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Summary Report: Sleep on Earth and in Space: Risk Factors, Health and Performance Outcomes, and Countermeasures

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Goals

The workshop goals were to:

- Review state-of-the-art knowledge of the effects of environmental factors on sleep;
- Review state-of-the-art knowledge of the effects of sleep or insufficient sleep on multiple physiological and psychological functions;
- Encourage inter-disciplinary work, including countermeasure development, on these topics; and
- Provide information for a report to NASA and amendments to the NASA Evidence Book on relevant topics.

Presenters were requested to address the following overarching issues:

- What are evidence-based thresholds or dose-response relationships for the duration of sleep, the quality of sleep, and/or the timing of sleep on health and performance outcomes in space and on Earth?
- What are the known and potential acute and chronic effects of inadequate sleep duration, timing, and/or reduced sleep quality on health and performance outcomes during prolonged spaceflight? This includes the time constants for effects over weeks and months of reduced sleep duration or quality, as well as what is known about recovery rates and recycle dynamics (i.e., repeated periods of sleep restriction and recovery)?
- Are there phenotypic (trait-like and stable) differences among people in vulnerability to the effects of sleep loss and/or sleep quality on health and performance outcomes? If so, are there biomarkers for these differences?
- What are the appropriate measures and metrics (a) for sleep duration and quality, and (b) to establish the effects of sleep deficit on health and performance outcomes?
- When achieved sleep falls below desired levels, what mitigating strategies and countermeasures for health and performance outcomes can be used?

Lessons Learned and Recommendations

The presentations at the Sleep Workshop clearly highlight that sleep is a key inter-disciplinary physiological function. Insufficient sleep adversely affects multiple physiological and psychological functions, and thereby health and performance. As a result, lessons learned emerging from this workshop will be applicable for various research disciplines and flight medical operations at NASA, as well as for many other organizations. An overview of major recommendations emerging from the workshop are summarized below, with topic-specific descriptions and suggestions for future work discussed in the Appendix.

Findings from the largest, most systematic assessment of sleep in space indicate that the average nightly sleep duration on both Space Shuttle and International Space Station (ISS) is approximately 6 hours. Based on terrestrial studies evaluating performance under chronic sleep restriction (CSR) to 6 hours per night, performance decrements could manifest. Several astronaut guests at the workshop indicated that for them, however, 6 hours seemed sufficient. Since (i) research has shown subjective perception of sleep latency, number of awakenings and total sleep time is inaccurate, (ii) subjective assessment of alertness does not correlate well with objective performance metrics, especially under conditions of CSR, and (iii) sleep's physiological function is not solely to restore alertness (detailed below), self-reports of astronauts about obtaining sufficient sleep may not be appropriate for determining the amount of sleep needed in space. Worthy of consideration, however, is that sleep “need” for one metric may not be the same for another metric. Hence, research questions regarding sleep need remain:

- Is there a sleep ‘need’ metric that needs to be defined relative to specific Behavioral Health and Performance Element (BHP) outcomes?
- Is the standard ‘sleep need’ of astronauts the same as the general population, or are they self-selected and therefore more heavily skewed towards that part of the population who "needs" less sleep?
- Does sleep architecture (i.e., amounts and timing of different sleep stages) change in space relative to sleep architecture on the ground, in a population analogous to astronauts?
- Does “sleep need” in space change from “sleep need” on the ground?
- How can we predict individual differences in response and recovery from insufficient sleep or circadian misalignment?

Potential causes of sleep disruption on ISS include shifting schedules to accommodate operational tasks such as nighttime dockings, and operational tempo. Environmental factors such as noise levels and temperature, have been attributed as causes of sleep disruption. Questions remain regarding less salient environmental factors on the ISS, and their effect on sleep and circadian outcomes. For example,

- What are the effects of high carbon dioxide (CO_2) and low oxygen (O_2) combined both acutely and chronically on sleep and other health and performance metrics? What happens when these are associated with circadian misalignment, such as in slam shifts?
- What happens to physiology under long-term Mars (24.65-hour days) orbit?
- What are the effects of different aspects of radiation (including non-ionizing radiation) on sleep and circadian rhythms and how do insufficient sleep and circadian misalignment affect response to radiation?

Unknowns about the effects of sleep and insufficient sleep on physiology, behavior and performance include the following questions:

- What is the relationship between motion sickness and other vestibular problems in space, and insufficient sleep?
- How do interactions with automation change with insufficient sleep?
- Are distractions processed differently when an individual has insufficient sleep?
- How do team interactions change with insufficient sleep?
- What is the effect of sleep on the human microbiome?
- What are the changes in lymph flow with sleep and sleep restriction? Is there an effect of circadian phase and circadian misalignment on lymph and glymph flow?
- What is the relationship between muscle and bone loading and sleep restriction?
- For all the documented changes in physiology with insufficient sleep and circadian misalignment on earth, are there additional changes in microgravity?

