Study Title: Evaluation of SmartSleep Technology for Improving the Efficacy and Restorative Quality of Sleep in Healthy Adults in Order to Mitigate Cognitive Performance Deficits Due to Sleep Restriction and Emergency Awakenings

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Study Protocol and Statistical Analysis Plan

BACKGROUND

Sleep Duration and Sleep Quality in Spaceflight

Adequate healthy sleep is essential in spaceflight to ensure astronauts maintain a high level of cognitive performance capability and do so without undue stress. However, studies have consistently found that chronic sleep restriction (i.e., sleep durations <6.5h) and astronauts' perceptions of poor sleep quality were common in spaceflight shuttle missions (Barger et al., 2014) and in International Space Station (ISS) missions (Barger et al., 2014; Jones et al., 2022). The latter study by Jones et al. (2022) yielded N=2,856 Reaction Self-Test (RST) assessments (i.e., RST = brief psychomotor vigilance test [PVT-B] with subjective ratings) that included n=394 evaluations pre-flight; n=2,109 evaluations in-flight; n=353 evaluations post-flight. This extensive study on N=24 astronauts on ISS for 6-month missions revealed that reductions in sleep duration and perceived poor sleep quality on ISS were associated with decrements in astronauts' performance on the brief psychomotor vigilance test (PVT-B) and increases in their perceptions of stress and physical exhaustion throughout the mission (Jones et al., 2022). Nearly half of the astronauts reported sleeping 6h/day or less on any given day in spaceflight, which is consistent with the earlier findings of Barger et al. (2014). When sleep duration on ISS was 6h or less per day, statistically significant deficits in PVT-B performance occurred (Jones et al., 2022). This result is consistent with Earth-based experiments showing that chronic restriction of sleep to 4h per night, 5h per night, or 6h per night resulted in sleep-dose-response cumulative psychomotor vigilance deficits, which involved statistically reliable decreases in PVT response speed and increases in lapses of attention, as well as deficits in cognitive speed and working memory performance (Dinges et al., 1997; Van Dongen et al., 2003; Belenky et al., 2003; Lim & Dinges, 2008; Mollicone et al., 2008), and increases in sleep propensity, evident in decreasing sleep latency (Carskadon & Dement, 1981). Importantly, these neurobehavioral performance deficits become progressively worse as sleep restriction to below 7h per day continued across consecutive days.

Sleep Medication Use in Spaceflight

Historically, NASA physicians have prescribed sleep medications to address sleep deficits in spaceflight, but among other concerns articulated by Barger et al. (2014), the use of hypnotic medications in space can pose a risk to astronauts' performance capability on awakening, especially in the event of an emergent awakening, that is, an emergency alarm requiring astronauts to perform at a high level within 30 seconds of the alarm. These concerns have been supported by a ground-based, double-blind, placebo-controlled study of zolpidem and zaleplon intake pre-sleep to assess their adverse effects on various cognitive tasks in N=34 astronauts, astronaut candidates, and flight controllers at NASA JSC (Johnston et al., 2015; Dinges et al., 2018). Results showed that pre-sleep ingestion of sleep medications, especially 10-mg zolpidem, posed a substantial risk to performance at emergent awakenings from sleep (Johnston et al., 2015; Dinges et al., 2018).

SmartSleep Slow-Wave EEG Enhancement Could Mitigate Some of the Effects of Chronic Sleep Loss in Spaceflight

There is a need for a technology that can improve sleep quality in space and biologically maximize the performance benefits of limited sleep duration, without unduly affecting the ability of astronauts to awaken abruptly due to an in-flight emergency. Studies have found that enhancement of EEG slow waves during sleep increased subsequent cognitive performance

(Bellesi et al., 2014; Bernardi et al., 2015; Ngo et al., 2013). Accumulating evidence suggests that many of the benefits of sleep are associated with sleep EEG slow waves. Slow waves reflect the near-synchronous alternation by millions of neurons between depolarized, active up-states, and hyperpolarized, inactive down-states that are thought to mediate the restorative effects of sleep on brain networks and cells (Tononi and Cirelli 2006). Sleep slow waves support system and synaptic consolidation by promoting specific patterns of neuromodulatory and electric activities. Subjective sleep quality is also related to the size and number of slow waves that occur nightly (Kecklund and Åkerstedt 1997).

Pharmacologic approaches to improve sleep by increasing slow waves are limited by issues of dependence and tolerance and are often associated with residual side effects during subsequent wakefulness (Feld et al. 2013). Moreover, pharmacological agents cannot be completely washed out of the metabolic cycle in cases where an individual, like an astronaut, is unexpectedly awakened from sleep and needs to function quickly and accurately.

SmartSleep is a new slow-wave enhancing technology that monitors and stages sleep electroencephalography (EEG) in real-time and delivers auditory stimulation during non-REM sleep in a closed-loop fashion at a volume that is dynamically modulated by sleep depth. Stimulation is stopped if the likelihood of sleep disturbance exceeds a conservative threshold. Pilot testing has indeed shown that the system can be used to increase the amount of slow waves occurring each night in a majority of individuals (Diep et al. 2020). Importantly, the increase in slow waves is correlated with the number of sub-awareness auditory tones played. SmartSleep consists of a sleep app and a headband worn during sleep that is comfortable and easily translatable for spaceflight.

SmartSleep offers an alternative to the dilemma of risking the adverse effects of chronic sleep restriction and low sleep quality in spaceflight, versus risking the adverse effects of medications on sleep and waking in ever-longer duration spaceflight. If increased amounts of slow-wave activity in sleep via SmartSleep can translate to cognitive performance benefits and/or sleep quality benefits, even during periods of chronically restricted sleep time to 5h/night, it will offer a significant advantage over the sleep medication alternative. If this is the case, it will also be essential to determine whether the enhanced slow-wave activity during sleep provided by SmartSleep will increase sleep inertia and thereby impair cognitive performance immediately following an emergent awakening. It is therefore imperative that the safety of increasing slow-wave activity be demonstrated to benefit subsequent waking cognitive performance while not exacerbating sleep-inertia performance deficits at emergent awakening. Operational safety needs to be demonstrated before the use of SmartSleep in the space program. Finally, to the best of our knowledge, a non-pharmacological slow-wave enhancing technology has not been tested in a chronic sleep restriction paradigm, despite the high prevalence of chronic sleep loss in astronauts and in the general population.

OBJECTIVES

For the above reasons, we designed a double-blind, placebo-controlled laboratory study of SmartSleep to determine what effect it has on daytime cognitive performance and on emergent awakenings from sleep in a chronic sleep restriction paradigm (i.e., 5h/night for 4 nights). This study is the first to evaluate slow-wave activity enhancement and its effects on performance and sleep inertia during sleep using a chronic sleep restriction paradigm to do the following:

Objective 1: Evaluate whether slow wave sleep enhancement via the SmartSleep stimulus algorithms benefits daytime cognitive performance during a period of chronic sleep restriction as commonly observed during spaceflight. We assessed cognitive performance with the Cognition test battery (developed for NASA; Basner et al., 2015) across a range of cognitive domains and across a number of high fidelity spatial cognition tasks and space-operationally relevant tasks including Robotic On-Board Trainer (ROBoT); Six Degrees of Freedom Docking Simulator (6DF); and Lunar Landing Simulation.

Objective 2: Investigate whether SmartSleep slow-wave enhancement increases

performance decrements induced by sleep inertia after an emergent awakening.

Objective 3: Identify the best modality of acoustic stimulation in terms of slow-wave enhancement and cognitive performance among three different stimulation techniques: Continuous Fixed Interval (1 Hz, inter-tone interval stimulation), Block (5 seconds on versus 5 seconds off), and In-Phase Adjustable (constant stimulation with tones to be delivered during each upstate of the slow wave).

SPECIFIC AIMS

The overarching goal of this project is to mitigate the effects of chronic sleep loss by optimizing the SmartSleep technology and demonstrating its safety at the same time. It has the following Specific Aims:

Specific Aim 1: Determine whether slow-wave sleep can be enhanced via closed-loop auditory stimulation of EEG slow waves in healthy adult subjects using SmartSleep Headband technology, when sleep is restricted in duration to 5h per night over 4 consecutive nights.

Hypothesis 1: Slow wave sleep will be enhanced via closed-loop auditory stimulation of EEG slow waves relative to sham stimulation, when sleep is restricted in duration to 5h per night over 4 consecutive nights.

Specific Aim 2: Determine whether post-sleep cognitive performance functions sensitive to sleep restriction can be enhanced when SmartSleep closed-loop auditory stimulation is used on sleep-restricted nights relative to a sham SmartSleep control condition. Hypothesis 2: Daytime cognitive performance will be higher after closed-loop auditory stimulation of EEG slow waves relative to sham stimulation, when sleep is restricted in duration to 5h per night over 4 consecutive nights.

