Fiscal Year:	FY 2023	**Task Last Updated:**	FY 11/01/2023
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		
PI Address 2:	FLG 142, P.O. Box 118205		
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) 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:	Wostyn et al. have proposed that impaired waste clearance from the brain and eye ocular contributes to Spaceflight Associated Neuro-ocular Syndrome (SANS) (cf. (Wostyn 2018)). Moreover, the enclosed environment of the International Space Station (ISS) results in elevated CO2 levels in comparison to ambient air on Earth, which is linked to a greater incidence of headaches in the crew (Law 2014). Research with rodent models has shown that elevated CO2 impairs brain waste clearance (Goodman 2020). Moreover, a human neuroimaging study reports that brain structures involved in waste clearance are enlarged when people breathe elevated CO2 (Zong 2020). Thus, it is essential to examine whether elevated CO2 impacts clearance through the brain’s waste system, providing a potential mechanism through which elevated CO2 might be associated with SANS. Therefore, in the current directed project, we will conduct a dose-response investigation of whether and how CO2 levels impact brain waste clearance. Specific Aims: Aim 1: Characterize the dose-response effect of elevated CO2 on clearance of gadolinium contrast into the human brain's glymphatic system over a period of approximately 24 hours. We hypothesize that increasing CO2 across three dose levels (1.0%, 1.5%, and 2.0%) will slow contrast clearance in a linear dose-response fashion. 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 be associated 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 be associated with individual differences in glymphatic clearance rates. We completed this study with MRI at 90 and 360 minutes after intravenous gadolinium injection. Delayed brain and ocular signal enhancement is thought to reflect waste clearance. We found some structures that showed higher signal enhancement and others that showed less signal enhancement when participants breathed elevated CO2 relative to ambient air.
Bibliography Type:	Description: (Last Updated: 01/24/2024)
Articles in Peer-reviewed Journals	Richmond SB, Rane S, Hanson MR, Albayram M, Iliff JJ, Kernagis D, Rosenberg JT, Seidler RD. "Quantification approaches for magnetic resonance imaging following intravenous gadolinium injection: A window into brain-wide glymphatic function." Eur J Neurosci. 2023 May;57(10):1689-1704. https://doi.org/10.1111/ejn.15974 ; PubMed PMID: 36965006 , May-2023