Fiscal Year:	FY 2016	**Task Last Updated:**	FY 11/07/2016
PI Name:	Dinges, David F. Ph.D.		
Project Title:	Markers of Susceptibility to Neurobehavioral Decrements in Space Flight		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Neurobehavioral and Psychosocial Factors Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **BHP**:Behavioral Health & Performance (archival in 2017)		
Human Research Program Risks:	(1) **Bmed**:Risk of Adverse Behavioral Conditions and Psychiatric Disorders (2) **Sleep**:Risk of Performance Decrements and Adverse Health Outcomes Resulting from Sleep Loss, Circadian Desynchronization, and Work Overload (IRP Rev F)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	19104-4209	**Congressional District:**	2
Comments:			
Project Type:	GROUND	**Solicitation:**	2011 Crew Health NNJ11ZSA002NA
Start Date:	10/01/2012	**End Date:**	06/30/2016
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date change to 6/30/2016 per NSBRI (Ed., 3/1/16) NOTE: End date change to 3/31/2016 per NSBRI (Ed., 9/30/15) NOTE: End date changed back to 9/30/2015 per NSBRI submission October 2013 (Ed., 10/16/13) NOTE: Original end date was 9/30/2015; Changed to 9/30/13 per NSBRI 6/2/2012 (Ed., 6/4/12)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Goel, Namni (University of Pennsylvania) Mollicone, Daniel (Pulsar Informatics, Inc.) Rao, Hengyi (University of Pennsylvania) Basner, Mathias (University of Pennsylvania) Mignot, Emmanuel (Stanford University School of Medicine)		
Grant/Contract No.:	NCC 9-58-NBPF02801		

Performance Goal No.:	
Performance Goal Text:	
Task Description:	This project is responsive to the National Space Biomedical Research Institute (NSBRI) Neurobehavioral and Psychosocial Factors Team goal to validate objective markers of susceptibility to stress, fatigue, and neurobehavioral decrements associated with long-duration spaceflight, and to the NASA Human Research Program (HRP) Behavioral Health and Performance (BHP) gap to find individual characteristics that predict successful adaptation and performance in an isolated, confined, and extreme environment, especially for long duration missions. Sleep loss is common in space flight but there are currently no valid objective markers of the large inter-individual differences in susceptibility to its neurobehavioral effects. To fill this important gap, the project seeks to validate promising novel markers of susceptibility to fatigue-related neurobehavioral decrements. Specific Aim 1 identified core dimensions of neurobehavioral responses to chronic partial sleep loss. This was achieved by conducting dimensionality reduction using Principal Components Analysis (PCA) of a historical database of N=139 sleep-deprived subjects. The PCA included three cognitive performance outcomes: Psychomotor Vigilance Test (PVT) for behavioral alertness; Digit Symbol Substitution Test (DSST) for cognitive processing speed; and Digit-Span (DS) performance for working memory. PCA also included two primary subjective outcomes: Karolinska Sleepiness Scale (KSS), and Tiredness Visual Analog Scale (TVAS); and a measure of physiological sleep homeostatic drive (i.e., power spectral analyses [PSA] of delta frequency power in the NREM sleep EEG). The PCA included demographic covariates (i.e., age, gender, BMI, ethnicity), which contributed no variance to the neurobehavioral outcomes from sleep restriction identified by PCA. PVT performance and sleep homeostatic responses (i.e., slow wave activity in the non-REM EEG) were the two fully orthogonal components that emerged from the PCA dimensionality reduction of core neurobehavioral outcomes from sleep loss, indicating they were the more reliable and sensitive assays for detecting the phenotypic effects of sleep loss. Therefore, these two domains served as the sleep-deprivation outcomes for evaluation of biomarker prediction. Non-sleep-deprived PVT time on task performance and salivary amylase activity (sAA) were dropped as candidate predictors due to insufficient variance in baseline conditions. Remaining predictor variables (i.e., potential biomarkers) to be evaluated in the study were derived from baseline (non-sleep-deprived) neuroimaging (i.e., resting arterial spin labeling [ASL fMRI] cerebral