Fiscal Year:	FY 2022	**Task Last Updated:**	FY 04/27/2022
PI Name:	Seidler, Rachael D. Ph.D.		
Project Title:	Bed Rest Combined with 0.5% CO2 as a Spaceflight Analog to Study Neurocognitive Changes: Extent, Longevity, and Neural Bases		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Behavior and performance		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HFBP**:Human Factors & Behavioral Performance (IRP Rev H)		
Human Research Program Risks:	(1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (2) **Sensorimotor**:Risk of Altered Sensorimotor/Vestibular Function Impacting Critical Mission Tasks		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	rachaelseidler@ufl.edu	**Fax:**	FY
PI Organization Type:	UNIVERSITY	**Phone:**	352-294-1722
Organization Name:	University of Florida		
PI Address 1:	Applied Physiology & Kinesiology		
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PI Web Page:			
City:	Gainesville	**State:**	FL
Zip Code:	32611-8205	**Congressional District:**	3
Comments:	NOTE: PI moved to University of Florida in July 2017; previous affiliation was University of Michigan.		
Project Type:	GROUND	**Solicitation / Funding Source:**	2014-15 HERO NNJ14ZSA001N-MIXEDTOPICS. Appendix E: Behavioral Health & Human Health Countermeasures Topics
Start Date:	06/29/2017	**End Date:**	06/30/2023
No. of Post Docs:	3	**No. of PhD Degrees:**	
No. of PhD Candidates:	4	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
Contact Monitor:	Whitmire, Alexandra	**Contact Phone:**	
Contact Email:	alexandra.m.whitmire@nasa.gov		
Flight Program:			
Flight Assignment:	NOTE: End date changed to 6/30/2023 per NSSC information (Ed., 2/20/23) NOTE: End date changed to 1/1/2023 per L. Barnes-Moten/JSC (Ed., 1/12/22) NOTE: Changed end date to 1/01/2022 per NSSC information (Ed., 3/12/21) NOTE: Changed end date to 1/01/2021 per L. Juliette/HRP (Ed., 2/19/2020) NOTE: Changed end date to 12/28/2019 per NSSC information (Ed., 10/9/19)		
Key Personnel Changes/Previous PI:	April 2021 report: For the augmentation study. Dr. Dawn Kernagis of University of North Carolina is a co investigator.		

COI Name (Institution):	Bloomberg, Jacob Ph.D. (NASA Johnson Space Center) Mulavara, Ajitkumar Ph.D. (Universities Space Research Association) Kuehn, Simone Ph.D. (Max Planck Institute for Human Development) Stahn, Alexander Ph.D. (University of Pennsylvania) Roberts, Donna M.D. (Medical University of South Carolina) Kernagis, Dawn Ph.D. (University of North Carolina)
Grant/Contract No.:	80NSSC17K0021
Performance Goal No.:	
Performance Goal Text:	
Task Description:	This original project is currently in no-cost extension, and a directed study is being performed, “Dose-Response Relationship of CO2 and Glymphatic Function.” This Annual Report covers the directed study only, as a final report has been previously submitted for the original project. Recent characterizations of glymphatic and meningeal lymphatic systems in rodents and in humans has resulted in a re-evaluation of the anatomical routes for cerebrospinal fluid (CSF) and interstitial fluid flow, as well as the physiological roles for these pathways in central nervous system (CNS) health. Information on the brain glial lymphatic, or ‘glymphatic’ pathway in humans was published in just the past two years, and described in mice in 2012 (Iliff et al. 2012, Iliff et al. 2013, de Leon et al. 2017, Ringstad et al. 2017). A bona fide lymphatic vasculature lining dural sinuses and meninges was first described in mice in 2015, and 2017 in humans (Aspelund et al. 2015, Louveau et al. 2015, Absinta et al. 2017). Fundamentally, research is needed to confirm whether specific factors driving this flow in rodents also apply to humans. These questions have direct relevance to NASA mission operations because, in addition to changing in response to irregular sleep patterns, it has been hypothesized that changes in cerebral blood flow (CBF) and molecular signaling in response to exercise, hypo/hyperoxia, and hypo/hypercarbia can have a significant impact on glymphatic function (Xie et al. 2013). No data currently exist specific to glymphatic responses from hypercapnia in humans or in mice. It is compelling, however, that nearly half of the subjects participating in a recent head down tilt bed rest campaign (“VaPER”), which combined 30 days of bed rest with 0.5% CO2 levels, developed early signs of SANS (Laurie et al. 2019). These subjects also exhibited other “hits” in Zwart and Smith’s multiple hit model of SANS, including B vitamin status and genotype for 1-carbon metabolism genes (Zwart et al. 2019). Thus, it is important to examine whether elevated CO2 impacts clearance through the brain’s glymphatic system, providing a potential mechanism through which elevated CO2 might be associated with SANS. Therefore, in the current directed project, we are conducting a dose-response investigation of whether and how CO2 levels impact contrast clearance through the brain’s glympatic system. Preliminary results show clearance of injected contrast through to various brain and optic regions over a period of six hours in ambient air. References Iliff, J. J., M. Wang, Y. Liao, B. A. Plogg and W. Peng (2012). "A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid ß." Sci Transl Med 4: 147ra111. Iliff, J. J., H. Lee and M. Yu (2013). "Brain-wide pathway for waste clearance captured by contrast- enhanced MRI." J Clin Invest 123: 1299-1309. de Leon, M. J., Y. Li and N. Okamura (2017). "Cerebrospinal