Published in final edited form as:
Acta Astronaut. 2012 ; 77: 207–213. doi:10.1016/j.actaastro.2012.04.002.

Predicting Risk in Space: Genetic Markers for Differential Vulnerability to Sleep Restriction

Namni Goel, PhD and **David F. Dinges, PhD**
Division of Sleep and Chronobiology, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, 19104, USA

Abstract

Several laboratories have found large, highly reliable individual differences in the magnitude of cognitive performance, fatigue and sleepiness, and sleep homeostatic vulnerability to acute total sleep deprivation and to chronic sleep restriction in healthy adults. Such individual differences in neurobehavioral performance are also observed in space flight as a result of sleep loss. The reasons for these stable phenotypic differential vulnerabilities are unknown: such differences are not yet accounted for by demographic factors, IQ or sleep need, and moreover, psychometric scales do not predict those individuals cognitively vulnerable to sleep loss. The stable, trait-like (phenotypic) inter-individual differences observed in response to sleep loss—with intraclass correlation coefficients accounting for 58%-92% of the variance in neurobehavioral measures—point to an underlying genetic component. To this end, we utilized multi-day highly controlled laboratory studies to investigate the role of various common candidate gene variants—each independently—in relation to cumulative neurobehavioral and sleep homeostatic responses to sleep restriction. These data suggest that common genetic variations (polymorphisms) involved in sleep-wake, circadian, and cognitive regulation may serve as markers for prediction of inter-individual differences in sleep homeostatic and neurobehavioral vulnerability to sleep restriction in healthy adults. Identification of genetic predictors of differential vulnerability to sleep restriction—as determined from candidate gene studies—will help identify astronauts most in need of fatigue countermeasures in space flight and inform medical standards for obtaining adequate sleep in space. This review summarizes individual differences in neurobehavioral vulnerability to sleep deprivation and ongoing genetic efforts to identify markers of such differences.

Keywords

genetics; individual differences; neurobehavioral performance; sleep duration; sleep homeostasis; sleep deprivation

*Corresponding author: Namni Goel, Ph.D., Associate Professor, Division of Sleep and Chronobiology, Unit for Experimental Psychiatry, Department of Psychiatry, University of Pennsylvania Perelman School of Medicine, 1017 Blockley Hall, 423 Guardian Drive, Philadelphia, PA 19104-6021. Phone, 1-215-898-1742; Fax, 1-215-573-6410; goel@mail.med.upenn.edu.

The authors declare no conflicts of interest.

1. Prevalence and Consequences of Sleep Loss in US Population

There is extensive scientific literature demonstrating that adequate sleep quantity and quality are essential for maintenance of performance capability and for healthy neurobehavioral functioning [1,2]. It is estimated that 20% to 40% of the adult US population sleep less than 7 hours per night [3]—the minimum sleep duration necessary to prevent cumulative deterioration in performance on a range of cognitive tasks [4,5]. The proportion of individuals curtailing their sleep due to lifestyle is increasing [3] and is likely higher than surveys indicate, since physiological sleep duration is typically at least one hour less than self-reported sleep duration [6,7]. Moreover, sleep loss has become a significant public health concern as population studies have found that reduced sleep duration (less than 7 hours) is associated with increased risks of obesity, morbidity, and mortality [8-10].

Sleep loss, including chronic partial sleep deprivation (PSD) or sleep restriction—a condition experienced by millions of people on a consecutive and daily basis—can result from medical conditions, sleep disorders, work demands, stress/emotional distress, and social/domestic responsibilities [3]. In addition, for the majority of people, sleep loss directly causes significant risks via increased fatigue and sleep propensity, and via deficits in mood and neurocognitive functions including vigilant and executive attention, cognitive speed and working memory, and executive functions [1,3,11].

1.1. Sleep Loss in Space

In addition to its prevalence in the general adult population, disturbed sleep quality and reduced sleep duration are common in space operations [12-14]. Such loss in astronauts has been attributed to operational factors that include the following: high workload; shift work; altered light-dark cycles; performance of critical operational tasks [15-17]; space adaptation syndrome; motion sickness; noise and vibration; movement of other astronauts; excitement; stress; and ambient temperature [16-20].

NASA has determined that a number of factors in space flight—especially work-rest schedules—disrupt and shorten sleep, producing acute sleep loss (e.g., for slam shifts) and chronic partial sleep loss [12]. NASA evidence-based reviews [13] have concluded that such decrements pose a clear risk to operational performance during long-duration space flight, and to behavioral health and psychosocial functions. An Institute of Medicine panel assessed NASA HRP's evidenced-based reviews and concurred with the importance of mitigating the risks posed by fatigue, and noted that individual differences in the effects of sleep loss and fatigue on human performance are important considerations [21]. Thus, biomarkers are needed to predict large individual differences in fatigue and neurobehavioral decrements in response to fatiguing conditions in spaceflight.

Moreover, the identification and validation of such markers of susceptibility to stress, fatigue and neurobehavioral decrements potentially associated with long-duration spaceflight must be a priority, in order to personalize and optimize the use of countermeasures to prevent these conditions during prolonged spaceflight. The search for such markers is consistent with the current medical emphasis on “personalized medicine,” which seeks to maximize health of individuals through the systematic use of genetic or other biomarker information to optimize preventative and therapeutic care. Such markers are therefore a component of effective countermeasure utilization in spaceflight.