blood flow); resting heart rate variability (HRV); results of genome wide association analyses (GWAS); and the results of quantitative analyses of baseline sleep polysomnography (PSG). As discovery capability for novel biomarkers of sleep-loss vulnerability has evolved over the last 4 years, the project has taken on new importance and opportunity (e.g., we had a recent preliminary finding of a metabolic marker of slept debt [Weljie et al. PNAS, 2015]). Instead of focusing on candidate genes as predictors of the vulnerability in a few subjects (which has not yielded a predictor relative to DQB1*0602, COMT Va1158Met, or PER3 VNTR genes), we shifted to conducting a genome-wide association study (GWAS) with our collaborator, Dr. Emmanuel Mignot, at Stanford University. Blood samples from N=358 unique human subjects (n=271 who underwent chronic partial sleep deprivation [PSD]; n=24 who underwent acute total sleep deprivation [TSD]; and n=63 who underwent both PSD and TSD) collected during our extensive laboratory studies supported by the National Institutes of Health (NIH), and the Office of Naval Research (ONR), were provided to Dr. Mignot for blinded GWAS analysis, to determine if a genetic variant is associated with the phenotypic trait of neurobehavioral vulnerability to sleep loss, as measured by PVT performance (the most sensitive neurobehavioral assay to sleep loss [Basner et al., 2013]). In addition, subjects' nocturnal polysomnographic (PSG) sleep records on pre-sleep-loss nights were subjected to power spectral analyses and machine learning algorithms to identify possible PSG biomarkers of PVT performance vulnerability to sleep loss. The results are being correlated with the results of the genetic analyses of the blood samples. We are conducting whole genome single nucleotide polymorphism (SNP) typing to first study known polymorphisms that have recently been found to be associated with sleep disorders in multiple studies. Thus, our biomarker search in quantitative analyses of sleep physiology is predicated on the hypothesis that presumably healthy individuals who are more cognitively vulnerable to sleep loss may be so because of an (as yet) occult disturbance of sleep that reduces waking state stability (measured by PVT performance) not evident in human-scored sleep physiology. Data analyses will be completed and papers prepared and submitted for publication in the coming months. Finding biomarkers of neurobehavioral vulnerability to sleep loss addresses multiple NASA BHP risk and gaps including indicators of vulnerabilities and resiliencies to sleep loss (Sleep Gap 4), methods to enhance behavioral health and prevent decrements during space flight (BMed1), characteristics of individuals resilient to neurobehavioral decrements from sleep loss (BMed5), and psychological measures that help select individuals for long-duration space flight (Team Gap 4). Finding valid biomarkers will help optimize crew resources and fatigue management during long-duration space flight, and it will have benefit for fatigue management in many Earth-based, safety-sensitive operations. The project deliverables will be a biological or behavioral assay for discriminating those who are more resistant versus those more susceptible to the adverse effects of fatigue on neurobehavioral functions.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The research builds on an extensive body of work we have conducted to help manage the cognitive and neurobehavioral performance of astronauts in space while being exposed to chronic partial or total sleep deprivation. The acquisition of critical knowledge of objective markers of the large inter-individual differences in susceptibility to the neurobehavioral decrements from sleep-related fatigue help predict successful adaptation and performance in isolated, confined, and extreme environments. The discovery of predictive biomarkers will have utility in a broad range of Earth-based applications in which sleep restriction, stress, and neurobehavioral stability have major adverse impacts on human performance (e.g., improved safety in all transportation modes; the operation of power plants; patient care by medical professionals; capability of first responders; etc.).