Specific Aim 3: Identify the acoustic stimulation modality with maximal benefits for slow-wave enhancement and daytime cognitive performance, when sleep is restricted in duration to 5h per night over 4 consecutive nights. Hypothesis 3: One of the three acoustic stimulation modalities enhances EEG slow waves significantly better than the other two modalities, and is also associated with enhanced cognitive performance during the daytime, when sleep is restricted in duration to 5h per night over 4 consecutive nights.

Specific Aim 4: Investigate systematic effects of consecutive nights of sleep restriction on slow-wave enhancement and daytime cognitive performance. Hypothesis 4: With increasing homoeostatic sleep drive induced by consecutive nights of sleep restriction, the observed slow-wave enhancement will mitigate some of the effects of chronic sleep loss on daytime cognitive performance.

Specific Aim 5: Assess any potential adverse effects of SmartSleep utilization during sleep restriction, especially related to sleep inertia after emergent awakening. Hypothesis 5: Cognitive functioning after emergent awakenings in the acoustic stimulation conditions will be non-inferior relative to sham stimulation based on a non-inferiority margin of 2 lapses on the PVT-B.

METHODS RELATED TO SPECIFIC AIMS

SmartSleep Technology

The SmartSleep technology uses two small sensors in the headband to continuously detect the brain's slow wave sleep (delta/theta frequency) in real time, and a closed-loop algorithm customizes the timing and volume of tones to optimize the sleep pattern. Thus, the device uses "quiet audio tones" (sub-awareness) to increase slow waves, which can enhance sleep quality/depth, thereby enhancing subsequent waking cognitive performance without the unwanted sedating effects of medications on cognitive functions during emergency awakenings. Philips completed commercial development of the SmartSleep technology (https://www.usa.philips.com/c-e/smartsleep-advocacy.html). The Philips SmartSleep website states that SmartSleep is a, "Wearable sleep headband and mobile app clinically proven to improve the quality of your sleep", and that it "increases your energy in the same sleep time", it is

"for people who typically sleep <7 hours per night", and it is a "drug-free sleep enhancement technology."

There is evidence that it is possible to enhance slow waves through non-pharmacological means, particularly with auditory stimulation (Bellesi et al., 2014; Tononi et al., 2010; Ngo et al., 2015; Ngo et al., 2013; Papalambros et al., 2017). The enhanced slow waves are indistinguishable from spontaneous ones in shape, origin, distribution, and propagation (Riedner et al., 2011).

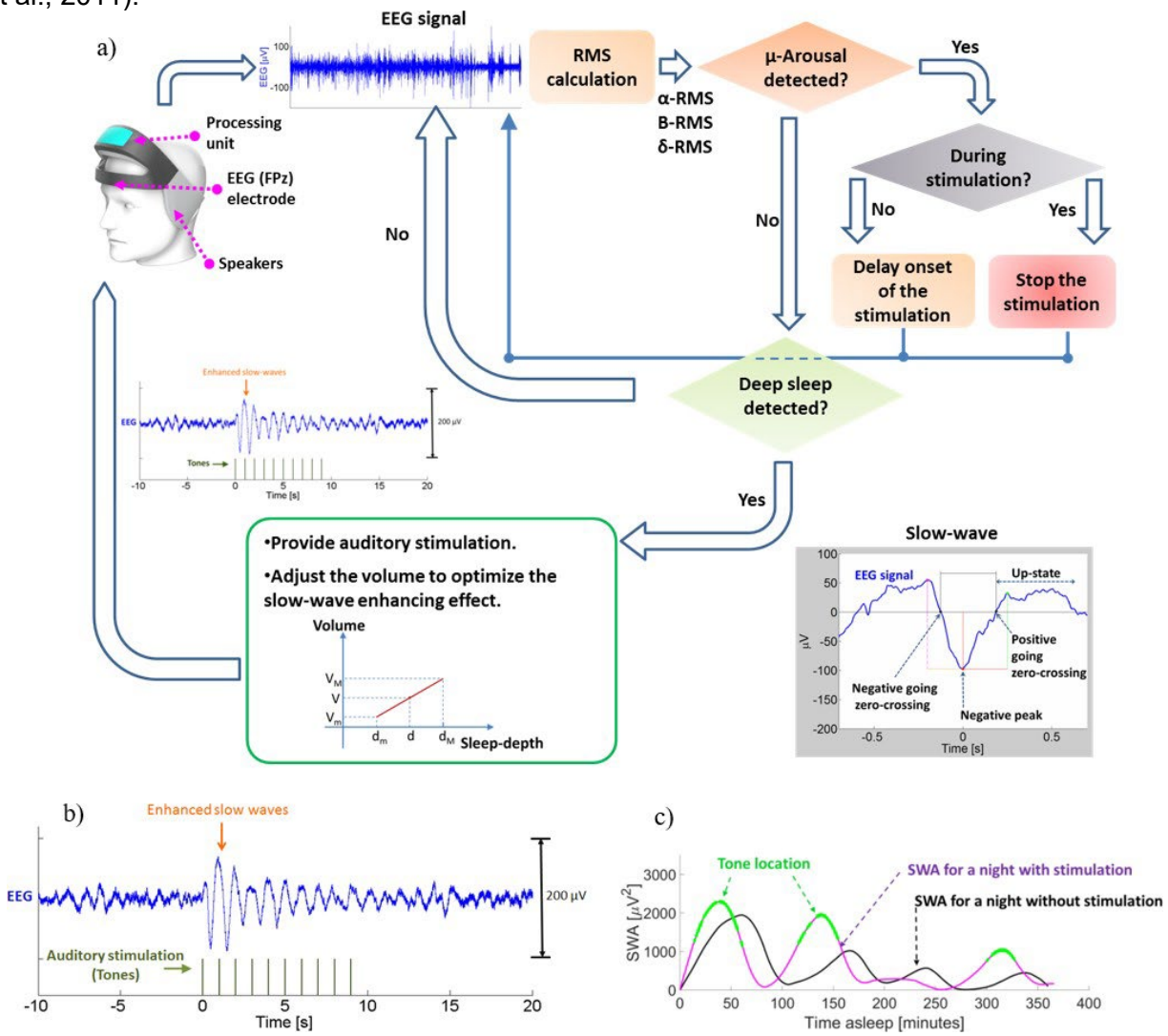

***Figure 1**. **a)** The presence of EEG patterns (high power in the alpha 8-12 Hz and/or beta 15-30 Hz bands) indicative of (micro) arousals is first evaluated. If arousal-like activity is detected in the EEG during stimulation, the stimulation stops. If the arousal-like activity is detected outside the stimulation period, the onset of the next stimulation period is delayed. If no arousal-like activity is detected, then the system attempts to detect deep sleep based on slow wave activity (SWA) and the temporal density of detected slow-waves. On detection of sufficiently deep sleep, the auditory stimulation is delivered. **b)** Enhancement of slow waves when stimulation is delivered. **c)** SWA enhancement due to stimulation. The green markers indicate the time at which the stimulation was delivered*

In the last few years, Philips in collaboration with the University of Wisconsin-Madison, have developed a closed loop, real-time, embedded, and sleep wearable system that monitors sleep EEG and delivers auditory stimulation during deep sleep (N3) at a volume that is dynamically modulated by sleep depth. Sleep depth is estimated by taking the ratio between the EEG power in the 0.5 to 4 Hz band and the power in the 15 to 30 Hz band. The system consists of a headset

with a single dry EEG electrode placed on the forehead and an integrated processing unit embedded in the headband (Figure 1a). The reference electrode is positioned on the right mastoid with conductive gel to improve impedance. This system focuses on the detection of deep sleep (N3) and wakefulness such that it targets the stimulation to periods where sleep is deep and stimulation related disturbance is prevented. The N3 (wake) detection sensitivity and specificity are 73.5% (76.4%) and 96.9% (82.5%), respectively. The stimulation is delivered through speakers in a headset in the form of 50-millisecond audible tones with a one-second inter-tone interval. As reported in several publications (Ngo et al., 2013; Papalambros et al., 2017; Santostasi et al., 2015), the slow-wave activity (SWA) enhancing effect is optimized by synchronizing the first tone to the up-phase of a detected slow-wave. If the likelihood of sleep disturbance exceeds a pre-established threshold, the stimulation is stopped.

At this point, it is unclear which acoustic stimulation paradigm produces the best results in terms of slow-wave enhancement and cognitive performance improvement. In this study, we will systematically compare three acoustic stimulation modalities and sham. The four stimulation modalities will be provided by Phillips and are as follows:

- Continuous Fixed Interval: 1 Hz inter-tone interval stimulation
- Block: 5 seconds on versus 5 seconds off, and
- In-Phase Adjustable: constant stimulation with tones to be delivered during each upstate of the slow wave.
- Sham: No auditory stimulation while wearing the SmartSleep headband

The slow wave amplitude enhancement produced by the auditory stimulation is shown in Figure 1b. The amplitude of deep sleep EEG clearly increases when the auditory stimulation (indicated by the green vertical lines in Figure 1b) is delivered. An illustration of SWA enhancement is shown in Figure 1c where the black curve is the SWA of a sham sleep session (without stimulation but while the device is worn) and the pink curve is the SWA of a sleep session with stimulation. The green markers (i.e., tone location) indicate the periods where the stimulation was delivered.