To address some of these research questions, it is recommended that other disciplines at NASA incorporate sleep and circadian metrics (e.g., sleep duration, cumulative sleep loss, circadian misalignment, timing of the measurement) as potential contributors in their analyses.

For all of these issues, countermeasures may need to be developed and implemented. Metrics are also needed to decide sleep "need"/threshold or response. Appropriate sleep/wake and work schedules, combined with appropriately timed lighting and other habitat variables (e.g., noise, O_2 and CO_2 levels) plus supportive crew leadership and team support, can facilitate good sleep hygiene. In recent years, Flight Surgeons, BHP Operational Psychologists and Psychiatrists, and others at NASA have provided training and education to crew members and ground support personnel regarding best practices for optimal sleep. Questions in regards to countermeasures include:

- How do dietary factors regulate circadian and sleep function? Are there protocols specific to timing and intensity that can be provided, for helping to optimize sleep and circadian entrainment?
- What are the effects of exercise on sleep? Are there protocols specific to timing and intensity that can be provided for helping to optimize sleep and circadian entrainment?
- Does sleep induced by medication provide the same benefits and sleep without medications?

Additional recommendations provided include the following:

- Transitioning actigraphy to operational use to capture continued data about crew sleep timing and duration immediately prior to mission, during the mission and immediately post-mission.
- Implementing data mining efforts to assess sleep in space relative to other factors and/or outcomes.

Summary of Talks

Introduction: Sleep and Circadian Rhythms in Spaceflight - A Review

Dr. Charles Czeisler introduced the session by presenting on "Sleep and Circadian Rhythms in Spaceflight – A Review," discussing data about circadian rhythms and sleep of astronauts in space and the effects of insufficient sleep on performance in space. Published data exist regarding core body temperature, activity, hormones, and light exposure from multiple investigators and missions. There were at least two incidents related to insufficient sleep that adversely affected mission goals: STS-32 in which there was an error related to work scheduling of mission controllers and the 1997 Mir collision. In the 1990's, NASA implemented lighting countermeasures to reduce circadian misalignment at times of early launches. A recently completed study of sleep and sleep-related medications in space (ISS and Space Shuttle) using actigraphy and logs found that insufficient sleep and the use of hypnotics were both frequent.

Recommendation: NASA should continue to monitor sleep timing and duration, sleep quality, times of circadian misalignment, and use of medications that affect (e.g., promote or inhibit) sleep, and ability to awaken from sleep and perform appropriately if necessary, of personnel in space, and to investigate whether any of these are involved in incidents, accidents, and/or errors.

Panel 1: Mission Factors for Sleep in Space

Dr. David Alexander, presented on "High Carbon Dioxide and Low Oxygen," beginning with an overview of current spaceflight stressors, which includes schedule shifting, and possible impacts of these stressors to operations. He then discussed CO_2 levels on ISS, which have averaged around 3.8 mm of mercury, but have in the past reached levels of up to 6 mm. Terrestrial evidence has shown that increased levels of CO_2 are associated with sleep disruption. Accordingly, crew surgeons' observations indicate that increasing levels of CO_2 have been associated with complaints about backaches, and reports of increased irritability and performance impacts (e.g., more frequent procedure errors), noting that crew members were blinded to CO_2 levels when reporting symptomology. Dr. Alexander discussed a recent NASA-led evaluation that found reported headaches have a statistically significant positive correlation with CO_2 levels (Law et al., 2014). Given terrestrial studies that show potential physiological and behavioral changes under conditions of high CO_2 levels, and some crew member reports that attribute increased CO_2 levels to more frequent awakenings, more research is recommended to understand acceptable levels in current and future spaceflight. There are additional concerns surrounding potential synergistic effects of CO_2 and microgravity.

Recommendation: The effects of CO_2 on sleep, cognitive function, and physiological outcomes (such as bone reabsorption) should be further investigated.

Dr. Erin Flynn-Evans presented on "Scheduling and Circadian Misalignment," reporting on three prevalent stressors in-flight: workload, circadian shifting, and abrupt schedule changes. High workload has been prevalent on space missions, and has been associated with extended wakefulness as schedules 'creep up' against scheduled sleep times. Given terrestrial research that shows increasing workload demands are associated with sleep loss, it is likely that in addition to scheduling practices, workload contributes to reduced sleep in space.