Task Progress:	The project consists of two discrete Specific Aims. Specific Aim 1 has been accomplished by evaluating core dimensions of neurobehavioral responses to both chronic partial and acute total sleep loss. Through dimensionality reduction via Principal Components Analysis (PCA) of a historical database of cognitive, subjective, and physiological responses to acute and chronic sleep loss in N=139 healthy adults, it was determined that Psychomotor Vigilance Test (PVT) performance variables (especially response speed and total response errors), as well as EEG delta activity from non-REM sleep physiology (via polysomnography [PSG]) were the most reliable and sensitive assays for determining the effects of sleep loss. This was achieved by conducting a factor analysis of a historical database of cognitive, subjective, and physiological responses to sleep restriction in healthy adults. Analyses of the historical database again established that PVT performance outcomes were the most reliable and sensitive assays for determining the effects of sleep loss. These dimensions will serve as targets for prospectively assessing the predictive power (separately and in combination) of each of the objective markers being evaluated (i.e., resting brain activity, heart rate variability, GWAS results, and sleep physiology results). Specific Aim 2 is being accomplished through the analysis of blood samples from N=358 unique human subjects (n=271 PSD; n=24 TSD; n=63 PSD/TSD) collected during our extensive laboratory studies of partial and chronic sleep restriction that were supported by NIH, NSBRI, and ONR. These samples are being evaluated in a genome-wide association study (GWAS), to determine if a genetic variant in different individuals is associated with the phenotypic trait of neurobehavioral vulnerability to sleep restriction. Phenotypic response will be evaluated using objective neurobehavioral responses to chronic partial sleep loss at the level it can be experienced in space flight. These trait response measures will include behavioral alertness assessed by Psychomotor Vigilance Test (PVT) performance and polysomnography during baseline. In the past year, the project (1) further confirmed the sensitivity of the PVT as a highly sensitive neurobehavioral measure of vulnerability to sleep loss; (2) identified a metabolic state marker of sleep debt (Weljie et al. PNAS, 2015); (3) completed (but not yet fully analyzed) GWAS on N=358 subjects who underwent sleep loss; and (4) initiated quantitative analyses of baseline sleep polysomnography.
Bibliography Type:	Description: (Last Updated: 01/21/2020)
Articles in Peer-reviewed Journals	Basner M, Mcguire S, Goel N, Rao H, Dinges DF. "A new likelihood ratio metric for the psychomotor vigilance test and its sensitivity to sleep loss." Journal of Sleep Research. 2015 Dec;24(6):702-13. Epub 2015 Jun 29. http://dx.doi.org/ ; PubMed PMID: 26118830 , Dec-2015
Articles in Peer-reviewed Journals	Basner M, Spaeth AM, Dinges DF. "Sociodemographic characteristics and waking activities and their role in the timing and duration of sleep." Sleep. 2014 Dec;37(12):1889-906. http://dx.doi.org/ ; PubMed PMID: 25325472; PubMed Central PMCID: PMC4548514 , Dec-2014
Articles in Peer-reviewed Journals	Goel N, Abe T, Braun ME, Dinges DF. "Cognitive workload and sleep restriction interact to influence sleep homeostatic responses." Sleep. 2014 Nov 1;37(11):1745-56. http://dx.doi.org/ ; PubMed PMID: 25364070; PubMed Central PMCID: PMC4196058 , Nov-2014
Articles in Peer-reviewed Journals	Goel N, Bale TL, Epperson CN, Kornstein SG, Leon GR, Palinkas LA, Stuster JW, Dinges DF. "Effects of sex and gender on adaptation to space: Behavioral health." Journal of Women's Health. 2014 Nov;23(11):975-86. Review. http://dx.doi.org/ ; PubMed PMID: 25259837; PubMed Central PMCID: PMC4235984 , Nov-2014
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Articles in Peer-reviewed Journals	Weljie AM, Meerlo P, Goel N, Sengupta A, Kayser MS, Abel T, Birnbaum MJ, Dinges DF, Sehgal A. "Oxalic acid and diacylglycerol 36:3 are cross-species markers of sleep debt." Proc Natl Acad Sci U S A. 2015 Feb 24;112(8):2569-74. http://dx.doi.org/ ; PubMed PMID: 25675494; PubMed Central PMCID: PMC4345602 , Feb-2015
Awards	Dinges DF. "Pioneer Award, National Space Biomedical Research Institute (NSBRI), February 2016." Feb-2016
Awards	Basner M. "Journal Publication Award for the Most Outstanding Space Medicine Article published in the Aerospace Medicine and Human Performance Journal. Awarded by the Space Medicine Association, April 2016." Apr-2016