A previous version of SmartSleep was tested in a study supported by the Australian Cooperative Research Center for alertness, safety and productivity. The results of this study (Diep et al., 2020) demonstrated that >65% of participants exhibited enhanced slow wave energy in the stimulation condition (STIM) with an average of 28.4% increase with respect to sham. Furthermore, large effect sizes were observed for improved executive function (Verbal Fluency) and morning vigilance (PVT) following stimulation relative to sham.

STUDY DESIGN

The study was conducted at the University of Pennsylvania. This placebo-controlled, double-blind, cross-over laboratory study of SmartSleep stimulations included sleep restriction to 5h time in bed for sleep on 4 consecutive nights, preceded by an 8h sleep adaptation night, and followed by a 10h recovery night (Figure 2).

The proposed sample was a total of 12 subjects to be recruited and screened for their ability to engage in the protocol and their similarities to astronauts (e.g., age 30-55y, educational background, healthy, etc.). The protocol involved monitoring of sleep-wake behaviors by actigraphy and sleep diary 2 weeks prior to and 1 week following the 7-day laboratory protocol. Participants were required to remain in the laboratory for the entire 7- day and 6-night protocol for cognitive testing at alarm awakening from sleep (sleep inertia test battery) and throughout each 19h waking period (full Cognition test battery every 4 hours). In addition, participants completed a spatial cognition battery and three tasks with operational relevance to spaceflight (Six Degrees of Freedom, ROBoT, and the Lunar Lander Simulator) once a day. The 6 laboratory nights consisted of a baseline night (8h time in bed [TIB]), 4 nights of 5h TIB (each with one of the four SmartSleep stimulus conditions), and a recovery night of 10h TIB at the end. Each of the 12 subjects received one of the SmartSleep stimulus conditions (Continuous Fixed Interval, Block,

In-Phase Adjustable, and Sham) on one of the 4 sleep restriction nights, according to a balanced orthogonal Latin Square design. This was a fully within-subjects design with high statistical power for the given sample size. This allowed us to investigate how the methodology works across the build-up of chronic sleep restriction (Figure 2).

Subjects	1	2	3	4	5	6	7	8	9	10	11	12
Lab Day 1	Familiarization testing: Cognition performance testing and operational simulation testing											
Night 1 (8h TIB)	Adaptation to SmartSleep cap: sham stim recording nocturnal sleep EEG with no emergent awakening											
Lab Day 2	Cognition performance testing and operational simulation testing											
Night 2 (5h TIB)	Sham	Stim 1	Stim 2	Stim 3	Sham	Stim 1	Stim 2	Stim 3	Sham	Stim 1	Stim 2	Stim 3
	Emergent Awakening (Sleep Inertia Test Bout)											
Lab Day 3	Cognition performance testing and operational simulation testing											
Night 3 (5h TIB)	Stim 1	Sham	Stim 3	Stim 2	Stim 3	Stim 2	Stim 1	Sham	Stim 2	Stim 3	Sham	Stim 1
	Emergent Awakening (Sleep Inertia Test Bout)											
Lab Day 4	Cognition performance testing and operational simulation testing											
Night 4 (5h TIB)	Stim 2	Stim 3	Sham	Stim 1	Stim 1	Sham	Stim 3	Stim 2	Stim 3	Stim 2	Stim 1	Sham
	Emergent Awakening (Sleep Inertia Test Bout)											
Lab Day 5	Cognition performance testing and operational simulation testing											
Night 5 (5h TIB)	Stim 3	Stim 2	Stim 1	Sham	Stim 2	Stim 3	Sham	Stim 1	Stim 1	Sham	Stim 3	Stim 2
	Emergent Awakening (Sleep Inertia Test Bout)											
Lab Day 6	Cognition performance testing and operational simulation testing											
Night 6 (10h TIB)	Recovery sleep: sham stim recording nocturnal sleep EEG with no emergent awakening											

Figure 2: Overview of the study design. Each of the 12 subjects underwent one adaptation night (8h TIB), four sleep-restriction nights (5h TIB), and one recovery night (10h TIB). Each subject was exposed to all four SmartSleep acoustic stimulations on the four sleep restriction nights (Stim1: Continuous Fixed Interval; Stim2: Block; Stim3: In-phase adjustable; and Sham) according to a balanced orthogonal Latin Square design. Subjects performed a sleep inertia test bout consisting of a 3-min. Psychomotor Vigilance Test (PVT-B) and a Digit-Symbol Substitution Test (DSST) after emergent awakenings. They also performed cognitive and operational testing throughout the wake periods.

The following cognitive and spaceflight-relevant operational tasks were administered throughout the waking period on all days of the protocol (Figure 3):

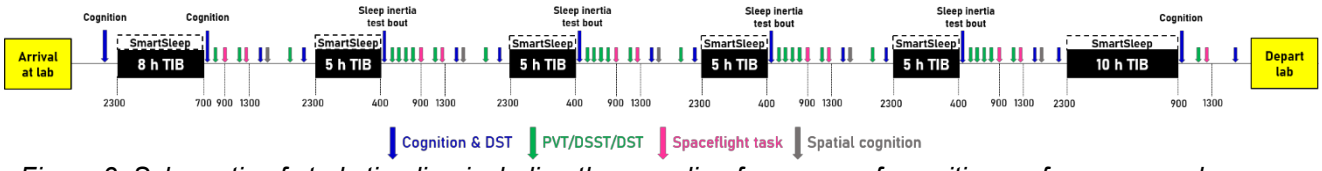

Figure 3: Schematic of study timeline including the sampling frequency of cognitive performance and

spaceflight operationally relevant task assessments. Black rectangles signify sleep periods with the nightly sleep opportunity presented in white text and wake periods are interspersed between each sleep period. Time of day is displayed along the bottom of the laboratory protocol timeline. Cognitive and spaceflight relevant operational tasks that were administered together are grouped and color-coded; each test grouping is associated with a colored arrow and all test administrations are positioned along the study timeline. Cognition, which included a DST, is colored blue; a short cognitive test battery comprised of the PVT, DSST, and DST are colored green, spaceflight operational tasks (ROBoT, 6DF, and Lunar Lander) are colored pink, and spatial cognition is colored gray. Sleep inertia test bouts were administered upon awakening after each sleep restricted night and are identified with text above the blue Cognition arrow. Descending subtraction Task (DST); Brief Psychomotor Vigilance Test (PVT); Digit-Symbol Substitution Test (DSST) after emergent awakenings.

Sleep Inertia Test Bout

The Sleep Inertia Test Bout was administered at the time of emergent awakenings, and consisted of two measures that were developed and validated to be sensitive to sleep inertia: the Brief Psychomotor Vigilance Test (PVT-B) to assess behavioral alertness and psychomotor speed (Basner et al., 2011); and the Digit Symbol Substitution Test (DSST) to assess cognitive processing throughput. In addition, we administered the Descending Subtraction Task (DST), a validated measure of working memory sensitive the effects of sleep loss and sleep inertia (Dinges, 1990; Dinges et al., 1985), as well as Visual Analog Scales (VAS) to assess subjective ratings of mental fatigue, tiredness, physical exhaustion, level of stress, sleep quality, and sleepiness.

The PVT-B is a well-validated test based on vigilant attention and reaction time (Basner & Dinges, 2011; Lim & Dinges, 2008). Subjects are instructed to monitor a rectangular box on the screen and press the space bar as quickly as possible each time a millisecond counter appears. Each PVT-B reaction time is displayed for one second as feedback. Subjects are asked to respond as quickly as possible without committing false starts in the absence of stimuli.

The 1.5-minute Digit Symbol Substitution Test (DSST) is validated to be sensitive to fatigue from sleep loss (Van Dongen et al., 2003; Dinges et al., 1985). The test is based on the original version in the Wechsler Adult Intelligence Scale. Subjects are presented with a legend that pairs unique symbols to digits (1 through 9). Symbols are then sequentially presented on the screen in random order. Subjects are instructed to press the corresponding number key as soon as possible. On each test administration, the symbol and digit correspondence is randomly reassigned. The DSST measures cognitive throughput based on perception and memory.

The Descending Subtraction Test (DST) is a measure of working memory that is sensitive to fatigue from sleep loss and sleep inertia (Dinges, 1990; Dinges et al., 1985). The DST requires participants to mentally subtract numbers in a sequential fashion as quickly as possible. For example, if the starting number is 987, the participant subtracts nine from 987, with the difference being 978, the participant then subtracts eight from 978, and so on subtracting by seven, six, five, four, three, and two, from each difference at which point, the participant then recycles the subtraction sequence beginning at nine again. The DST was two minutes in duration and responses were entered on a keyboard.