2. Stable Phenotypic Individual Differences in Response to Sleep Loss

Our laboratory was the first to experimentally demonstrate that subjects undergoing acute total sleep deprivation (TSD)—in which no sleep is obtained—show differential

vulnerability to sleep loss, demonstrating robust inter-individual (trait-like, phenotypic) differences in response to the same laboratory conditions, as measured by various physiological and subjective sleep measures and neurobehavioral tasks sensitive to sleep loss [22,23]. The intraclass correlation coefficients (ICCs)—which express the proportion of variance in the data explained by systematic interindividual variability—revealed that stable responses accounted for 58% and 68% of the overall variance in Psychomotor Vigilance Test (PVT) lapses (greater than 500 ms reaction times) between multiple sleep-deprivation exposures in the same subjects [4,23-25]. Thus, individuals who showed high PVT lapse rates during TSD after one exposure also showed high PVT lapse rates during a second exposure; similarly, those with low PVT lapse rates during one exposure showed low PVT lapse rates during a second exposure. Most importantly, because these high ICCs were found when the subjects were exposed to TSD 2-3 times under markedly different conditions (e.g., high versus low stimulation [24]; 6 h versus 12 h sleep time per night [22]), the vast differences in cognitive vulnerability to sleep deprivation are considered trait-like. While some individuals are highly vulnerable to cognitive performance deficits when sleep deprived (Type 3 responses), others show remarkable levels of cognitive resistance to sleep loss (Type 1 responses), and others show intermediate (Type 2) responses [23,26].

Other researchers have confirmed our findings of large, stable differences in cognitive responses to acute TSD [27,28]. Notably, such differences have not been accounted for by baseline functioning, by circadian morningness-eveningness (chronotype), by demographic factors (e.g., age, sex, IQ), or by habitual sleep timing; psychometric scales also have not reliably identified cognitively vulnerable individuals [4,22,25]. Our group [4,29-31] and others [32] have found similar differential vulnerability to chronic PSD, in which sleep is restricted to 3-7 hours time in bed per night.

It is important to recognize that the stable variance accounted for by individual differences in the magnitude of cognitive changes with sleep deprivation is often considerable and comparable to, or larger than, the effect sizes of many experimental and clinical interventions. Moreover, the differential effects are found even in healthy adults who sleep the same duration each night and otherwise have comparable normal cognitive capability when not sleep deprived [22,27]. Finding biomarkers for these large and stable cognitive differences in response to sleep deprivation would be a substantial advance in understanding their possible origins and in harnessing the predictability of them for operational scenarios including space. Such identification may also permit a greater utilization of personnel and resources in space and other work and operational settings.

3. Genetic Markers of Differential Vulnerability to Sleep Loss

The stable, trait-like inter-individual differences observed in response to acute TSD— with intraclass correlation coefficients accounting for 58%-92% of the variance in neurobehavioral measures [22,23]—point to an underlying genetic component. Until recently, however, the genetic basis of such differential vulnerability to sleep loss in normal healthy subjects has received little attention [1,33]. Available recent data suggest that common genetic variations (polymorphisms) involved in sleep-wake, circadian, and cognitive regulation may underlie symptomatic aspects of these large inter-individual differences in neurobehavioral vulnerability to sleep deprivation in healthy adults [1,33-35]. Specifically, we used laboratory studies to investigate the role of five common candidate gene variants [*PERIOD3 (PER3), DQB1*0602,* catechol-O-Methyltransferase *(COMT),* Circadian Locomotor Output Cycles Kaput (*CLOCK*), and prepro-hypocretin/prepro-orexin (*HCRT*)]—each independently—in relation to cumulative neurobehavioral and sleep homeostatic responses to sleep restriction. These and other relevant genetic biomarker findings are reviewed below.

3.1. *PERIOD3* VNTR Polymorphism: Role of a Circadian Gene in Differential Vulnerability to Acute TSD and Chronic PSD

Three related studies investigated the role of the variable number tandem repeat (VNTR) polymorphism of the circadian gene *PERIOD3* (*PER3*)—which shows similar allelic frequencies in African Americans and Caucasians [36,37] and is characterized by a 54-nucleotide coding region motif repeating in 4 or 5 units—in response to TSD using a small group of the same subjects specifically recruited for the homozygotic versions of this polymorphism. Compared with the 4-repeat allele ($PER3^{4/4}$; 14 subjects), the longer, 5-repeat allele ($PER3^{5/5}$; 10 subjects) was associated with higher sleep propensity including SWA in the sleep EEG both before and after TSD and worse cognitive performance, as assessed by a composite score of 12 tests, following TSD [38]. A subsequent report—using the same 24 subjects—clarified that the $PER3^{5/5}$ overall performance deficits were selective: they only occurred on certain executive function tests, and only at 2-4 hours following the melatonin rhythm peak, from approximately 6-8 am [39]. Such performance differences were hypothesized to be mediated by sleep homeostasis [38,39]. Another publication using the same subjects showed that $PER3^{5/5}$ subjects had more slow-wave sleep and elevated sympathetic predominance and a reduction of parasympathetic activity during baseline sleep [40]. These studies found no significant differences in the melatonin and cortisol circadian rhythms, *PER3* mRNA levels, or in a self-report morningness-eveningness measure [38,39], although another study using these same subjects found *PER3* expression and sleep timing were more strongly correlated in $PER3^{5/5}$ subjects [41].