fluid clearance in Alzheimer disease measured with dynamic PET." J Nucl Med 58: 1471-1476. Ringstad, G., S. A. S. Vatnehol and P. K. Eide (2017). "Glymphatic MRI in idiopathic normal pressure hydrocephalus." Brain 140: 2691-2705. Aspelund, A., S. Antila, S. T. Proulx, T. V. Karlsen, S. Karaman, M. Detmar, H. Wiig and K. Alitalo (2015). "A dural lymphatic vascular system that drains brain interstitial fluid and macromolecules." J Exp Med 212: 991-999. Louveau, A., I. Smirnov, T. J. Keyes, J. D. Eccles, S. J. Rouhani, J. D. Peske, N. C. Derecki, D. Castle, J. W. Mandell, K. S. Lee, T. H. Harris and J. Kipnis (2015). "Structural and functional features of central nervous system lymphatic vessels." Nature 523: 337-341. Absinta, M., S. K. Ha and G. Nair (2017). "Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI." Elife 6: e29738. Xie, L., H. Kang, Q. Xu, M. J. Chen, Y. Liao, M. Thiyagarajan, J. O’Donnell, D. J. Christensen, C. Nicholson, J. J. Iliff, T. Takano, R. Deane and M. Nedergaard (2013). "Sleep drives metabolite clearance from the adult brain." Science 342: 373-377. Laurie, S., Macias, BR, Dunn, JT, Young, M, Stern, C, Lee, SM, & Stenger, MB (2019). "Optic disc edema after 30 days of strict head-down tilt bed rest." Ophthalmology 126(3): 467-468. Zwart, S., Laurie, SS, Chen, JJ, Macias, BR, Lee, SMC, Stenger, M, Grantham, B, Carey, K, Young, M, & Smith, SM (2019). "Association of genetics and B vitamin status with the magnitude of optic disc edema during 30-day strict head-down tilt bed rest." JAMA Ophthalmol 137(10):1195–1200.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	This research will examine brain function under various levels of CO2, providing data on the impact of hypercapnic environments on the timeline for clearance of waste through the brain.

Task Progress:	We are completing the aims listed below. A manuscript reporting our preliminary findings is currently under review. We propose a coordinated, multi-institution program to characterize glymphatic and neurobehavioral function in response to risks associated with working and living in space. Human subjects' data collection will be completed at the University of Florida site. Specific Aims: Aim 1: Characterize the dose-response effect of elevated CO2 on clearance of gadolinium contrast into the human brain glymphatic system over a period of approximately 24 hours. We hypothesize that increasing CO2 from 2 mmHg (2,500 ppm) to 3 mmHg (~4,000 ppm) and 4 mmHg (~6,600 ppm) will slow contrast clearance in a linear dose-response fashion. Our glymphatic MR imaging approach parallels techniques used successfully in other studies (Absinta, Ha et al. 2017, Deike-Hofmann 2019). We will acquire MR images (T1-SPACE, 3D MPRAGE and T2-Flair with high in-plane resolution) immediately before and one hour after intravenous injection of a standard gadolinium contrast agent (gadobutrol). We will scan subjects at an additional two time points, approximately three and eight hours after contrast administration. The exact timing of these additional scans will be determined via pilot testing, funded by our Office of Naval Research grant, to identify the timeline for peak distribution of gadolinium into the brain's lymphatic vessels and the ventricles, perineural space of the optic nerve, and aqueous chamber of the eye (Deike-Hofmann 2019). Participants will complete four MRI scans breathing ambient air or one of three elevated CO2 levels. Aim 2: Assess changes in brain-derived stress biomarkers in the blood that correlate with neurological changes in response to elevated CO2. We hypothesize that increasing CO2 will lead to an increase in biomarkers in peripheral blood in a dose-response fashion. Moreover, we predict that individual differences in these biomarkers will associate with individual differences in glymphatic clearance rates. Aim 3: Evaluate neurobehavioral responses in response to elevated CO2. We hypothesize that elevated CO2 will lead to deficits in neurobehavioral function in a dose-response fashion. Moreover, we predict that individual differences in these responses will associate with individual differences in glymphatic clearance rates. References: Absinta, M., S. K. Ha and G. Nair (2017). "Human and nonhuman primate meninges harbor lymphatic vessels that can be visualized noninvasively by MRI." Elife 6: e29738. Deike-Hofmann, K., Reuter, J, Haase, R, Paech, D, Gnirs, R, Bickelhaupt, S, Forsting, M, Heubel, CP,Schlemmer, H-P, Radbruch, A (2019). "Glymphatic pathway of gadolinium-based contrast agents through the brain: overlooked and misinterpreted." Invest Radiol 54: 229-237.
Bibliography Type:	Description: (Last Updated: 01/24/2024)
Abstracts for Journals and Proceedings	Richmond S, Hupfeld KE, McGregor H, Schwartz D, Luther M, Beltran N, Kofman I, De Dios Y, Riascos R, Wood S, Bloomberg J, Silbert L, Iliff J, Seidler R, Piantino J. "Effects of spaceflight and analog environments on perivascular morphology." 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. Abstracts. 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. , Feb-2022
Abstracts for Journals and Proceedings	Richmond S, Levendovszky S, Ramclam R, Kernagis D, Albayram M, Rosenberg J, Iliff J, Seidler R. "Glymphatic function in extreme environments. Poster presentation at the 2022 NASA Human Research Program Investigators' Workshop." 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. Abstracts. 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. , Feb-2022