The Visual Analog Scales (VAS) measured subjective ratings with end points of “Mentally Sharp” (0) and “Mentally Fatigued” (10); “Tired” (0) and “Fresh, Ready to Go” (10); “Energetic” (0) and “Physically Exhausted” (10); “Not Stressed At All” (0) and “Very Stressed” (10); “Low Sleep Quality” (0) and “High Sleep Quality” (10); and “Not Sleepy At All” (0) and “Very Sleepy” (10).

Cognition Test Battery

Cognition was developed for spaceflight by Dr. Mathias Basner and his team at the University of Pennsylvania (Basner et al., 2015; Moore et al., 2017). It consists of 10 brief neuropsychological tests that cover a range of cognitive domains that are relevant for spaceflight and go beyond what is measured with NASA’s standard WinSCAT test battery (e.g., emotion recognition and risk decision-making). Fifteen unique versions of each test allow for repeated

administration of the battery. Importantly, a ground-based study in N=46 astronaut surrogate subjects allows for correcting for practice effects and stimulus set difficulty effects.
Links to cerebral networks have been established with fMRI (Roalf et al., 2014). The battery was specifically designed for the high-performing astronaut population and was validated in both astronaut and astronaut surrogate populations on the ground and on the ISS (Moore et al., 2017). Overall, the battery has been administered 7,222 times in 720 unique subjects (mean age 35.1 years, SD 9.0 years, range 20-62 years; 71% male), including 5 astronauts on 6-month ISS missions, 2 astronauts on 12-month ISS missions, 8 astronauts in a ground-based study at Johnson Space Center (JSC), and 198 subjects in several space analog environments (including head-down tilt bed rest, HERA, and Antarctic research stations). The sensitivity of the battery to environmental stressors typically encountered on the ISS (e.g., sleep deprivation and high levels of CO2 [Basner et al., 2017]) has been established. Furthermore, we demonstrated that a subset of 3 Cognition tests (Digit Symbol Substitution, Abstract Matching, and Fractal 2-Back) was able to predict 30% of 6DF-docking performance variance on a task that is regularly used on the ISS (Johannes et al., 2016). Finally, Cognition is part of ISS Standard Measures. Therefore, Cognition constitutes a well-established and validated instrument for measuring spaceflight effects on cognitive performance.

The Cognition battery (Basner et al., 2015; Moore et al., 2017) was administered on calibrated laptop computers. On average, 5 ISS astronauts required only 16.5 min to answer a brief survey followed by their performance on the 10 Cognition tests. We have generated software that automatically extracts key Cognition accuracy and speed outcomes. Facilitating our large database of Cognition tests, we determined loading and difficulty of individual stimuli via Item Response Theory (Embretson and Reise, 2000), which increases the power for our analyses relative to analyses based on standard accuracy outcomes (e.g., percent correct). The data analysis process was as follows: (1) extract one key accuracy and speed outcome for each test; (2) correct outcomes for practice and stimulus set difficulty effects; and (3) standardize outcomes based on baseline performance of all subjects (we will also generate speed, accuracy, and efficiency scores across cognitive domains).

Spatial Cognition Tasks

Spatial cognition was assessed using a variety of virtual 3D navigation tasks, which probes similar cognitive functions as real-world navigation and recruit similar neural networks (Cushman et al., 2008; Ekstrom et al., 2003; Wolbers et al., 2004). These tasks specifically target the hippocampus and other areas that support the encoding and retrieval of spatial locations, show considerable connectivity to the hippocampus, and support visuospatial imagery, episodic memory retrieval and self-processing operations. A subset of these tests has been specifically developed for in-flight assessments, which is currently prepared for flight certification in collaboration with Cadmos/ESA as part of the ISS experiment HypoCampus. This subset has been optimized relative to crew burden/compliance and scientific return, and with the respect to the underlying test constructs. Briefly, we employed a virtual cognitive map task to assess spatial memory formation (Craig et al., 2016); navigation strategies were tested using a modified paradigm originally proposed by Wiener et al. (2013), which allowed us to evaluate the selection and adoption between beacon, response cue, and spatial strategies. We also employed a plus maze task to specifically assess switching capabilities between navigational strategies (Harris et al., 2012). This paradigm has been shown to be sensitive to navigational switching, which is likely to be attributed to decreased functional connectivity between the hippocampus and pre-frontal cortex as well as dysregulation of the locus coeruleus noradrenergic system. To specifically target topographical memory, a digital version of the Four Mountains Task was performed (Chan et al., 2016; Hartley & Harlow, 2012). Path integration was assessed using a triangle completion task (Goeke et al., 2015). The task has been specifically adapted to the needs of spaceflight with respect to directions (including pitch and yaw), duration, velocity and complexity. In addition, a modified paradigm suggested by Wolbers et al. (2008) was employed to specifically assess spatial updating. Spatial orientation ability was

determined using the Perspective Taking paradigm suggested by Hegarty & Waller (2004). All tasks have been successfully established as part of various NASA/ESA and DLR studies (e.g. HERA C3, HERA C4, ESA Bed Rest 'RSL', ESA Bed Rest 'Cocktail'). The frequency of tests administrations was optimized for each task and varied between single up to daily test administrations.

Spaceflight Relevant Operational Tasks

The Robotic On-Board Trainer (ROBoT) was used as an in-lab operational task. ROBoT is NASA's platform for training astronauts to perform docking and grappling maneuvers using the Canada Arm. Proficiency with this system is mandatory for all astronauts who fly. The system is based on highly realistic 3D simulations of the arm and associated physics. The physical system involves a left-hand translational controller (x/y/z directions) and a right-hand rotational controller (pitch/roll/yaw), plus two laptop computer screens. The key performance metrics include: (i) docking position accuracy, (ii) docking orientation accuracy, (iii) total task time, and (iv) smoothness of approach trajectory.

The Six Degrees of Freedom Docking Simulator (6DF) was used as an in-lab operational task. It is a high fidelity docking simulation task that has been used to investigate the performance of cosmonauts in the manual docking of a Soyuz spacecraft on the ISS. The experimental docking simulator consists of a series of docking flight tasks of varying skill level that have dynamic and informational equivalence to real docking maneuvers, based on mathematical models for real-hand control of the Soyuz spacecraft. In the evaluation of flight quality, there are 12 physical/mathematical parameters that describe the position and the motion of the spacecraft and space station with regard to each other.

The Lunar Landing Simulation was used as an in-lab operational task. It includes a sequence of activities from the Apollo Program and the Autonomous Landing and Hazard Avoidance Technology (ALHAT) Project. Subjects operate the terminal descent phase of a lunar landing. To complete the landing there is a primary flight display, landing display, and automatic and manual control modes.

STATISTICAL APPROACH

We conducted a randomized, double-blind, cross-over laboratory study on the effects of the slow-wave enhancing smart sleep technology on cognitive performance during 4 consecutive nights of sleep restriction (5h time in bed). We compared the four auditory stimulation modalities (continuous fixed interval, block, in-phase adjustable, and sham) relative to their slow-wave and performance enhancing properties. Each subject was exposed to all 4 modalities (within-subject study design). We used a balanced orthogonal Latin Square design (i.e., each stimulus modality will appear in each of the 4 sleep restriction nights exactly once, and each modality will be preceded by each other modality exactly once).

Cognitive test data were standardized to baseline performance. We used linear mixed effect models (in SAS version 9.4, SAS Institute, Cary, NC) with random subject intercept to account for the clustered nature of the data. The model included factors for stimulus modality (4 levels), sleep restriction night (4 levels), and their interaction. We were both interested in the main effects (modality and sleep restriction) and their interaction, but acknowledge the limited power for detecting a significant interaction. If the type-III fixed effect estimate indicates a significant difference between groups, we compared them in post-hoc tests. The primary outcome was be the number of lapses (errors of commission; response times >355 ms) on the brief Psychomotor Vigilance Test (PVT-B) after emergent awakenings and during the day. Performance on the Digit Symbol Substitution (DSST), Descending Subtraction Task (DST), and spaceflight relevant task (ROBoT) were treated as secondary outcomes. The other cognitive tests (Cognition, Spatial Cognition, tasks with operational relevance for spaceflight) were treated as tertiary outcomes. Statistical tests for secondary and tertiary outcomes were adjusted with the false discovery rate method (Curran-Everet, 2000).

For the power calculations (Figure 4), we assumed a correlation between measurements of 0.8, and varied the standard deviation of the difference between modalities/sleep restriction nights from 0.8 to 1. We expect to have >80% power to find a medium effect size of 0.5 statistically significantly different for standard deviations <0.9.