A subsequent neuroimaging study found that 27 healthy subjects categorized according to homozygosity for the *PER3* VNTR genotype (15 $PER3^{4/4}$ subjects, 12 $PER3^{5/5}$ subjects) showed markedly different cerebral blood flow profiles using blood oxygenation level dependent functional magnetic resonance imaging (BOLD fMRI) and corresponding differences in vulnerability of executive function performance in response to TSD [42]. More studies examining the relationship of the neural mechanisms mediating trait-like differential vulnerability to sleep deprivation with selective candidate genes (beyond the *PER3* VNTR polymorphism) are warranted.

The *PER3* findings in TSD may not generalize to responses to chronic PSD. We recently evaluated whether the *PER3* VNTR polymorphism contributed to sleep homeostatic responses and cumulative neurobehavioral deficits during chronic PSD in $PER3^{4/4}$ (40% of our population), $PER3^{4/5}$ (49% of our population) and $PER3^{5/5}$ (11% of our population) healthy adults [29]. During chronic PSD, $PER3^{5/5}$ subjects had slightly but reliably elevated sleep homeostatic pressure as measured by NREM SWE compared with $PER3^{4/4}$ subjects. The $PER3^{4/4}$, $PER3^{4/5}$ and $PER3^{5/5}$ genotypes also demonstrated large, but equivalent cumulative increases in sleepiness and cumulative decreases in cognitive performance and physiological alertness, with increasing daily inter-subject variability in all genotypes. In contrast to the aforementioned data in TSD [38,39], the *PER3* VNTR variants did not differ on baseline sleep measures or in their physiological sleepiness, cognitive, executive functioning or subjective responses to chronic PSD. Thus, the *PER3* VNTR polymorphism does not appear to be a genetic marker of differential vulnerability to the cumulative neurobehavioral effects of chronic PSD. It remains possible, however, that the $PER3^{5/5}$ genotype may contribute to differential neurobehavioral vulnerability to acute TSD because it involves wakefulness at a specific circadian time in the early morning hours (6-8 am), when subjects in the PSD study were asleep [29].

3.2. *DQB1*0602 Allele* Predicts Interindividual Differences in Physiological Sleep Structure, Sleepiness and Fatigue in PSD

The human leukocyte antigen *DQB1*0602* allele, found in 12-38% of healthy adult sleepers in the general population, is closely associated with narcolepsy, a sleep disorder characterized by excessive daytime sleepiness, fragmented sleep, and shortened REM latency, although it is neither necessary nor sufficient for its development [43,44].

In one large study, *DQB1*0602* positive healthy sleepers showed shorter nighttime REM sleep latency, greater sleep continuity, and more REM sleep, but no differences in daytime sleepiness [43]. Positivity for *DQB1*0602* also was related to more sleep-onset REM sleep periods and greater REM sleep duration during naps [45]. Thus, *DQB1*0602* positive subjects displayed subclinical presentations of some sleep features that were reminiscent of narcolepsy.

We evaluated whether *DQB1*0602* was a novel marker of differential vulnerability to homeostatic, sleepiness and neurobehavioral deficits during chronic PSD in healthy sleepers positive and negative for *DQB1*0602* [30]. *DQB1*0602* positive subjects showed decreased sleep homeostatic pressure with differentially steeper declines, and greater sleepiness and fatigue during baseline. During chronic PSD, positive subjects displayed SWE elevation comparable to negative subjects, despite higher sleepiness and fatigue. *DQB1*0602* positive subjects also had more fragmented sleep during baseline and PSD and showed differentially greater REM sleep latency reductions and smaller stage 2 reductions, along with differentially greater increases in fatigue [30]. Both groups demonstrated comparable cumulative decreases in cognitive performance and increases in physiological sleepiness to chronic PSD, and did not differ on executive function tasks [30].

Thus, *DQB1*0602* associated with inter-individual differences in sleep homeostasis, physiological sleep, sleepiness and fatigue, but not cognitive responses, during baseline and PSD. *DQB1*0602* may be a genetic marker for predicting such individual differences in both basal (fully-rested) and sleep loss conditions; moreover, its positivity in healthy subjects may represent a continuum of some sleep-wake features of narcolepsy, though more research is needed. The influence of the *DQB1*0602* allele on sleep homeostatic and neurobehavioral responses has not yet been examined in healthy subjects undergoing acute TSD or replicated in an independent sample of individuals undergoing chronic PSD.