Studies have demonstrated circadian misalignment prior to and/or in flight, during Apollo, Mir, Space Shuttle and ISS missions. Scheduling practices likely contribute heavily to circadian misalignment; however, insufficient light exposure on orbit likely contributes as well. Potential issues that have emerged from other spaceflight investigations – such as reduced amplitude of circadian body temperature rhythm, and reduced melanopsin production during spaceflight among albino BALB/cJ mice – were highlighted as potentially dampening the physiological response to lighting cues and inhibiting the maintenance of circadian alignment in spaceflight missions. Results from a recent investigation objectively evaluating sleep duration on orbit demonstrated that sleep medications are regularly used on the ISS; additional analyses suggest that circadian misalignment contributes to elevated medication use during spaceflight.

Recommendation: The relative contribution of the risk factors of heavy workload, circadian shifting, and abrupt schedule changes, and the resulting increased use of pharmacological countermeasures in the spaceflight environment, should be investigated. Appropriate mitigations for these factors should be designed and tested.

Dr. Robert Hienz presented on "Radiation Effects on Sleep," posing the question of whether on Exploration Missions to Mars, there will be additive or synergistic effects of the combined effects of radiation exposure and sleep disruption/loss on astronaut performance. In studies evaluating radiation exposure in levels expected during future spaceflight missions, neurobehavioral effects (e.g., performance decrements on the rodent Psychomotor Vigilance Test [rPVT]) are observed in exposed rodents. Studies assessing exposure to half the doses expected to be received en route to Mars, show no change in the amount of sleep in rats; however, changes have been seen in delta wave amplitude and peak theta wave activity in irradiated rats, suggesting a potential change in sleep architecture.

Additional evidence for potential adverse effects (e.g., performance decrements, reported fatigue levels) is seen in cancer patients experiencing radiation therapy. This type of radiation, however, is much less potent than what will be experienced in-flight. Additional rodent studies are therefore recommended.

Recommendation: Further research is needed to determine sleep and circadian outcomes relevant to radiation exposure anticipated in exploration missions. Additional measures beyond the rPVT should be included. Research assessing the effects of non-ionizing radiation should be considered.

Panel 2: Insufficient Sleep and Health Outcomes (1)

Dr. Mark Rosekind presented on "Sleep in an Operational Environment – What Can Go Wrong?," emphasizing that the National Transportation Safety Board (NTSB), an independent agency that answers only to the President and to Congress, determines probable cause of transportation accidents and makes recommendations to prevent reoccurrence. While the NTSB does not regulate or enforce, its recommendations are accepted 82% of the time. Dr. Rosekind stressed that the fatigue-related challenges of a 24/7 society include sleep loss, extended wakefulness, circadian/time-of-day misalignment, and sleep disorders, as well as other factors. As an example of these factors interacting in many transportation crashes, Dr. Rosekind reviewed several transportation accidents in which fatigue was cited as a probable cause. Fatigue poses three aspects of risk relative to operational performance: poor performance, variability in performance, and inaccurate reports of alertness. He noted the effects of inadequate sleep do not always involve falling asleep; fatigue-related effects are typically found in performance deficits before sleep "attacks" occur.

Dr. Rosekind emphasized that operators and management must acknowledge the risk of inadequate sleep to performance safety, and the need to take preventative action to protect against it. Countermeasures discussed included naps: a NASA study permitted pilots a planned 40-minute nap in their cockpit seats during long-haul flights, finding that on 93% of the nap opportunities pilots were able to quickly fall asleep and stay asleep for over 20 minutes. When compared to a control group that received no nap during the prolonged flights, the napped pilots experienced only a quarter of the microsleeps while working as the control (no-nap) group. Additionally, in the world of automated systems, Dr. Rosekind emphasized the need to not permit fatigued operators to over-rely on automation (and fail to vigilantly track it), and to avoid the risk of distraction.

Recommendation: Continue to work with and learn from other government agencies on effective management of sleep and circadian rhythms.

Dr. David Dinges presented on the "Neurobehavioral and Neurocognitive Effects of Sleep Loss," emphasizing the results of extensive scientific work on sleep and fatigue-related performance failures. Neurobehavioral functions and operational performance that rely on them are under temporal and homeostatic control related to circadian and sleep biology. Reductions in sleep result in decrements in neurobehavioral functions and performance. When sleep restriction is chronic, its effects on brain and behavior are cumulative across days. It is not possible to sustain reversal of these deficits without adequate recovery sleep. Stimulants like caffeine and Modafinil may temporarily mask the deficits, but no stimulant is somnolytic (i.e., a substitute for sleep).