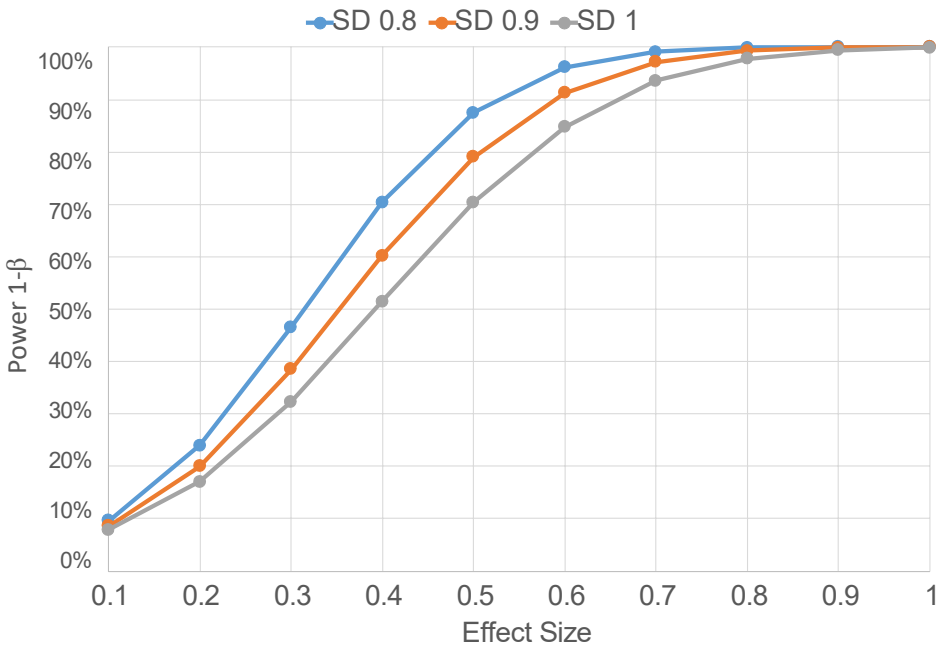

Figure 4: Power calculations

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University of Pennsylvania

Institutional Review Board
3600 Civic Center Blvd., 9th Floor
Philadelphia, PA 19104
Phone: 215-573-2540
(Federalwide Assurance # 00004028)

DATE:	22-Dec-2020
TO:	David F Dinges
CC:	Carlin, Michele Basner, Mathias Cordoza, Makayla
RE:	
IRB PROTOCOL#:	832679
PROTOCOL TITLE:	Evaluation of SmartSleep Technology for Improving the Efficiency and Restorative Quality of Sleep in Healthy Adults in Order to Mitigate Cognitive Performance Deficits Due to Sleep Restriction and Emergency Awakenings
SPONSOR:	NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
REVIEW BOARD:	IRB #2

IRB CONTINUING REVIEW: NOTICE OF APPROVAL

Dear Dr. Dinges,

The above referenced protocol was reviewed and re-approved by the Institutional Review Board using the expedited procedure set forth in 45 CFR 46.110 on 18-Dec-2020. This study has been determined to be eligible for expedited review category(ies) 9.

This approval is for the period 18-Dec-2020 to 17-Dec-2021.

The documents included with the application noted below are approved:

-HSERA Continuing Review, confirmation code: dcibcdad, submitted on 12/01/2020

NOTE: Approval by the IRB at this time DOES NOT constitute authorization to initiate or continue in-person research during the COVID-19 pandemic. Please review Guidance on Notification to the IRB of In-Person Research Resumption During Phase II (Effective 7/13/2020) on the IRB website here for further details: https://irb.upenn.edu.

ONGOING REQUIREMENTS:

- You must obtain IRB review and approval under 45 CFR 46 if you make any changes to the protocol, consent form, or any other study documents subject to IRB review requirements. Implementation of any changes

cannot occur until IRB approval has been given.

- Reportable event, such as serious adverse events, deviations, potential unanticipated problems, and reports of non-compliance must be reported to the IRB in accordance with Penn IRB SOP RR 404.
- When enrolling subjects at a site covered by the University of Pennsylvania's IRB, a copy of the IRB approved informed consent form with the IRB approved from/to stamp must be used unless a waiver of written documentation of consent has been granted.

COMMITTEE APPROVALS: You are responsible for assuring and maintaining other relevant committee approvals. This human subjects research protocol should not commence until all relevant committee approvals have been obtained.

If your study is funded by an external agency, please retain this letter as documentation of the IRB's determination regarding your proposal.

If you have any questions about the information in this letter, please contact the IRB administrative staff. A full listing of staff members and contact information can be found on our website: http://www.irb.upenn.edu

***This letter constitutes official University of Pennsylvania IRB correspondence. ***

University of Pennsylvania Research Study Summary for Potential Subjects

Protocol Title: Evaluation of SmartSleep Technology for Improving the Efficiency and Restorative Quality of Sleep in Healthy Adults in Order to Mitigate Cognitive Performance Deficits due to Sleep Restriction and Emergency Awakenings

Principal Investigator: David F. Dinges, M.S., M.A., Ph.D.; Phone: 215-898-9949
1013 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104
Emergency Contact: Matthew S. Kayser, M.D., Ph,D.; Phone: 267-972-7353

You are being invited to participate in a research study. Your participation is voluntary and you should only participate if you completely understand what the study requires and what the risks of participation are. You should ask the study team any questions you have related to participating before agreeing to join the study. If you have any questions about your rights as a human research participant at any time before, during or after participation, please contact the Institutional Review Board (IRB) at (215) 898-2614 for assistance.

The research study is being conducted to learn about how the SmartSleep technology (headband) affects cognitive performance of healthy adults undergoing conditions of chronic sleep restriction and awakenings from sleep – two common conditions in spaceflight that pose challenges to astronauts' performance. The study also aims to find the best SmartSleep settings for enhancing slow-wave sleep and cognitive performance. You are being asked to join this study because of your expressed interest and availability. In addition, you are within the desired age range (27-55 years old), you have an education level of at least a Bachelor's or Master's degree (or the equivalent work experience) in a relevant field, or have a history of military service, and you are free of psychological or psychiatric conditions that preclude participation.

If you agree to join the study, your participation will last for approximately 5 weeks, and will include:

- 2 days of screening roughly 3 weeks prior to the in-lab phase;
- a 21-day at-home phase;
- a 7-day/6-night period of continuously staying in the laboratory with an 8-hour baseline night of sleep, 4 nights of 5 hours of restricted sleep, followed by 10 hours of recovery sleep;
- another 7-day at-home phase; and
- a follow-up session roughly 1 week after completion of the in-lab phase.

There is no direct benefit to you from being in the study. The most common risks of participation are stress from repeatedly performing mental performance tests on a computer to ascertain cognitive performance; headache due to the amount of computer work; sleepiness from being asked to remain awake during many segments of the study; slight discomfort, skin irritation or pressure marks from sensitivity to wearing the SmartSleep headband and electrodes; and symptoms associated with non-restful sleep (e.g. fatigue, irritability, etc.) due to potential sleep disruption by the auditory stimulation.

Please note that there are other factors to consider before agreeing to participate such as additional procedures, use of your personal information, and other possible risks not discussed here. If you are interested in participating, a member of the study team will review the full information with you. You are free to decline or stop participation at any time during or after the initial consenting process. You will be compensated for your time and effort.

Title of the Research Study: Evaluation of SmartSleep Technology for Improving the Efficiency and Restorative Quality of Sleep in Healthy Adults in Order to Mitigate Cognitive Performance Deficits Due to Sleep Restriction and Emergency Awakenings

Protocol Number: 832679

Principal Investigator:
David F. Dinges, M.S., M.A., Ph.D.
1013 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104
215-898-9949
dinges@pennmedicine.upenn.edu

Co-Investigators:
Mathias Basner, M.D., M.Sc.
1019 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104
215-573-5866
basner@pennmedicine.upenn.edu

Alexander Stahn, Ph.D.
1015 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104
215-898-9666
astahn@pennmedicine.upenn.edu

Makayla Cordoza, Ph.D., R.N
1012 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104
215-898-9665
Makayla.cordoza@pennmedicine.upenn.edu

Study Coordinator:
Michele Carlin
1013 Blockley Hall
423 Guardian Drive
Philadelphia, PA 19104
215-898-9665
michele3@pennmedicine.upenn.edu

Emergency Contact:
Matthew S. Kayser, M.D., Ph.D.
267-972-7353
Matthew.Kayser@uphs.upenn.edu

You are being asked to take part in a research study. This is not a form of treatment or therapy. It is not supposed to detect a disease or find something wrong. Your participation is voluntary which means you can choose whether or not to participate. If you decide to participate or not to participate there will be no loss of benefits to which you are otherwise entitled. Before you make a decision you will need to know the purpose of the study, the possible risks and benefits of being in the study and what you will have to do if you decide to participate. The research team is going to talk with you about the study and give you this consent document to read. You do not have to make a decision now; you can take the consent document home and share it with friends, family doctor and family.