3.3. *Catechol-O-Methyltransferase (COMT) Val158Met* Polymorphism: Role of a Cognitive Gene in Differential Vulnerability to TSD and Chronic PSD

The valine158methionine (Val158Met) polymorphism of the *catechol-O-methyltransferase (COMT gene)*, replaces valine (*Val*) with methionine (*Met*) at codon 158 of the *COMT* protein. As a result of this common substitution, activity of the *COMT* enzyme, which modulates dopaminergic catabolism in the prefrontal cortex, is reduced 3-to-4-fold in *COMT Met* carriers compared with *Val* carriers, translating into more dopamine availability at the receptors and higher cortical dopamine concentrations [46]. This *COMT* polymorphism functionally predicts less efficient prefrontal cortex functioning and poor working memory performance in healthy subjects who have the high-activity *Val* allele [47-50].

In sleep and neurodegenerative disorders, the *COMT* Val158Met polymorphism has been linked to daytime sleepiness. *Val/Val* female narcoleptic patients fell asleep two times faster than the *Val/Met* or *Met/Met* genotypes during the multiple sleep latency test (MSLT) while the opposite was true for males [51]. *Met/Met* narcoleptic patients also showed more sleep onset REM periods during the MSLT while *Val/Val* subjects showed less sleep paralysis [51] and were more responsive to modafinil's stimulating effects [52]. *Met/Met* and *Val/Met*

Parkinson's disease subjects demonstrated higher subjective daytime sleepiness than *Val/Val* subjects [53].

In healthy men, the *COMT* Val158Met polymorphism also was associated with sleep physiology. In acute TSD, this polymorphism predicted interindividual differences in brain alpha oscillations in wakefulness and 11–13 Hz EEG activity in wakefulness, rapid-eye movement (REM) and non-REM sleep [54]. It also modulated the effects of the wake-promoting drug modafinil on subjective well-being, sustained vigilant attention and executive functioning, and on 3.0-6.75 Hz and >16.75 Hz activity in non-REM sleep, but was not associated with subjective sleepiness, slow-wave activity or slow-wave sleep changes in recovery sleep following TSD or at baseline [55,56].

We recently evaluated whether *COMT* Val158Met polymorphism contributed to cumulative neurobehavioral deficits and sleep homeostatic responses during chronic PSD in *Met/Met* (15% of our population), *Val/Met* (50% of our population) and *Val/Val* (35% of our population) healthy adults [31]. *MetMet* subjects had differentially larger declines in NREM SWE—the putative homeostatic marker of sleep drive—compared with *Val/Met and Val/Val* subjects. The genotypes did not differ significantly at baseline in demographic characteristics, habitual sleep, circadian phase, cognitive performance, or physiological or subjective sleepiness [31]. All genotypes demonstrated comparable cumulative decreases in cognitive performance, and increases in subjective and physiological sleepiness to chronic PSD, with increasing daily inter-subject variability. The genotypes also did not differ on executive function tasks. The *COMT* Val158Met polymorphism related to individual differences in sleep homeostatic, but not neurobehavioral, responses to chronic PSD [31]. Thus, the *COMT* Val158Met polymorphism may be a novel genetic marker for predicting such differential sleep responses resulting from sleep deprivation, though replication studies are needed.

3.4. Adenosine Genes: Role for Predicting Individual Differences and Response to Total Sleep Deprivation

Several studies have investigated the role of select adenosine-related candidate genes in individual differences and in response to acute TSD. Rétey et al. [57] found that the 22G→A polymorphism of the adenosine deaminase gene *(ADA)* was associated with enhanced slow-wave sleep and NREM SWA, contributing to interindividual variability in baseline sleep. Specifically, individuals with the *G/A* genotype (7 subjects) showed 30 minutes more slow-wave sleep than subjects with the *G/G* genotype (7 subjects) and consistent with this finding, SWA was higher in *G/A* than *G/G* subjects. This polymorphism also related to differential responses to TSD: individuals with the *G/A* genotype (about 13% of the population) showed poorer performance on the PVT, higher sleep pressure, increased sleepiness and reduced vigor [58].

This group also found that the c.1083T>C polymorphism of the adenosine A2A receptor gene *(ADORA2A)* related to objective and subjective differences in the effects of caffeine on NREM sleep after TSD, with the *C/C* genotype (32% of the population) showing particular sensitivity to disturbed sleep after caffeine [59]. The polymorphism also associated with individual differences in various measures of baseline EEG during sleep and wakefulness [57]. While promising, replication of these data in independent samples is needed; in addition, the role of these two genetic variants in response to chronic PSD has not yet been investigated.

3.5. Other Candidate Genes Relating to Response to Sleep Loss

The orexin-hypocretin system is involved in normal regulation of sleep and wakefulness and is disturbed in narcolepsy [60]. The *-909 C/T* polymorphism of the prepro-hypocretin/prepro-orexin (*HCRT*) gene is associated with an increased risk of sudden onset of sleep/sleep attacks in Parkinson's patients, although it is not associated with susceptibility to narcolepsy [61,62]. We found that the *HCRT -909 C/T* polymorphism associated with differences in sleep homeostasis (measured by SWE) during fully-rested baseline conditions and differences in physiological sleepiness (measured by the Maintenance of Wakefulness Test) and sleep structure during both basal and PSD conditions (Goel et al, unpublished). The *C/C* genotype (12% of our population) appears particularly buffered from the physiological, but not the cognitive performance effects of sleep restriction.