Dr. Dinges noted that decrements in wake state stability and vigilance (via the Psychomotor Vigilance Test [PVT]) have been observed on the Reaction Self-Test on ISS in 24 astronauts studied throughout 6-month missions. Moreover, among astronauts, reduced sleep duration and poor sleep quality were found to be correlated with higher ratings of tiredness, physical exhaustion and stress, as missions progressed. He also noted that in the Russian MARS 500 project (i.e., the 520-day simulated mission to Mars) the majority of crew members (two out of the six) manifested sleep and circadian disturbances.

Recent experiments reveal that sleep loss attenuates emotional expressiveness (i.e., less facial expressiveness) in healthy adults, but they were not aware of it; furthermore, sleep loss lowers the psychological threshold for the perception of stress, but it does not increase the magnitude of negative affect in response to high-stress performance demands. In addition to profound adverse effects of inadequate sleep on vigilant attention and psychomotor speed, sleep loss affects cognitive processing speed and thereby reduces the rate at which tasks can be done accurately.

Six hours of sleep per day is inadequate to prevent the cumulative buildup of cognitive, behavioral and physiological deficits. The detection of these escalating deficits cannot be done subjectively: studies consistently show that people are poor judges of their actual performance capability when fatigued from sleep loss. Objective tests like the PVT and unobtrusive optical computer tracking of the speed of eyelid closures are more accurate ways to measure the degree of cognitive risk posed by sleep loss.

Recommendation: Identify and deploy ways to objectively and unobtrusively track the effects of sleep timing, as well as the effects of medications that promote sleep and wakefulness, on astronaut performance, risk of error, and both physical health (e.g., visual impairment, intracranial hypertension) and behavioral health (e.g., psychological stress and negative mood) in spaceflight.

Dr. Namni Goel presented on "Biomarkers of Neurobehavioral Vulnerability to the Effects of Sleep Loss," noting that sleep deprivation results in neurobehavioral changes (e.g., deficits in various aspects of performance), providing evidence for trait-like differential vulnerabilities in response to sleep loss. These traits appears to be stable over time and therefore provide phenotypic targets for searching for biomarkers for susceptibility to both acute and chronic partial sleep loss. Evidence for the short-term stability in individual differences in response to total sleep deprivation (TSD) was presented. Subjects with a "Type 3" response had high rates of PVT performance lapses (errors of omission) after both their first and second exposures to TSD. Similarly, those individuals with "Type 1" responses had low PVT lapse rates after both their first and second exposures to TSD. This differential vulnerability was phenotypically stable when evaluated over an average of 13 months, and was found for a range of neurobehavioral variables including subjective sleepiness, and performance involving vigilant attention, cognitive throughput, and working memory. Experiments involving CSR in the range of 3-5 hours also revealed substantial individual differences in the responses to CSR, and this differential vulnerability was stable over time (i.e., phenotypic).

Phenotypes are a product of genotypes, as well as being influenced by epigenetic or environmental factors. Evidence for a genetic contribution to phenotypic differential vulnerability to TSD has been found in a study of twins, where 56% of the total variance in monozygotic twins' PVT performance after repeated TSD exposures was due to variance between twin pairs, whereas 14% of the variance in dizygotic twins was due to variance between pairs. This indicates the state instability in PVT performance resulting from total sleep deprivation is a highly stable, genetically determined trait. There are no predictors for the phenotypic differences in neurobehavioral vulnerability to acute TSD and CSR. Prediction via candidate gene approaches has focused on genetic alleles involved in sleep-wake, circadian, and cognitive regulation. Recently, a promising metabolic marker was found for sleep debt from CSR in both humans and rats.

Recommendation: Continue efforts to evaluate the effectiveness of different biomarkers in experiments, including spaceflight studies.

Dr. Andy Liu addressed the issue of "Human-Automation Interaction," which is a key element in a wide range of human endeavors (e.g., aviation, nuclear power plants, trains, automobiles), including spaceflight. Human-automation-related accidents can have serious consequences. In many current scenarios, the operator tells the automation what to do via an interface; there is a need, however, for automation to have a sense of what the operator is trying to do so the automation can make helpful suggestions. Function allocation between human and machine may change at a designated point (e.g., cruising portion of flight to landing), which can be the critical time when accidents happen. With greater automation, there is less mental workload on the human operator, and therefore less engagement.

Dr. Liu then addressed the role of fatigue in the human-automation interface. He noted that lapses of attention (which are a primary effect of fatigue from sleep loss and extensive time on task) may have an effect on performance. Short-term memory failures can lead to problems of identifying the system state. Executive function deficits will diminish the ability to make decisions. Few studies have been conducted on the combination of automation and fatigue. Studies of fatigue and operation of unmanned aerial vehicles (UAVs) reveal that one night of sleep loss increased reaction times, although other aspects of performance were less affected. It was not clear whether this was an "operationally relevant" change.