If you do not understand what you are reading, do not sign it. Please ask the researcher to explain anything you do not understand, including any language contained in this form. If you decide to participate, you will be asked to sign this form and a copy will be given to you. Keep this form; in it you will find contact information and answers to questions about the study. You may ask to have this form read to you.

What is the purpose of the study?
The purpose of this study is to learn more about how the SmartSleep technology affects cognitive performance of healthy adults undergoing conditions of chronic sleep restriction and emergency awakenings from sleep—two common conditions in spaceflight that pose challenges to astronauts' performance. The study also aims to find the best SmartSleep settings for enhancing slow-wave sleep and cognitive performance.

Why was I asked to participate in the study?
You are being asked to join this study because of your expressed interest and availability. In addition, you are within the desired age range (27–55 years old), you have an education level of at least a Bachelor's degree or Master's degree (or the equivalent work experience) in a relevant field or have a history of military service, and you are free of psychological or psychiatric conditions that preclude participation.

How long will I be in the study? How many other people will be in the study?
The study will be conducted over a period of approximately 5 weeks, including 2 days of screening ~3 weeks prior to the in-lab phase (each session lasting about 4 hours), a 21-day at-home phase, a 7-day/6-night period of continuously staying in the laboratory, another 7-day at-home phase, and a 2-hour follow-up session ~1 week after completion of the in-lab phase. Up to 3 other participants may be in the laboratory with you at all times (with individual sleeping rooms); however, if a participant withdraws or is withdrawn from the protocol, the study will continue with the remaining participants. The study will take place over a period of 2 years. We aim to recruit a total of 12 people (approximately 6 males and 6 females) as final participants to undergo the 7-day/6-night in-laboratory protocol.

Where will the study take place?
Screening session #1 will take place at our office in Blockley Hall, University of Pennsylvania School of Medicine near the Hospital of the University of Pennsylvania (HUP), and in the Center for Human Phenomic Science (CHPS) located in the Perelman Center for Advanced Medicine (PCAM). Screening session #2 will take place at our office in Blockley Hall and at the Chronobiology Isolation Lab (CIL), located at the Hospital of the University of Pennsylvania (HUP). The 7-day/6-night in-lab phase will take place in the CIL. The follow-up session will take place at our office in Blockley Hall. All the laboratory and screening sessions will be scheduled via phone call.

What will I be asked to do?
You will first be asked to complete two screening sessions (4 hours each) to determine your eligibility for this study. The actual in-laboratory phase of the study will be conducted over a 7-day/6-night period. If you complete the in-laboratory phase of the study, you will be asked to return for a follow-up session approximately 7 days later.

Screening session #1: You will first attend an initial 4-hour laboratory session for a confidential medical check which will include a blood draw (approximately 3 tablespoons), a urinalysis (approximately 1 ounce), and a series of questionnaires regarding your health and medical history, in order to determine your eligibility to participate in the study.

- In order to ensure that you are healthy and to determine your eligibility for the study, blood and urine samples will be drawn in the Center for Human Phenomic Science (CHPS), which is located in the Perelman Center for Advanced Medicine (PCAM). These samples will be used for determining the presence of HIV antibodies and other active infections, such as the cold or flu virus (from blood), and current use of stimulant or hypnotic (sleep promoting) drugs (from urine). We require an objective measure that you are free of these drugs using blood and urine samples. You will be asked to fast prior to the blood draw. This means that you should not eat or drink anything except prescription drugs and water for at least 10 hours before the visit.
- You will receive confidential results regarding your HIV antibody test. If you have a positive test, you will be offered counseling about HIV infection from a physician on our research team. Additionally, you will be referred to a physician and your positive test result will be reported to the PA Department of Health as required by law.
- If you are found to have an active virus in your blood, you will be told of the presence of the virus and you will be ineligible to participate in the study. You will, however, be compensated for your time up to that point of the screening process. See compensation section for rates for the screening period.
- You will have a physical examination, which will include a heart check-up (EKG) at the Center for Human Phenomic Science (CHPS).
- Also, during the initial screening session, you will be asked to complete a series of questionnaires about your usual attitudes, moods, and psychosocial wellbeing.
- You will receive an actiwatch (device worn on your wrist like a watch) and a diary (small booklets with an evening page and morning page) for completion at home.

Screening session #2: If you meet all of the initial screening eligibility criteria for the study, you will be scheduled for a second 4-hour screening session.
During the second screening session, you will complete the following:

- An additional blood and/or urine sample may be collected, if necessary;
- Review of actiwatch and diary logs with a staff member;
- Initial training related to the Cognition, Mini-Cognition and Spatial Cognition assessment tools (see in-laboratory procedures for more information);
- You will be scheduled for the 7-day in-laboratory phase of the study; and
- You will continue to wear the actiwatch and complete the diary booklet.

In-Laboratory Phase:

- The 7-day/6-night in-laboratory phase of the study will be carried out in the Chronobiology Isolation Lab (CIL), where you will remain in an isolated environment with up to three other subjects.
- You will not be able to attend work or classes remotely. The environment you will live in during the in-laboratory phase will be shielded from external influences. You will not be allowed to have any visitors, and you will not be able to make or receive any telephone calls (except in case of an emergency). You will not be able to wear a regular watch or fit bit, use your cell phone, make/receive phone calls, texts, or e-mails, or perform any work on a personal laptop or handheld device.
- You will be provided with 3 meals/day, an optional light meal in the evening, and you will have access to snacks throughout the day. You will have to refrain from caffeine and alcohol. Throughout the in-laboratory phase, we will schedule your daily activities and a trained staff member will be present to monitor your activities.
- During the entire 7-day/6-night in-laboratory session, a trained staff member will be present to monitor your activities and help keep you awake. You will be expected to complete various computerized tasks and surveys. In between the performance testing, you will be free to engage in leisurely activities (i.e., reading books or magazines, completing puzzle books, writing, conversing with other participants, watching television), but you must stay in the laboratory.
- During the entire 7-day/6-ngiht in-laboratory session, you will be monitored via audio recordings and video cameras. In order to maintain your privacy, your activity will not be monitored in the restroom area.
- Sleep Conditions: During the first night (baseline) of the 7-day in-laboratory session, you will get an 8-hour sleep opportunity, in which your bedtime will be 11 pm and you will get up at 7 am. Following this adaptation night of sleep, you will have 4 consecutive nights of sleep restriction (time in bed limited to 5 hours), in which your bedtime will be 11 pm and your wake-time will be 4 am. Finally, you will receive one night of 10 hours of recovery sleep, in which your bedtime will be 10 pm and you will get up at 8 am.

- SmartSleep Technology: On each of the in-lab nights, you will be asked to wear a device that looks like a headband, called the SmartSleep device. It uses two small EEG sensors to detect and record brain activity during slow-wave sleep, a special kind of restorative sleep rhythm. The device will, on some nights, deliver soft tones that are supposed to help increase slow-wave sleep and enhance overall sleep quality. The tones will be delivered at different frequencies (~65 dB/no louder than a normal speaking voice) and sub-awareness volumes on different nights and the tones are not expected to disturb your sleep.
- Daily Tasks: During the 7-day in-laboratory phase, you will complete three different neurocognitive test batteries (Cognition, Mini-Cognition, and Spatial Cognition). The computer will administer tests and questions to you. These tests measure cognitive ability and performance, including memory, tracking, and reaction time. Also, you will be asked to make a number of different ratings about your feelings, mood, and attitudes.
    1. **The Mini-Cognition test battery** consists of four measures –the Brief Psychomotor Vigilance Test (PVT-B), which assesses behavioral alertness and psychomotor speed; the Digit Symbol Substitution Test (DSST), which assesses cognitive processing; and the Emotional Recognition Task (ERT), which gauges emotional processing. The Mini-Cognition test battery will always be preceded by the Descending Subtraction Test (DST), which measures working memory performance. In addition, there will be a few brief surveys at the end, which will assess mental fatigue, tiredness, physical exhaustion, level of stress, sleep quality, and sleepiness. You will complete this throughout the day on all study days, in addition to multiple times on the mornings of the early awakening in order to assess how cognitive performance changes during the first few hours after an early awakening.
    2. **Cognition** is a brief, comprehensive computerized neuroimaging-based test battery for spaceflight that is validated for astronauts. It will measure performance levels on 10 neuropsychological tests that cover a range of cognitive domains (including memory, emotion recognition, and risk decision making). It will always be preceded by the Descending Subtraction Test (DST), which measures working memory performance. You will complete this test on a daily basis, multiple times a day.
    3. **Spatial Cognition** is a neurocognitive test that contains tasks that are critical in terms of the requirements for long-duration exploratory missions (e.g. navigating on Mars), but they also provide precise behavioral information of the underlying circuitry that is expected to be affected by the social support system. You will complete this test on a daily basis.