The *T3111C* polymorphism of *CLOCK,* a core circadian gene, has been associated with aspects of sleep, sleepiness, and morningness-eveningness in healthy adults [63-65] and with insomnia in bipolar disorder and major depressive disorder [66]. We found that the *CLOCK T3111C* polymorphism predicted individual differences in executive functioning performance on the Tower of London, which assesses planning and problem solving abilities, and sleepiness and mood differences during sleep loss, whereby *3111C* carriers (40% of our population) showed the deficits (Goel et al, unpublished). The *CLOCK T3111C* polymorphism may be a genetic marker for a cognitive-mood diathesis more so than a sleep-circadian diathesis, since it did not predict sleep homeostatic or circadian measures relative to PSD.

In summary, a number of common genetic polymorphisms involved in circadian, sleep-wake, and cognitive regulation appear to underlie inter-individual differences in basal (fully-rested) sleep parameters and homeostatic regulation of sleep in response to sleep loss (both chronic restriction and acute total sleep deprivation) in healthy adults.

4. Future Directions

Because of reported differences in behavioral, sleep homeostatic and physiological responses to chronic PSD and acute TSD [4,67,68], it is possible that specific candidate genes play different roles in the degree of vulnerability and/or resilience to the neurobehavioral and homeostatic effects of acute TSD and chronic PSD. In support of this possibility, and as reviewed above, we found that the *PERIOD3* VNTR polymorphism related to individual differences in sleep homeostatic (i.e., NREM SWE) but not neurobehavioral responses to chronic PSD [29]. This same genetic polymorphism has also been associated with individual differences in sleep homeostatic and executive performance responses to acute TSD [38,39]. In addition, we recently found that the *COMT* Val158Met polymorphism predicted individual differences in sleep homeostatic responses to chronic PSD [31], but such prediction has not been found to acute TSD [55]. Future studies are needed to explore this critical avenue of research and to determine predictors of those individuals most vulnerable to the neurobehavioral effects of both types of sleep loss.

Thus far, most candidate gene studies involving sleep physiological and neurobehavioral variables have used smaller sample sizes and typically have only examined homozygotic individuals. Larger sample sizes and assessment of phenotype-genotype relationships in both homozygous and heterozygous individuals are needed to definitively determine whether such candidate genes involved in regulation of sleep-wake, circadian and cognitive functions are associated with inter-individual neurobehavioral responses to sleep loss across an entire population. Moreover, replication of findings in independent samples is required to determine whether findings are reliable and are not due to chance. Finally, other genetic approaches, including dual candidate gene techniques and GWAS studies, are needed to

complement single candidate gene methods, for assessing individual differences at baseline as well as in response to sleep loss.

In upcoming years, we will continue to actively search for other potential genetic markers of basal sleep measures and of sleep homeostatic and neurobehavioral differential vulnerability to sleep deprivation. Among other advantages, identification of such markers will provide a viable means to determine astronauts and individuals in the general population who may need more who may need effective countermeasures (e.g., caffeine, naps, etc) early and repeatedly. Genetic markers may also identify those individuals who can tolerate longer periods with little or no sleep without developing the unstable cognitive performance found in more vulnerable individuals.

5. Conclusions

The impairing effects of sleep loss on a variety of neurobehavioral functions are well-established consequences of sleep deprivation. They include fatigue and sleepiness and unstable wakefulness; deficits in attention, working memory and executive functions; reduced mood-affect regulation; and increased accidents and injuries. However, there are substantial differences among people—including astronauts—in the extent to which they experience such deficits when sleep deprived. Common genetic variations (polymorphisms) involved in sleep-wake, circadian, and cognitive regulation may serve as markers for prediction of inter-individual differences in sleep homeostatic and neurobehavioral vulnerability to sleep restriction in healthy adults. Identification of such genetic predictors—as determined from candidate gene and other types of genetic studies—will help identify astronauts most in need of fatigue countermeasures in space flight and inform medical standards for obtaining adequate sleep in space.

Acknowledgments

The preparation of this manuscript was supported by the National Space Biomedical Research Institute through NASA NCC 9-58; NIH NR004281; and the Department of the Navy, Office of Naval Research (Award No. N00014-11-1-0361). These funding sources had no role in any aspect of the preparation of this manuscript.

References

1. Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. Semin Neurol. 2009; 29:320–339. [PubMed: 19742409]
2. Banks, S.; Dinges, DF. Chronic Sleep Deprivation. In: Kryger, MH.; Roth, T.; Dement, WC., editors. Principles and Practice of Sleep Medicine. 5th. Elsevier; Philadelphia: 2011. p. 67-75.
3. Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction in humans. J Clin Sleep Med. 2007; 3:519–528. [PubMed: 17803017]
4. Van Dongen HPA, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: Dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep. 2003; 26:117–126. [PubMed: 12683469]
5. Belenky G, Wesensten NJ, Thorne DR, Thomas ML, Sing HC, Redmond DP, Russo MB, Balkin TJ. Patterns of performance degradation and restoration during sleep restriction and subsequent recovery: A sleep-dose response study. J Sleep Res. 2003; 12:1–12. [PubMed: 12603781]
6. Silva GE, Goodwin JL, Sherrill DL, Arnold JL, Bootzin RR, Smith T, Walsleben JA, Baldwin CM, Quan SF. Relationship between reported and measured sleep times: The Sleep Heart Health Study (SHHS). J Clin Sleep Med. 2007; 3:622–630. [PubMed: 17993045]
7. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Self-reported and measured sleep duration: how similar are they? Epidemiology. 2008; 19:838–845. [PubMed: 18854708]
8. Krueger PM, Friedman EM. Sleep duration in the United States: A cross-sectional population-based study. Am J Epidemiol. 2009; 169:1052–1063. [PubMed: 19299406]