In addition to fatigue, "boredom" in UAV operations increases over time, resulting in distraction and a decrease of directed attention. Studies of fatigue and tele-operation (e.g., use of a secondary task to measure workload) reveal that primary task performance was same whether the operator was sleepy or not, but secondary task performance was very sensitive to sleep loss (i.e., there was less “spare” attention to deal with contingencies). Another experiment evaluated sleep restriction and a "slam shift," finding that performance was the same over all subjects and sessions, but there were differences in secondary task measures that indicate the effect of mental workload. Dr. Liu concluded that the effects of fatigue are likely to influence appropriate allocation, and that the most important issue is the interaction across task or mode transitions.

Recommendation: Additional research is needed assessing operator-automation interactions under conditions of sleep loss. Appropriate countermeasures need to be developed and tested.

Dr. Pete Roma presented on “Team Performance Relative to Sleep Loss,” focusing on the risk of performance decrements from sleep loss due to inadequate cooperation, coordination, communication, and psychosocial adaptation within a team. He noted that although sleep loss and circadian factors cause neurobehavioral deficits in individuals, these risk factors can affect team cohesion (i.e., working well together) as well as social cohesion (i.e., living well together, interpersonal liking, cooperation, communication). Fatigue-related deficits in one or more team members can compromise outcomes such as team task completion, success versus failure, completion quality, disaster prevention via cumulative (e.g., maintenance) or acute (e.g., emergency) responses, and social outcomes (e.g., social integration, mutual support, effective conflict resolution). Examples of fatigue effects on teams include: 1) U.S. west coast professional sports teams playing on the east coast, are more likely to win in night games than their opponents, and 2) military teams undergoing continuous operations drills with preplanned targets committed more firing errors as sleep loss progressed, became operationally less efficient, and withdrew after 45 to 48 hours due to feeling they were ineffective, and 3) military studies in which soldier teams were very sleep deprived yet remained cohesive as a team, but their leaders felt isolated. Furthermore, results from a planetary exploration simulation (PES) experimental platform in which a 3-person crew has an extended workload and circadian misalignment, revealed that total crew performance showed changes with circadian phase.

Working in well-coordinated teams can serve as a countermeasure to some effects of fatigue. However, sleep deprivation increases defensiveness such that people can be less willing to accept unequal offers and trust one another. Dr. Roma described his Team Performance Task (TPT) (or Price of Cooperation Assay) for assessing team cooperation, noting that in experiments using TPT, cooperation and productivity decreases at night, while ambition stays constant. He concluded that sleep and circadian factors can adversely affect team performance outcomes.

Recommendation: Additional research assessing fatigue effects on team performance and communication, and development and testing of countermeasure recommendations to mitigate these effects.

Panel 3: Insufficient Sleep and Health Outcomes (2)

Dr. Janet Mullington reported on “Sleep Effects on Inflammation and Immune Function,” reporting that insufficient sleep is associated with increased susceptibility to the common cold and pneumonia, and to decreased response to vaccines. Inflammatory response to stressors is worse in poor sleepers and there is impaired development of immunological memory. Insufficient sleep is also associated with increased pain sensitivity (i.e., decreased threshold) and increased inflammatory markers. Some of these markers did not return to baseline levels after the first "recovery" (e.g., normal duration) night.

Recommendation: Continued work on the effects of insufficient sleep on inflammation and immune function in space, and on the influence of active inflammation or immune challenge on sleep in space.

Dr. Steven Shea reported on "Cardiovascular Function Related to Insufficient Sleep," observing that short sleep is associated with increased cardiovascular disease including Coronary Heart Disease (CHD) and stroke. One mechanism may be that sympathetic activation occurs with sleep loss. The epinephrine response to exercise is circadian time dependent, with the highest times at the same time as reported heart attacks. Circadian misalignment from weekly shifting of the sleep/wake cycle reduced the survival rate of hamsters with cardiomyopathy and in elderly mice. Ischemia/reperfusion tolerance is time-of-day dependent. Shiftwork is associated with higher fatal CHD, non-fatal myocardial infarction, and total CHD. The combination of sleep loss and circadian misalignment causes decreased insulin response to a meal, increased post-prandial glucose and reduced insulin but no change in HR, SBP, DSP or sympathetic tone.

Recommendation: Continued work is needed on the effects of insufficient sleep on cardiovascular system, including autonomic nervous system, function.