  In addition, you will complete some surveys once daily during the 7-day in-lab portion of the study (roughly 45 minutes total), including the following questionnaires:
    1. Positive and Negative Affect Schedule (PANAS) as a measure of affect.
    2. Profile of Mood States Short Form (POMS-SF) as a measure of mood states.
    3. Beck Depression Inventory (BDI-II) as a measure of depression.
    4. Beck Anxiety Inventory (BAI) as a measure of anxiety.
    5. Visual Analog Scale (VAS) as a measure of mental fatigue, tiredness, physical exhaustion, level of stress, sleep quality, and sleepiness.

Finally, you will be required to complete several other computerized simulation tasks (Six Degrees of Freedom, ROBoT, and the Lunar Lander Simulator). You will complete these tests once a day, and you will be recorded on a visual/audio tape for later analysis.

1. The **Six Degrees of Freedom Docking** simulation task is a high fidelity docking simulation task which consists of a series of docking flight tasks of varying skill level that have both dynamic and informational equivalence to real docking maneuvers.
2. The **Robotic On-Board Trainer (ROBoT)** is NASA's platform for training astronauts to perform docking and grappling maneuvers using the Canada Arm. The system is based on highly realistic 3D simulations of the arm and associated physics.
3. The **Lunar Landing Simulator** will require you to operate the terminal descent phase of a lunar landing. To complete the landing, there is a primary flight display, landing display, and automatic and manual control modes.

- Physiologic Monitoring: We will monitor your heart using a continuous heart rate monitor (high-frequency Heart Rate Variability [HF-HRV] measuring device) that you will wear continuously throughout the study, except when showering.
- You will continue to wear the actiwatch during the in-laboratory phase of the study.

After In-Laboratory Phase:

- You will receive an actiwatch (device worn on your wrist like a watch) and a diary (small booklets with an evening page and morning page) for completion at home for 1 week following the 7-day in-laboratory phase.
- After this 1 week at-home phase, you will return for a follow-up session to return the actiwatch and diary, as well as to discuss your experience in the study.

What are the risks?

1. While in the study, you will be required to perform a variety of mental performance tests on a computer. These tests can become difficult to perform under certain acute stressors or when you are sleepy and may, therefore, cause you some distress. As the tests become more difficult to perform, you will be asked to maintain your best effort to perform them to the best of your ability and to accept that your performance may be lower than you would like. Should you feel that you are unable to perform these tasks during the course of the study, you are free to withdraw your consent to participate in this experiment and then sleep in the laboratory, if needed.
2. You may experience some discomfort associated with the collection of the blood samples, including possible bruising of the arm, dizziness, fainting, and a small risk of infection.
3. There is the potential that you may develop a headache during the study due to the amount of computer work.
4. You may become sleepy during some segments of the study when you are asked to remain awake. This experience is similar to that of a shift worker when he/she works the night shift. A member of the staff will be available at all times to assist you in remaining awake. There may be times during these segments of the study when you will be asked to interact with a

staff member to avoid falling asleep. Should you feel that you are unable to remain awake, you are free to withdraw your consent to participate in this experiment and then go to sleep in the laboratory. There are no known lasting adverse effects from missing nighttime sleep.

5. You will be seated throughout most of the waking periods spent inside the laboratory, which may cause some muscular pain. If this sustains even after making slight changes in body position or using a cushion, you should notify the staff. A heating pad may be used, and if necessary, the research physician would be notified to discuss other potential remedies.
6. There is the possibility that you may develop some stomach discomfort due to the lack of physical activity.
7. Measuring heart activity (high-frequency Heart Rate Variability [HF-HRV]) involves minor risks. The device (electrocardiogram [ECG]) used to monitor heart rate is electrically isolated and conforms to hospital standards for electrical safety. The sticker used to attach the electrodes may cause some minor discomfort and/or skin irritation.
8. The application of the headband of the SmartSleep device may include slight discomfort caused by skin abrasions or irritation from sensitivity to some of the materials. Some discomfort may occur due to pressure of the headband on ears. Red marks or pressure marks should go away within 1 hour of removing the device. The headband can be adjusted for comfort or to reduce pressure.
9. There may some minor skin irritation and redness from abrasive scrub used to prepare the skin for the SmartSleep electrodes and the tape used to attach the electrodes. Therefore, there may be some discomfort with the application or removal of the electrodes from the scalp, including skin abrasions, blisters, tape irritation, and unpleasant odor.
10. There are no known risks associated with the auditory stimulation, which consists of low intensity brief tones (softer than a telephone dial tone) delivered by the headphones attached to the SmartSleep device. However, there may be mild discomfort or slight difficulty sleeping while wearing the sensors and SmartSleep device.
11. There is a chance that sleep will be disrupted by the stimulation. We expect that this will not be noticeable for most people, but some individuals may feel less rested the next morning which can cause symptoms associated with non-restful sleep; fatigue, daytime sleepiness, concentrating difficulties, or irritability.
12. There is minimal risk associated with videotaping subjects during the study. There is a possible risk of a loss of confidentiality in very rare circumstances. As the data collection and analysis for this study will continue, the tapes (with no personal identification) will be kept in a secure location. Access to these tapes will be restricted to the Principal Investigator, his staff, the University of Pennsylvania IRB, and the granting body (NASA).
13. As a volunteer subject in this research study, you are not considered a patient at the Hospital of the University of Pennsylvania. During the 6 nights (7 days) in the laboratory for this study, you will be staying overnight in a clinical research facility. In the unlikely event that you should require emergency hospital treatment during your stay in our research facility, located within the Hospital of the University of Pennsylvania, there will be a resident emergency physician on call who may be summoned for part of your medical care.

14. The investigators reserve the right to terminate your participation in the study at any time if they feel it is necessary for your welfare or for research purposes.
15. It is possible that during the course of the research study, the research staff may notice an unexpected finding(s). Should this occur, the finding(s) will be considered by the appropriate personnel and the PI will inform you if necessary. These possible finding(s) may or may not be significant and may lead to anxiety about your condition and to further work-up by your physician.

What if new information becomes available about the study?
During the course of this study, we may find more information that could be important to you. This includes information that, once learned, might cause you to change your mind about being in the study. We will notify you as soon as possible if such information becomes available.

How will I benefit from the study?
There is no benefit to you; however, your participation could help us understand how SmartSleep technology affects the cognitive performance of healthy adults with chronic sleep restriction. This is common in spaceflight and poses challenges to optimal performance in astronauts. The study also aims to find the optimal settings for enhancing slow-wave sleep and cognitive performance using SmartSleep, which may be used to improve astronauts' responses to emergencies during spaceflight. In the future, these discoveries might be applied beyond the benefits of human space exploration in ways which could benefit you indirectly. For example, these discoveries might help other people working with sleep restriction in high-performing jobs, such as emergency responders.

What other choices do I have?
Your alternative to being in the study is not to be in the study.

What happens if I do not choose to join the research study?
You may choose to join the study or you may choose not to join the study. Your participation is voluntary. There is no penalty if you choose not to join the research study. You will lose no benefits or advantages that are now coming to you, or would come to you in the future.

When is the study over? Can I leave the study before it ends?
The study is expected to end after all participants have completed all visits and all the information has been collected. The study may be stopped without your consent for the following reasons:

- The Principal Investigator feels it is best for your safety and/or health-you will be informed of the reasons why;
- You have not followed the study instructions;
- The Principal Investigator, the sponsor or the Office of Regulatory Affairs at the University of Pennsylvania can stop the study anytime.

You have the right to drop out of the research study at any time during your participation. There is no penalty or loss of benefits to which you are otherwise entitled if you decide to do so.

If you no longer wish to be in the research study, please contact Michele Carlin at 215-898-9665 and simply inform her that you would no longer like to participate.

Once you are in the 7-day in-laboratory phase of the study, you may decide to withdraw from the study at any time by communicating your desire to a study team member in mission control. If you elect to withdraw your consent, the study coordinator, PI and physician of record will be notified immediately and will make direct contact with you (via phone or in person). In addition, you may be withdrawn from the study at any time if the PI or physician of record determines that it is not in your best interest to continue. If necessary, the physician of record will speak directly with you to provide additional services or information. In the event you withdraw/are withdrawn from the study, the rest of the research participants will continue with the study protocol.

How will confidentiality be maintained and my privacy be protected?
We will do our best to make sure that the personal information obtained during the course of this research study will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

If you test positive for HIV or Hepatitis C, by law we have to report the infection to the City of Philadelphia Health Department/PA Department of Health. We would report your name, gender, racial/ethnic background, and the month and year you were born. This is to keep track of how many people in the U.S. have HIV infection. It is also to make sure that states get enough money from the federal government to support the medical care of people living with HIV. The Health Department does not share the names of HIV infected people with anyone else. It removes all personal identifiers, such as your name, before giving information on the number of HIV infections to the federal government.