9. Ferrie JE, Shipley MJ, Cappuccio FP, Brunner E, Miller MA, Kumari M, Marmot MG. A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort. Sleep. 2007; 30:1659–1666. [PubMed: 18246975]
10. Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, Miller MA. Meta-analysis of short duration and obesity in children and adults. Sleep. 2008; 31:619–626. [PubMed: 18517032]
11. Lim J, Dinges DF. A meta-analysis of the impact of short-term sleep deprivation on cognitive variables. Psychol Bull. 2010; 136:375–389. [PubMed: 20438143]
12. NASA. Human Research Program Evidence Book. Houston: 2008.
13. Whitmire A, Leveton LB, Barger L, Brainard G, Dinges DF, Klerman E, Shea C. Risk of Performance Errors due to Sleep Loss, Circadian Desynchronization, Fatigue, and Work Overload. Evidence-based review by NASA Behavioral Health and Performance program, Johnson Space Center. 2009:85–117.
14. Mallis MM, DeRoshia CW. Circadian rhythms, sleep, and performance in space. Aviat Space Environ Med. 2005; 76:B94–B107. [PubMed: 15943202]
15. Culbertson, F. Testimony before the Committee on Science. U.S. House of Representatives; Washington, DC: 1997.
16. Dijk DJ, Duffy JF, Czeisler CA. Age-related increase in awakenings: impaired consolidation of non REM sleep at all circadian phases. Sleep. 2001; 24:565–577. [PubMed: 11480654]
17. Salnitsky, VP.; Gerasimovich, AA.; Guschin, VI. Psychological aspects, Institute for Biomedical Problems. State Research Center of Russian Federation; Moscow: 2000. p. 1-112.
18. Gundel A, Polyakov VV, Zulley J. The alteration of human sleep and circadian rhythms during spaceflight. J Sleep Res. 1997; 6:1–8. [PubMed: 9125693]
19. Monk TH, Buysse DJ, Billy BD, Kennedy KS, Willrich LM. Sleep and circadian rhythms in four orbiting astronauts. J Biol Rhythms. 1998; 13:188–201. [PubMed: 9615283]
20. Santy PA, Kapanka H, Davis JR, Stewart DF. Analysis of sleep on Shuttle missions. Aviat Space Environ Med. 1988; 59:1094–1097. [PubMed: 3202794]
21. Institute of Medicine. Review of NASA's human research program evidence books: A letter report. National Academies Press; Washington, DC: 2008. p. 1-100.
22. Van Dongen HPA, Baynard MD, Maislin G, Dinges DF. Systematic interindividual differences in neurobehavioral impairment from sleep loss: Evidence of trait-like differential vulnerability. Sleep. 2004; 27:423–433. [PubMed: 15164894]
23. Van Dongen HP, Maislin G, Dinges DF. Dealing with interindividual differences in the temporal dynamics of fatigue and performance: importance and techniques. Aviat Space Environ Med. 2004; 75:A147–A154. [PubMed: 15018277]
24. Dijkman M, Sachs N, Levine E, Mallis M, Carlin MM, Gillen KA, Powell JW, Samuel S, Mullington J, Rosekind MR, Dinges DF. Effects of reduced stimulation on neurobehavioral alertness depend on circadian phase during human sleep deprivation. Sleep Res. 1997; 26:265.
25. Van Dongen HPA, Dijkman MV, Maislin G, Dinges DF. Phenotypic aspect of vigilance decrement during sleep deprivation. Physiologist. 1999; 42:A–5.
26. Goel N, Dinges DF. Behavioral and genetic markers of sleepiness. J Clin Sleep Med. 2011; 7:S19–S21. [PubMed: 22003324]
27. Leproult R, Colecchia EF, Berardi AM, Stickgold R, Kosslyn SM, Van Cauter E. Individual differences in subjective and objective alertness during sleep deprivation are stable and unrelated. Am J Physiol Regulat Integr Comp Physiol. 2003; 284:R280–R290.
28. Frey DJ, Badia P, Wright KP Jr. Inter- and intra-individual variability in performance near the circadian nadir during sleep deprivation. J Sleep Res. 2004; 13:305–315. [PubMed: 15560765]
29. Goel N, Banks S, Mignot E, Dinges DF. PER3 polymorphism predicts cumulative sleep homeostatic but not neurobehavioral changes to chronic partial sleep deprivation. PLoS ONE. 2009; 4:e5874. [PubMed: 19516903]
30. Goel N, Banks S, Mignot E, Dinges DF. DQB1*0602 predicts interindividual differences in physiologic sleep, sleepiness and fatigue. Neurology. 2010; 75:1509–1519. [PubMed: 20975052]

