Fiscal Year:	FY 2022	**Task Last Updated:**	FY 09/23/2021
PI Name:	Rosi, Susanna Ph.D.		
Project Title:	VNSCOR: Probing the Synergistic Effects of Radiation, Altered Gravity and Stress on Behavioral Cognitive and Sensorimotor Functions to Predict Performance Decrement in Astronauts		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
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		
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Zip Code:	94110-3518	**Congressional District:**	12
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2018 HERO 80JSC018N0001-Crew Health and Performance (FLAGSHIP, OMNIBUS). Appendix A-Flagship, Appendix B-Omnibus
Start Date:	10/01/2019	**End Date:**	09/30/2025
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	1	**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:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 09/30/2025 per L. Juliette/JSC (Ed., 5/7/22)		
Key Personnel Changes/Previous PI:	July 2020 report: Adam Ferguson, Ph.D., Associate Professor, Department of Neurological Surgery, Director of Data Science, Brain and Spinal Injury Center (BASIC), and the Weill Institute for Neurosciences at the University of California, San Francisco is now CoInvestigator. Drs. Mora and Wyrobek and Dr. Mao are no longer CoInvestigators on the project.		
COI Name (Institution):	Ferguson , Adam Ph.D. (University of California, San Francisco)		
Grant/Contract No.:	80NSSC19K1581		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The purpose of this application is to: 1) determine the possible synergistic and individual effects of radiation exposure (GCRsim), isolation confinement stress, and altered gravity on behavioral, cognitive, and sensorimotor performance; 2) establish if there are sex-dimorphic responses; 3) develop predictive biomarkers for individual sensitivity; 4) incorporate these results into a predictive statistical model for the extrapolation of performance decrement; and 5) estimate Central Nervous System (CNS) risks in astronauts. The central hypothesis of this proposal is that there is a synergistic effect of multiple factors (defined by GCRsim, isolation confinement stress, and altered gravity) encountered in deep space exposure that leads to enhanced inflammatory response, promotes synapse loss, and decreases synaptic integrity that leads to long-term loss of sensorimotor, behavioral, and cognitive functions. The rationale of the proposed research is to understand the mechanisms that underlie the cumulative and synergistic effects of radiation exposure, isolation confinement stress, and altered gravity on behavioral, cognitive, and sensorimotor deficits. Further, we will explore sex-dimorphic responses along with potential peripheral biomarkers associated with simulated deep space travel. Our studies will provide novel information regarding the cellular mechanisms of altered neuronal function involved in simulated deep space conditions (GCRsim, isolation confinement, and altered gravity). Finally, we will incorporate all the results to build risk assessment and performance decrement for astronauts. We will characterize molecular, cellular, tissue, and behavioral endpoints underlying CNS function in an individual manner with animals prescreening. We will use multiple behavioral and cognitive tests known to be comparable to human performance. We will use state of the art techniques to dissect cellular and molecular changes in the brain. The endpoints will be selected to probe key physiological processes that support tissue homeostasis plasticity in the brain. We will determine if and how cellular and molecular impairments are linked to compromised behavior in motor, social, and cognitive domains. By combining assessments of multiple processes that may have distinct time constants and magnitudes of responses to simulated deep space conditions we will begin to identify operationally-relevant brain functions impacted by the three stressors and relate these to human performance. Furthermore, by comparing outcome measures in both males and females we will begin to understand the distinct aspects of the responses controlled by sex and are therefore more likely to translate to humans. The proposed aims directly address Human Exploration Research Opportunities (HERO) announcement needs detailed in Appendix A that specify research needs (gaps) related to NASA Research and Technology Development to Support Crew Health and Performance in Space Exploration Missions. The specific gaps this proposal addresses are Topic 1, gap CNS 1 (Are there significant adverse changes in CNS performance in the context and time scale of spaceflight operations? If so, how is significance defined, and which neuropsychological domains are affected? Is there a significant probability that space radiation exposure would result in adverse changes? What are the pathways and mechanisms of change?), CNS 2 (Does space radiation exposure elicit key events in