Dr. Andrea Spaeth reported on "Sleep and Metabolism," highlighting epidemiological studies (both cross-sectional and prospective) linking short sleep duration and increased risk for obesity in adults, adolescents and children. Sleep duration affects the levels of leptin and ghrelin as well as insulin sensitivity. In inpatient studies, there is weight change and pre-diabetic type hormonal changes within an experimental protocol with sleep restriction in healthy individuals. Caloric intake increases on days with delayed bedtime and extended wake mainly due to increased calories at night. In individuals trying to lose weight, if there is sleep restriction, then more fat-free mass and less fat is lost compared with no sleep restriction. Human and animal work show that weight gain depends on the timing of eating, not just on the total number of calories.

Recommendation: Continued work is needed on the effects of insufficient sleep and the timing of eating on metabolism and nutrient needs. Also unknown is the effects of diet type and timing of eating on sleep in spaceflight.

Dr. Elizabeth Klerman reported on "Sleep and Reproductive Health," noting that the effects of sleep and circadian rhythms on reproduction and other hormones depends on sex, age and, in women, menstrual cycle phase. Shiftwork and night work schedules are associated with (in women) irregular menses, increased early miscarriage, decreased fertility/lower pregnancy rates and increased breast cancer (hypothesized to be from light at night suppressing melatonin, which has anti-oncotic properties). Obstructive sleep apnea (which disrupts sleep) is associated with decreased sex steroids in men and in delayed breast development (suggesting delayed reproductive development) in prepubescent girls. Sleep inhibits release of thyroid-stimulating hormone and cortisol and simulates growth hormone (in men more than in women) at sleep onset and prolactin at sleep onset. Melatonin secretion is strongly regulated by the circadian system and by environmental light levels. Melatonin is associated with reproduction – it is the signal for seasonal reproductive changes in some animals. Exogenous melatonin administration in humans can affect circadian rhythms, sleepiness and alertness.

Recommendation: Continued work is needed on the effects of insufficient sleep and circadian misalignment on reproductive hormones and reproductive physiology in spaceflight.

Panel 4: Insufficient Sleep and Health Outcomes (continued)

Dr. Charles Fuller reported on the "Vestibular System" relative to sleep, an area of study where there is a lot of anecdotal information, but limited data. Vestibular signaling alters sleep output, especially Rapid Eye Movement (REM) sleep and dream recall lucidity. There is also anecdotal correlation between motion sickness and sleepiness, and between rocking/rhythmic behaviors and sleep induction. The high prevalence of sleeping pills used during spaceflight, given the improved environmental sleeping conditions on the ISS, suggests that some other aspect of the space environment, such as microgravity itself, might contribute to the sleep disturbance long associated with spaceflight. The effects could be different for microgravity versus partial gravity environments (e.g., on Moon or Mars). It is not known how the circadian timing system is affected by variation in gravity; circadian organization does involve vestibular signaling/input.

Many systems are affected by the degree of gravity including metabolism, food intake, immune function, muscle phenotype, and bone and calcium metabolism. There is animal evidence that microgravity affects sleep homeostasis, REM sleep, fragmentation, distribution of sleep over 24 hours, and napping in the daytime. Planetary surfaces will provide intermediate gravity (G) levels, which will need to be understood relative to sleep homeostasis and biological timing. Ground studies, especially with humans, do not account for vestibular/G influence on sleep. For example, bed rest is still subject to 1G.

Recommendation: Sleep and circadian studies in microgravity are needed to determine whether spaceflight reduces the need for sleep through the circadian system, homeostatic system, or both. Consider starting with animal studies in spaceflight to develop data for translational research.

Dr. Eva Sevick presented on "Lymphatic and Glymphatic System," describing how open-ended capillaries pick up excess fluid from blood capillary filtration-captured macromolecules and cell debris, which is transmitted from peripheral lymphatics through valvular structures that propel fluid usually against gravity to the lymph nodes, where immune reactions occur. The excess fluid is then dumped back into the vasculature and in the gut, which is necessary for picking up dietary lipids. She illustrated imaging the lymphatics using a trace dye to track the vessels as they drain the fluid, noting that there is autonomous control of lymphatic pumping (i.e., lymph propulsion).

Manual lymphatic drainage is a countermeasure used by a massage therapist to move the fluid toward the draining lymph node. Lymph drainage above thoracic duct is aided by gravity, lymphangions pump against gravity. There is no lymphatic system in the brain (i.e., no convective fluid from blood capillary filtration); however, recently conducted research in rodents indicates that cellular waste leaves the brain likely through cerebral spinal fluid and the vascular system via dural venous sinuses. This system of glial lymphatics, or "glymphatics," is considered "the garbage truck of the brain." In both the lymphatic and glymphatic system, there appears to be increased efficiency when asleep or under sedation; animals that are anesthetized or asleep demonstrate faster clearance in the frontal cortex than when awake.