31. Goel N, Banks S, Lin L, Mignot E, Dinges DF. Catechol-O-Methyltransferase Val158Met polymorphism associates with individual differences in sleep physiologic responses to chronic sleep loss. PLoS ONE. 2011
32. Bliese PD, Wesensten NJ, Balkin TJ. Age and individual variability in performance during sleep restriction. J Sleep Res. 2006; 15:376–385. [PubMed: 17118094]
33. Goel N. Genetics of sleep timing, duration and homeostasis in humans. Sleep Med Clin. 2011; 6:171–182. [PubMed: 23450791]
34. Landolt HP. Genotype-dependent differences in sleep, vigilance, and response to stimulants. Curr Pharm Des. 2008; 14:3396–3407. [PubMed: 19075716]
35. Landolt HP. Genetic determination of sleep EEG profiles in healthy humans. Prog Brain Res. 2011; 193:51–61. [PubMed: 21854955]
36. Nadkarni NA, Weale ME, von Schantz M, Thomas MG. Evolution of a length polymorphism in the human PER3 gene, a component of the circadian system. J Biol Rhythms. 2005; 20:490–499. [PubMed: 16275768]
37. Ciarleglio CM, Ryckman KK, Servick SV, Hida A, Robbins S, Wells N, Hicks J, Larson SA, Wiedermann JP, Carver K, Hamilton N, Kidd KK, Kidd JR, Smith JR, Friedlaender J, McMahon DG, Williams SM, Summar ML, Johnson CH. Genetic differences in human circadian clock genes among worldwide populations. J Biol Rhythms. 2008; 23:330–340. [PubMed: 18663240]
38. Viola AU, Archer SN, James LM, Groeger JA, Lo JC, Skene DJ, von Schantz M, Dijk DJ. PER3 polymorphism predicts sleep structure and waking performance. Curr Biol. 2007; 17:613–618. [PubMed: 17346965]
39. Groeger JA, Viola AU, Lo JC, von Schantz M, Archer SN, Dijk DJ. Early morning executive functioning during sleep deprivation is compromised by a PERIOD3 polymorphism. Sleep. 2008; 31:1159–1167. [PubMed: 18714788]
40. Viola AU, James LM, Archer SN, Dijk DJ. PER3 polymorphism and cardiac autonomic control: effects of sleep debt and circadian phase. Am J Physiol Heart Circ Physiol. 2008; 295:H2156–H2163. [PubMed: 18835917]
41. Archer SN, Viola AU, Kyriakopoulou V, von Schantz M, Dijk DJ. Inter-individual differences in habitual sleep timing and entrained phase of endogenous circadian rhythms of BMAL1, PER2 and PER3 mRNA in human leukocytes. Sleep. 2008; 31:608–617. [PubMed: 18517031]
42. Vandewalle G, Archer SN, Wuillaume C, Balteau E, Degueldre C, Luxen A, Maquet P, Dijk DJ. Functional magnetic resonance imaging-assessed brain responses during an executive task depend on interaction of sleep homeostasis, circadian phase, and PER3 genotype. J Neurosci. 2009; 29:7948–7956. [PubMed: 19553435]
43. Mignot E, Young T, Lin L, Finn L. Nocturnal sleep and daytime sleepiness in normal subjects with HLA-DQB 1*0602. Sleep. 1999; 22:347–352. [PubMed: 10341385]
44. Dauvilliers Y, Tafti M. Molecular genetics and treatment of narcolepsy. Ann Med. 2006; 38:252–262. [PubMed: 16754256]
45. Mignot E, Lin L, Finn L, Lopes C, Pluff K, Sundstrom ML, Young T. Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. Brain. 2006; 129:1609–1623. [PubMed: 16597649]
46. Tunbridge EM, Harrison PJ, Weinberger DR. Catechol-o-methyltransferase, cognition, and psychosis: Val158Met and beyond. Biol Psychiatry. 2006; 60:141–151. [PubMed: 16476412]
47. Savitz J, Solms M, Ramesar R. The molecular genetics of cognition: dopamine, COMT and BDNF. Genes Brain Behav. 2006; 5:311–328. [PubMed: 16716201]
48. Egan MF, Goldberg TE, Kolachana BS, Callicott JH, Mazzanti CM, Straub RE, Goldman D, Weinberger DR. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. Proc Natl Acad Sci USA. 2001; 98:6917–6922. [PubMed: 11381111]
49. Dickinson D, Elvevåg B. Genes, cognition and brain through a COMT lens. Neuroscience. 2009; 164:72–87. [PubMed: 19446012]
50. Barnett JH, Jones PB, Robbins TW, Müller U. Effects of the catechol-O-methyltransferase Val158Met polymorphism on executive function: a meta-analysis of the Wisconsin Card Sort Test in schizophrenia and healthy controls. Mol Psychiatry. 2007; 12:502–509. [PubMed: 17325717]