The Institutional Review Board (IRB) at the University of Pennsylvania is responsible for protecting the rights and welfare of research volunteers like you; and therefore, the IRB has access to study information. Any documents you sign, where you can be identified by name will be kept in a locked cabinet in the research office located in Blockley Hall, University of Pennsylvania Perelman School of Medicine. These documents will be kept confidential. Confidentiality will be maintained by giving you a study code and all your study information will relate to this number. However, identifiers might be removed from your identifiable private information or identifiable biospecimens and that, after removal, could be used for future research studies or distributed to another investigator for future studies without additional informed consent.

You will be audio-recorded and videotaped throughout the mission. There are no cameras in the restrooms, but they are located in all other spaces of the Chronobiology Isolation Lab (CIL). You will be made aware of the recording devices that will be on for the entirety of the mission. By signing this consent form, you will be acknowledging that you have been informed of and agree to the presence and use of the devices in the study. You will not be asked questions in a public setting. The surveys and questionnaires will take place online through the use of a personal tablet or laptop provided by the study. These can be done in the privacy of your sleeping quarters. The

written daily log can also be completed in the privacy of your rooms if you so choose. This combined Informed Consent form and HIPAA Authorization will be completed prior to the study stating that you were informed about your personal protections.

You will be able to sign your consent form after an individual meeting where you will be able to ask any questions you may have to a member of the research team. There is no time limit to this session, which will be held in a private room.

Electronic Medical Records and Research Results:

What is an Electronic Medical Record?
An Electronic Medical Record (EMR) is an electronic version of the record of your care within a health system. An EMR is simply a computerized version of a paper medical record.

A clinical trial management system (CTMS) is used to register your information as a participant in a study and to allow for your research data to be entered/stored for the purposes of data analysis and any other required activity for the purpose of the conduct of the research.

If you are receiving care or have received care within the University of Pennsylvania Health System (UPHS) (outpatient or inpatient) and are participating in a University of Pennsylvania research study, we will use your existing medical record to register you as a research participant. If you have never received care within UPHS and are participating in a University of Pennsylvania research study that uses UPHS services, an EMR will be created for you for the purpose of maintaining any information produced from your participation in this research study. The creation of this EMR is required for your participation in this study. In order to create your EMR, the study team will need to obtain basic information about you that would be similar to the information you would provide the first time you visit a hospital or medical facility (i.e. your name, the name of your primary doctor, the type of insurance you have). We will only include the information which relates to medical care (health history and physical assessment, EKG, notes from the CHPS research nurses) and laboratory results from the screening sessions in your EMR.

Once placed in your EMR or in the CTMS, your information may be accessible to appropriate UPHS workforce members that are not part of the research team. Information within your EMR may also be shared with others who are determined by UPHS to be appropriate to have access to your EMR (e.g. health insurance company, disability provider, etc.).

What happens if I am injured from being in the study?
If you are injured and/or feel emotional discomfort while participating in the study you may contact the Principal Investigator or the emergency contact name on the first page of this form. Also, you may contact your own doctor, counselor or seek treatment outside of the University of Pennsylvania. Bring this document, and tell your doctor/counselor or his/her staff that you are in a research study being conducted at the University of Pennsylvania. Ask them to call the numbers on the first page of this form for information.

If you are injured and/or feel emotional discomfort from being in the study, the appropriate care will be provided without cost to you, but financial compensation is not otherwise available from the University of Pennsylvania. If you are injured and/or feel emotional discomfort while in the study but it is not related to the study, you and your insurance company will be responsible for the costs of that care.

Will I have to pay for anything?
There are no costs associated with participating in the study. Transportation to and from the research office and parking for screening sessions will be compensated. Participation in the study will be compensated (see below).

Will I be paid for being in this study?
If you complete the entire study, we will pay you approximately $1156 via a Greenphire ClinCard. The total amount may vary depending on how much of each study component you complete. The amounts you will receive for completing each section of the study are as follows:

- $40 for two screening visits (at $20 each);
- $42 for up to 21-day at-home pre-mission phase;
- $900 for the 6-night/7-day in-lab phase ($150 for six 24-hour in-lab period);
- $10 for the follow-up session;
- $14 for the 7-day at-home post-mission phase; and
- $150 bonus for completing the entire study.

In addition, you will be compensated for public transit to and from screening sessions and the study, or for parking during screening sessions. If you decide to withdraw from the study before the study is over, you will be fully compensated for your participation up to the point you chose to withdraw.

Please note that if you receive more than $600 compensation in one year for participation in research studies at the University of Pennsylvania, you must have an Individual Tax Identification Number or Social Security Number for tax purposes.

What information about me may be collected, used or shared with others?
The following personal health information will be collected, used for research, and may be disclosed during your involvement with this research study:

- Name, address, telephone number, date of birth;
- Personal and family medical history;
- Psychiatric history;
- Current and past medications and therapies;
- Social Security Number;
- Medical Record number;
- Information from a health history and physical examination that generally also includes blood pressure reading, heart rate, breathing rate and temperature; and
- Results of screening tests and CHPS nursing notes.

As a reminder of study appointments, some subjects prefer to have a contact via email. While email serves many purposes, email accounts are considered identifiable information and therefore the study staff is requesting permission to contact you via your email account. You have the right to not receive any study-related information via email.

Do you agree to receive emails to the email account of your choice with regards to study related items (i.e. appointment reminders, check-in's, etc.)?

____ Yes ____ No

Why is my information being used?
Your information is used by the research team to contact you during the study. Your information and results of tests and procedures are used to:

- Do the research;
- Oversee the research;
- To see if the research was done right.

Who may use and share information about me?
The following individuals may use or share your information for this research study:

- Dr. David Dinges, the Principal Investigator for the study and his study team;
- The University of Pennsylvania Institutional Review Boards (the committees charged with overseeing research on human subjects) and University of Pennsylvania Office of Regulatory Affairs;
- The University of Pennsylvania Office of Human Research (the office which monitors research studies);
- Authorized members of the University of Pennsylvania and the University of Pennsylvania Health System and School of Medicine workforce who may need to access your information in the performance of their duties (for example: to provide treatment, to ensure integrity of the research, accounting or billing matters, etc.).

Who, outside the School of Medicine, might receive my information?
<u>Individuals or organizations responsible for administering the study:</u>

- University of Pennsylvania

<u>Regulatory and safety oversight organizations:</u>

- The Office of Human Research Protections
- NASA (funding organization)

Other academic or industry partners who may collaborate on this project:
If samples or data collected through this project are shared with collaborators outside of Penn, direct identifiers such as your name or medical record number will not be shared. Other regulatory agencies, quality assurance and/or quality control auditors, and/or their designated representatives in the United States and other countries.

Once your personal health information is disclosed to others outside the School of Medicine, it may no longer be covered by federal privacy protection regulations. The Principal Investigator or study staff will inform you if there are any additions to the list above during your active participation in the trial. Any additions will be subject to University of Pennsylvania procedures developed to protect your privacy.

How long may the School of Medicine use or disclose my personal health information?
Your authorization for use of your personal health information for this specific study does not expire.

Your information may be held in a research database; however, the School of Medicine may not reuse or re-disclose information collected in this study for a purpose other than this study unless:

- You have given written authorization;
- The University of Pennsylvania's Institutional Review Board grants permission after ensuring that appropriate privacy safeguards are in place as permitted by law.

Can I change my mind about giving permission for use of my information?
Yes. You may withdraw or take away your permission to use and disclose your health information at any time. You can do this by sending a written notice to the research doctor at the address on page 2 of this form. If you withdraw your permission, the research doctor will no longer use or disclose (share) your Personal Health Information under the Authorization for the Study, unless the study doctor needs to use or disclose some of your Personal Health Information to preserve the scientific integrity of the study. Information collected before you cancel this Authorization may still be used by the researchers.

If you do not sign this Authorization, you cannot participate in the study. If you cancel this Authorization in the future, you will no longer be able to participate in the study.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to participate in this research study.

Who can I call with questions, complaints or if I'm concerned about my rights as a research subject?
If you have questions, concerns or complaints regarding your participation in this research study or if you have any questions about your rights as a research subject, you should speak with the Principal Investigator listed on page one of this form. If a member of the research team cannot be reached or you want to talk to someone other than those working on the study, you may contact the Office of Regulatory Affairs with any question, concerns or complaints at the University of Pennsylvania by calling 215-898-2614.

Signature agreement for the subject and person obtaining consent:
When you sign this document, you are agreeing to take part in this research study. If you have any questions or there is something you do not understand, please ask. You will receive a copy of this consent document.

Signature of Subject: _____

Print Name of Subject: _____

Date/Time: _____

Name of Person Obtaining Authorization: _____

Signature of Person Obtaining Authorization: _____

Date/Time: _____