Fluid in the spinal cord does end up in lymph nodes, but it is not known what happens with gravitational changes. Given the increased flow observed during sleep, if someone is experiencing reduced sleep, then it is likely they are not draining their glymphatic system sufficiently.

Recommendation: Conduct additional investigations to evaluate the effectiveness of the glymphatic system in a microgravity environment that causes fluid shifting.

Dr. Carol Everson presented on "Bone" and sleep loss, reporting that bone remodeling is a life-long process. In spaceflight, rates of decline of skeletal integrity are tenfold those found in post-menopausal women. Recent experiments show an association between sleep loss and decreased bone mineral density. Other recent studies have shown shift work is associated with early bone loss and increased fracture risk; most studies adjusted for body mass or body weight. Additionally, lab studies found that sleep loss causes increases in cell injury, increased alkaline phosphatase, and decreased osteocalcin.

Rats experiencing CSR have osteopenia, without decreased osteoclast activity; decreased marrow fat and diminished energy storage, increased hematopoiesis; increased megakaryocytes, and increased thrombocytosis risk. When these animals are allowed "recovery" sleep (for 4 months) some bone abnormalities return to normal, but other aspects do not and hormonal abnormalities remain. Pituitary hormones all decrease with sleep loss, which then leads to impaired bone formation. Marrow fat returned to normal after recovery sleep, but there was continued evidence of increased megakaryocyte numbers, and reduced osteoid percent lining bone, indicating ongoing reversal.

Recommendation: There is need for investigation of the many unknowns regarding muscle integrity and bone remodeling in sleep-restricted animals or how sleep relates to mechanical loading. Future directions for this work include determining whether stem cells undergo different types of differentiation during sleep loss.

Dr. Ruth Benca reported on "Well-Being & Depression" relative to sleep. She discussed the strong tie between sleep and mood regulation, presenting longitudinal studies that demonstrated a predictive relationship between insomnia and future depression. Studies assessing various aspects of 'well-being,' such as worry and responses to pain, also found increased deleterious outcomes under reduced sleep. Of additional concern for long-duration missions in isolation and confinement, evidence that sleep deprivation elevates negative affect in response to mild stressors, impairs emotional recognition, and increases risk-taking behavior and impulsivity. Related topics such as inter-individual differences in mood/behavioral responses to sleep loss, circadian misalignment and its relationship to mood, as well as the limitations of countermeasures (e.g., stimulants do not reverse all sleep deprivation effects on mood and motivated behavior) were further discussed. This presentation clearly demonstrated the close tie between sleep and various aspects of psychological well-being.

Recommendation: Efforts assessing behavioral outcomes including mood, affect, and psychological well-being in astronauts should incorporate the role of sleep and circadian factors in their analyses.

Panel 5: Physiological Countermeasures

Dr. Steven Lockley reported on the implementation of "Lighting Countermeasures for Spaceflight," explaining that light is the most powerful time cue for resetting the circadian pacemaker and ensuring correct synchronization of the internal clock with the environment. Failure to entrain the circadian pacemaker results in sleep disorders, fatigue, performance problems, and hormone and metabolic disorders. Appropriately timed blue light, in particular, is an effective countermeasure for nighttime performance decrements associated with circadian desynchrony and can restore performance to near-daytime levels. Light has also been shown to serve as an effective countermeasure for daytime performance decrements. Ground studies are underway to test the effects of a prototype light-emitting diode (LED) polychromatic lighting system on pre-sleep sleepiness, post-wake alertness, and circadian phase resetting. To effectively use light as a countermeasure, it is important to design lighting systems that optimize visual and non-visual effects, and to incorporate these systems into facilities where enhanced alertness and safety are important (e.g., offices, schools, factories, control rooms, hospitals, nuclear power plants). Solid-state LED lighting permits flexible, programmable lighting; hence, it is a desirable lighting design solution in many applications. LED-based Solid State Light Assemblies (SSLAs) are scheduled for launch in 2016 and subsequent installation on the ISS to replace aging fluorescent lights. The SSLAs were designed with three settings to address different operational needs: (i) high visual acuity; (ii) high circadian/alertness; and (iii) low circadian/alertness (pre-sleep). An ISS flight study is planned to evaluate the efficacy and acceptability of proposed SSLA lighting protocols for improving the vision, sleep, alertness, circadian rhythm regulation, and general well-being of astronauts during flight operations.

Recommendation: Continue work on the effects of different types of light and light stimuli on multiple physiological systems.

