includes the addition of sensors to measure respiration, body position and heart rate.

Actigraphy An actigraph is a small wrist-worn device that contains an accelerometer to measure sleep through inactivity relative to activity. Some actigraphs contain additional features, such as light-sensing diodes for the collection of ambient light information or event markers for recording pre-specified study events. Actigraphy data provides a high degree of accuracy with respect to sleep duration compared to EEG, but actigraphy does not provide information about sleep stage or power.

Sleep Diaries Sleep diaries are subjective logs regarding sleep timing, duration and quality that participants record daily. Although sleep diaries correlate with EEG and actigraphy, numerous studies have shown that participants typically overestimate sleep in sleep diaries. Sleep diaries are often used to enhance the reliability of actigraphy.

Subjective Rating Scales The Karolinska Sleepiness Score, Stanford Sleepiness Scale and Samn Perelli Scale are each single item ratings of self-assessed sleepiness. Such scales are widely used in field studies due to their ease of implementation and convenience. Self-ratings are the least reliable method for measuring alertness. Although these subjective scales are not necessarily representative of the magnitude of impairment experienced during sleep deprivation, such self-assessments do track circadian and homeostatic indicators of fatigue.

Melatonin. Under normal light dark conditions, melatonin (N-acetyl-5-methoxytryptamine) is produced during darkness by the pineal gland upon receiving input from the SCN (29, 54). In darkness or dim lighting, circadian-related performance impairment and alertness inversely correlate with the rise and fall of melatonin, such that as melatonin rises, alertness and performance fall. This makes melatonin production a biomarker for circadian-related performance impairment and reductions in alertness.

Melatonin may be measured in plasma or saliva and its metabolite, 6-sulfatoxymelatonin (aMT6s) may be measured in urine. In order to be useful as a biomarker, melatonin must be measured with some regularity over the course of 24 hours.

Cortisol. Cortisol follows a circadian rhythm with a morning peak and can be measured to evaluate circadian phase. Cortisol is also a stress hormone that is produced during episodes of

stress or anxiety and in response to sleep loss, making it difficult to use for circadian phase assessments in field studies.

Temperature. Core body temperature fluctuates with a circadian rhythm that parallels the rise and fall of alertness and performance. Collection of core body temperature may be achieved via a rectal thermistor or through ingestible temperature sensors. Oral and tympanic temperature also follow a circadian rhythm and have been used to evaluate circadian phase in field studies. Temperature measurements are subject to masking of the underlying rhythm by external factors and are considered somewhat less reliable markers of the circadian system than melatonin.

Neurobehavioral Assessment. Human performance impairment may be estimated using regularly timed standardized test batteries. Although a variety of test batteries have been used to assess the impact of sleep loss and circadian phase, the most common test used for this purpose is the psychomotor vigilance task (PVT). Reaction time, along with errors of omission (lapses) and errors of commission (false starts) as measured by the PVT are highly sensitive to circadian phase and acute sleep loss.

APPENDIX B: INTERNATIONAL SPACE STATION LIGHTING

The following information was provided by James Maida, Habitability and Human Factors Branch, NASA Johnson Space Center, and Charles Bowen, PhD, Human Factors Design Engineering Specialist from the Lockheed Martin Human Factors Design Team. This information illustrates the dim lighting that crewmembers experience on board the ISS.

The best-case average illumination on board Node 1 of ISS with eight out of eight fluorescent lamps burning is 13.82 foot-candles (fc). In contrast, on March 31, 2005, Node 1 was down to only one lamp burning, with an illuminance of 0.55 fc. Since color vision fails at approximately 0.30 fc, that lighting level is unacceptable for most tasks. The dim illumination in Node 1 presented a safety issue that was addressed, initially, by moving lamps from another area. The problem was ultimately solved by resupply of the ISS by STS-114, which flew in July 2005.

In other examples, when the U.S. Laboratory on ISS has all 12 lamps burning, the illumination is 57.79 fc. When only four of the 12 lamps are burning, illumination is reduced to 16.48 fc. Finally, in an airlock that has all four of its fluorescent lamps working, the illuminance is 17.55 fc. When the airlock is down to one lamp, the illuminance can be as low as 2.62 fc.

The above illuminances were determined by the radiance illuminance model of the Lawrence Berkeley National Laboratory (Berkeley, CA), with modifications for space flight applications.

Required illuminances for various tasks include: maintenance, 25 fc; transcribing, 50 fc; repair, 30 fc; reading, 50 fc; and night lighting, 2 fc.

Foot-candles can be converted to the international unit of lux by multiplying by 10. Thus, 10 fc = 100 lux.