51. Dauvilliers Y, Neidhart E, Lecendreux M, Billiard M, Tafti M. MAO-A and COMT polymorphisms and gene effects in narcolepsy. Mol Psychiatry. 2001; 6:367–372. [PubMed: 11443519]
52. Dauvilliers Y, Neidhart E, Billiard M, Tafti M. Sexual dimorphism of the catechol-O-methyltransferase gene in narcolepsy is associated with response to modafinil. Pharmacogenomics J. 2002; 2:65–68. [PubMed: 11990384]
53. Frauscher B, Högl B, Maret S, Wolf E, Brandauer E, Wenning GK, Kronenberg MF, Kronenberg F, Tafti M, Poewe W. Association of daytime sleepiness with COMT polymorphism in patients with parkinson disease: a pilot study. Sleep. 2004; 27:733–736. [PubMed: 15283009]
54. Bodenmann S, Rusterholz T, Dürr R, Stoll C, Bachmann V, Geissler E, Jaggi-Schwarz K, Landolt HP. The functional Val158Met polymorphism of COMT predicts interindividual differences in brain α oscillations in young men. J Neurosci. 2009; 29:10855–10862. [PubMed: 19726643]
55. Bodenmann S, Xu S, Luhmann U, Arand M, Berger W, Jung HH, Landolt HP. Pharmacogenetics of modafinil after sleep loss: Catechol-O-Methyltransferase genotype modulates waking functions but not recovery sleep. Clin Pharmacol Ther. 2009; 85:296–304. [PubMed: 19037200]
56. Bodenmann S, Landolt HP. Effects of modafinil on the sleep EEG depend on Val158Met genotype of COMT. Sleep. 2010; 33:1027–1035. [PubMed: 20815183]
57. Rétey JV, Adam M, Honegger E, Khatami R, Luhmann UF, Jung HH, Berger W, Landolt HP. A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans. Proc Natl Acad Sci USA. 2005; 102:15676–15681. [PubMed: 16221767]
58. Bachmann V, Klaus F, Bodenmann S, Schäfer N, Brugger P, Huber S, Berger W, Landolt HP. Functional ADA Polymorphism Increases Sleep Depth and Reduces Vigilant Attention in Humans. Cereb Cortex. 2011 Jul 6. Epub ahead of print.
59. Rétey JV, Adam M, Khatami R, Luhmann UF, Jung HH, Berger W, Landolt HP. A genetic variation in the adenosine A2A receptor gene (ADORA2A) contributes to individual sensitivity to caffeine effects on sleep. Clin Pharmacol Ther. 2007; 81:692–698. [PubMed: 17329997]
60. Hungs M, Mignot E. Hypocretin/orexin, sleep and narcolepsy. Bioessays. 2001; 23:397–408. [PubMed: 11340621]
61. Rissling I, Körner Y, Geller F, Stiasny-Kolster K, Oertel WH, Möller JC. Preprohypocretin polymorphisms in Parkinson disease patients reporting “sleep attacks”. Sleep. 2005; 28:871–875. [PubMed: 16124668]
62. Hungs M, Lin L, Okun M, Mignot E. Polymorphisms in the vicinity of the hypocretin/orexin are not associated with human narcolepsy. Neurology. 2001; 57:1893–1895. [PubMed: 11723284]
63. Katzenberg D, Young T, Finn L, Lin L, King DP, Takahashi JS, Mignot E. A CLOCK polymorphism associated with human diurnal preference. Sleep. 1998; 21:569–576. [PubMed: 9779516]
64. Mishima K, Tozawa T, Satoh K, Saitoh H, Mishima Y. The 3111T/C polymorphism of hClock is associated with evening preference and delayed sleep timing in a Japanese population sample. Am J Med Genet B Neuropsychiatr Genet. 2005; 133:101–104. [PubMed: 15578592]
65. Garaulet M, Sánchez-Moreno C, Smith CE, Lee YC, Nicolás F, Ordovás JM. Ghrelin, sleep reduction and evening preference: relationships to CLOCK 3111 T/C SNP and weight loss. PLoS ONE. 2011; 6:e17435. [PubMed: 21386998]
66. Serretti A, Benedetti F, Mandelli L, Lorenzi C, Pirovano A, Colombo C, Smeraldi E. Genetic dissection of psychopathological symptoms: insomnia in mood disorders and CLOCK gene polymorphism. Am J Med Genet B Neuropsychiatr Genet. 2003; 121B:35–38. [PubMed: 12898572]
67. Drake CL, Roehrs TA, Burduvali E, Bonahoom A, Rosekind M, Roth T. Effects of rapid versus slow accumulation of eight hours of sleep loss. Psychophysiology. 2001; 38:979–987. [PubMed: 12240674]
68. Rowland LM, Thomas ML, Thorne DR, Sing HC, Krichmar JL, Davis HQ, Balwinski SM, Peters RD, Kloeppel-Wagner E, Redmond DP, Alicandri E, Belenky G. Oculomotor responses during partial and total sleep deprivation. Aviat Space Environ Med. 2005; 76:C104–C113. [PubMed: 16018336]

Highlights

- We review individual differences in response to sleep loss.
- We discuss the role of candidate gene variants in response to sleep restriction.
- We discuss how genetic markers may identify astronauts needing countermeasures.