adverse outcome pathways associated with neurological diseases? What are the key events or hallmarks, their time sequence and their associated biomarkers (in-flight or post-flight)?), CNS 5 (How can new knowledge and data from molecular, cellular, tissue and animal models of acute CNS adverse changes or clinical human data, including altered motor and cognitive function and behavioral changes be used to estimate acute CNS risks to astronauts from GCR and SPE-solar particle event?), SM6.1 (Determine if sensorimotor dysfunction during and after long-duration spaceflight affects ability to control spacecraft and associated systems), SM 26 (Determine if exposure to long-duration spaceflight leads to neural structural alterations and if this remodeling impacts cognitive and functional performance), and IM 8 (IM8: We do not know the influence, direct, or synergistic, on the immune system of other physiological changes associated with spaceflight). [Ed. note November 2021: Gaps have been revised since the original proposal Task Description; please refer to the Human Research Roadmap for current gap information: https://]
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our research goals, hypothesis, and proposed aims directly address Human Exploration Research Opportunities (HERO) announcement needs detailed in Appendix A that specify research needs (gaps) related to NASA Research and Technology Development to Support Crew Health and Performance in Space Exploration Missions. The specific gaps this proposal addresses are in Topic 1, CNS 1 “Are there significant adverse changes in CNS performance in the context and time scale of space flight operations? Is there a significant probability that space radiation exposure would result in adverse changes? What are the pathways and mechanisms of change?”; Gap CNS2: “Does space radiation exposure elicit key events in adverse outcome pathways associated with neurological diseases? What are the key events or hallmarks, their time sequence and their associated biomarkers (in-flight or post- flight)?”; SM 26: “Determine if exposure to long-duration spaceflight leads to neuronal structural alterations and if this remodeling impacts cognitive and functional performance.”; IM 8: “We do not know the influence, direct or synergistic, on the immune system of other physiological changes associated with spaceflight.” [Ed. note November 2021: Gaps have since been revised ; please refer to the Human Research Roadmap for current gap information: https://]
Task Progress:	For the first time we identify GCRsim-induced deficits in spatial learning using composite principal components (PC) scores (optimally weighted z-scores) derived by manifold machine learning as primary endpoints. Spatial learning refers to an organism’s ability to encode information about their environment and to use this information to navigate through it. As astronauts will traverse unknown terrain on a Mars mission, deficits in this cognitive modality would greatly impair mission success. Importantly, we found that brief microglia depletion shortly after exposure mitigates long-term GCRsim-induced deficits in spatial learning, suggesting that while deep space radiation exposure could impair spatial learning there are tools that can alleviate such deficits. We did not observe deficits in other behavioral (anxiety-like, sociability) or cognitive (social memory, and recognition memory) paradigms. Previous findings have shown that charged particle exposure causes deficits in one or more of these measured domains; however, the current data demonstrate that when combined the 5 ions might have different combinatory effects that are not cumulative. While space radiation is the prominent stressor for deep space journeys, there are additional aggravating factors that might impact astronauts, including social isolation, zero gravity, distance from Earth, hostile environment, and altered sleep patterns. Determining if the combination of these stressors with GCRsim exposure impacts behavioral and cognitive function is a crucial next step for mission preparation.

Bibliography Type:	Description: (Last Updated: 09/04/2023)
Articles in Peer-reviewed Journals	Paladini MS, Feng X, Krukowski K, Rosi S. "Microglia depletion and cognitive functions after brain injury: From trauma to galactic cosmic ray." Neurosci Lett. 2021 Jan 10;741:135462. Epub 2020 Nov 28. https://doi.org/10.1016/j.neulet.2020.135462 ; PMID: 33259927 , Jan-2021
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Articles in Peer-reviewed Journals	Krukowski K, Grue K, Becker M, Elizarraras E, Frias ES, Halvorsen A, Koenig-Zanoff M, Frattini V, Nimmagadda H, Feng X, Jones T, Nelson G, Ferguson AR, Rosi S. "The impact of deep space radiation on cognitive performance: From biological sex to biomarkers to countermeasures." Sci Adv. 2021 Oct 15;7(42):eabg6702. https://doi.org/10.1126/sciadv.abg6702 ; PMID: 34652936; PMCID: PMC8519563 , Oct-2021