Fiscal Year:	FY 2021	**Task Last Updated:**	FY 04/25/2021
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:**	01/01/2023
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 is now 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:	To date, we have had eight participants in the study, all tested under ambient or normal air conditions. This was to help us better define the required scanning timeline for the CO2 portion of the study. Participants came to the MRI center and were administered gadobutrol via intravenous injection. They remained supine throughout the day, with the exception of getting in and out of the MR scanner and using the restroom. We scanned participants prior to injection and at several timepoints throughout the day. We administered multiple structural MRI sequences. Throughout the MRI visit, we are monitoring participant vital signs, including heart rate, blood pressure, respiration, and blood oxygen saturation to ensure subject safety after contrast injection. Our results illustrate increases in signal intensity as contrast disburses throughout the brain over the day, including into the dura and other regions.
Bibliography Type:	Description: (Last Updated: 01/24/2024)
Abstracts for Journals and Proceedings	Hanson MR, Richmond SB, Kernagis DN, Rosenberg JT, Albayram MS, Rane SD, Iliff JJ, Seidler RD. "Taking Out the Trash: The Time Course of IV Gadolinium-Based Contrast Agent Through the Glymphatic System in Humans." Lightning Talk Presentation, Society for Neuroscience (North-Central Florida) Regional Meeting, Virtual Format (2021). Lightning Talk Presentation, Society for Neuroscience (North-Central Florida) Regional Meeting, Virtual Format (2021). , Mar-2021
Abstracts for Journals and Proceedings	Richmond SB, Hanson MR, Kernagis DN, Rosenberg JT, Iliff JJ, Seidler RD. "Effects of Hypercapnic Environments on Glymphatic Function." Poster / Lightning Talk Presentation, 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. HRP IWS abstract booklet. 2021 NASA Human Research Program Investigators' Workshop, Virtual, February 1-4, 2021. , Feb-2021
Articles in Peer-reviewed Journals	Hupfeld KE, McGregor HR, Reuter-Lorenz PA, Seidler RD. "Microgravity effects on the human brain and behavior: dysfunction and adaptive plasticity." Neurosci Biobehav Rev. 2021 Mar;122:176-89. Review. https://doi.org/10.1016/j.neubiorev.2020.11.017 ; PMID: 33454290 , Mar-2021
Articles in Peer-reviewed Journals	Salazar AP, Hupfeld KE, Lee JK, Beltran NE, Kofman IS, De Dios YE, Mulder E, Bloomberg JJ, Mulavara AP, Seidler RD. "Neural working memory changes during a spaceflight analog with elevated carbon dioxide: A pilot study." Front Syst Neurosci. 2020 Jul 28;14:48. https://doi.org/10.3389/fnsys.2020.00048 ; PMID: 32848641; PMCID: PMC7399639 , Jul-2020
Articles in Peer-reviewed Journals	McGregor HR, Lee JK, Mulder ER, De Dios YE, Beltran NE, Kofman IS, Bloomberg JJ, Mulavara AP, Seidler RD. "Brain connectivity and behavioral changes in a spaceflight analog environment with elevated CO2." Neuroimage. 2021 Jan 15;225:117450. https://doi.org/10.1016/j.neuroimage.2020.117450 ; PMID: 33075558 , Jan-2021
Articles in Peer-reviewed Journals	Banker LA, Salazar AP, Lee JK, Beltran NE, Kofman IS, De Dios YE, Mulder E, Bloomberg JJ, Mulavara AP, Seidler RD. "The effects of a spaceflight analog with elevated CO2 on sensorimotor adaptation." J Neurophysiol. 2021 Feb 1;125(2):426-36. https://doi.org/10.1152/jn.00306.2020 ; PMID: 33296611 , Feb-2021
Articles in Peer-reviewed Journals	McGregor HR, Lee JK, Mulder ER, De Dios YE, Beltran NE, Kofman IS, Bloomberg JJ, Mulavara AP, Smith SM, Zwart SR, Seidler RD. "Ophthalmic changes in a spaceflight analog are associated with brain functional reorganization." Hum Brain Mapp. 2021 Sep;42(13):4281-97. https://doi.org/10.1002/hbm.25546 ; PMID: 34105833; PMCID: PMC8357001 , Sep-2021
Articles in Peer-reviewed Journals	Salazar AP, Hupfeld KE, Lee JK, Banker LA, Tays GD, Beltran NE, Kofman IS, De Dios YE, Mulder E, Bloomberg JJ, Mulavara AP, Seidler RD. "Visuomotor adaptation brain changes during a spaceflight analog with elevated carbon dioxide (CO2): A pilot study." Front Neural Circuits. 2021 Jun 7;15:659557. https://doi.org/10.3389/fncir.2021.659557 ; PMID: 34163332; PMCID: PMC8215599 , Jun-2021
Articles in Peer-reviewed Journals	Lee JK, Koppelmans V, Pasternak O, Beltran NE, Kofman IS, De Dios YE, Mulder ER, Mulavara AP, Bloomberg JJ, Seidler RD. "Effects of spaceflight stressors on brain volume, microstructure, and intracranial fluid distribution." Cereb Cortex Commun. 2021 Mar 30;2(2):tgab022. https://doi.org/10.1093/texcom/tgab022 ; PMID: 34296167; PMCID: PMC8152913 , Mar-2021