Dr. Laura Barger discussed "Exercise as a Countermeasure" to improve sleep, increase alertness, maximize performance, and facilitate circadian adjustment. Epidemiological data consistently document the association between exercise and improved sleep quality; however, experimental evidence of exercise promoting sleep is less compelling. There have been complications in investigating the efficacy of exercise in improving sleep due to a number of variables, including fitness of subjects, intensity, timing and modality of exercise. Self-report data from a randomized controlled trial with older adults indicate that aerobic physical activity with sleep hygiene education is an effective treatment approach to improve sleep quality, mood and quality of life in older adults with chronic insomnia.

Similarly, there is evidence to suggest that exercise can be used as a countermeasure for sleep apnea. One study found that vigorous physical activity of at least 3 hours per week is associated with a decrease in odds of prevalent sleep-disordered breathing (SDB). Dr. Barger also addressed the question of whether nighttime exercise disturbs sleep. According to a 2013 National Sleep Foundation Survey that surveyed 1,000 adults, exercise performance within 4 hours of bedtime was not associated with any measure of disturbed sleep.

Dr. Barger described a study she conducted for the NASA Johnson Space Center to assess the feasibility, acceptability, and efficacy of a combined lighting and exercise fatigue countermeasure for flight controllers working overnight shifts in the Mission Control Center. Alertness, performance, and mood were improved in the experimental condition, in which participants exercised under blue-enriched lighting, as compared to the control condition with no exercise or blue-enriched lighting. Results from a 1-year study in a financial services company where participants utilized treadmill workstations showed improvements in work performance, quality, and quantity in the workplace. In addition, a 15-day exercise study examined whether exercise can be a circadian synchronizer; exercise facilitated phase delays following a 9-hour delay in the sleep/wake cycle; with less evidence for exercise-mediated phase advances. Therefore, the sensitivity of the human circadian pacemaker to exercise is not constant across the time of day.

Recommendation: Prospective studies are needed to compare the effects of exercise with medical and non-medical treatments before including exercise as a first-line treatment for chronic insomnia.

Dr. Smith Johnston reported on "Operational Practices for Sleep Loss in Spaceflight Operations." Dr. Johnston discussed NASA's Clinical Practice Guidelines that guide flight surgeons through an evidence-based approach for treating crew members or other NASA personnel facing upcoming transmeridian travel or overnight shifts. Initially, the flight surgeon provides the individual with a series of questionnaires to establish a baseline related to their sleep behaviors, then provides education and training on key aspects such as sleep hygiene and the proper use of light and darkness. If further assistance is needed, the flight surgeon provides individualized schedules specific for the upcoming travel or work itinerary; these schedules offer protocols for using light and melatonin to hasten circadian entrainment and facilitate sleep onset. Hypnotics, chronobiotics and alertness medications are also available. Flight surgeons have established informal ground testing protocols. Crew members, prior to a mission, work with their flight surgeon to test hypnotics and other medications for efficacy and side effects, ensuring that once they are on a mission, they are taking the optimal medication and dose when needed.

The timing of food intake as a means to enhance lighting protocols for circadian shifting was further discussed. Dr. Johnston invited Dr. Patrick Fuller to share his hypotheses related to the use of meal timing as a supplemental zeitgeber to lighting. Per Dr. Fuller, rodent studies have shown that appropriately timed meals (regardless of the composition of the food) can facilitate circadian misalignment, and therefore facilitate sleep onset. Efforts to assess the effectiveness of these operational countermeasures are needed.

Recommendation: Continued evaluation of operational countermeasures related to sleep, circadian rhythms, and nutrition are required.

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13. ABSTRACT *(Maximum 200 words)*

In September 2014, the National Space Biomedical Research Institute (NSBRI) and the Behavioral Health and Performance Element (BHP) in the NASA Human Research Program (HRP), held a collaborative workshop on Sleep in Space. Workshop participants included subject matter experts external to NASA, representatives from the National Transportation and Safety Board (NTSB), and NASA representatives including researchers, flight surgeons, and management. A panel consisting of Shuttle and ISS astronauts provided valuable crew-member perspectives. Workshop presentations focused on sleep in spaceflight, as well as terrestrial research which identifies deleterious performance and health outcomes associated with chronic partial sleep restriction. Outcomes included sleep-related changes in immune, the lymphatic system, team performance, and bone health. This report highlights recommendations for both NASA operations and research related to maintaining sleep and circadian rhythms in future exploration missions. For example, workshop participants recommended other disciplines (e.g. bone, cardiovascular, human factors) at NASA incorporate sleep and circadian metrics (e.g., sleep duration, cumulative sleep loss, circadian misalignment, timing of the measurement) as potential contributors in their analyses. Objective measures of sleep feasible in the spaceflight environment were also recommended for both current and future missions.

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