Fiscal Year:	FY 2018	**Task Last Updated:**	FY 05/31/2018
PI Name:	Eisch, Amelia Ph.D.		
Project Title:	HZE Particle Exposure-Induced Improvement of Pattern Separation in Mature Mice: Alterations in Mission-Relevant Behaviors and Neural Circuitry		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:	NOTE: Previously at University of Texas Southwestern Medical Center at Dallas, 2000-2016		
Project Type:	Ground	**Solicitation / Funding Source:**	2013-14 HERO NNJ13ZSA002N-RADIATION
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No. of PhD Candidates:	10	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	3
No. of Bachelor's Candidates:	7	**Monitoring Center:**	NASA JSC
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Flight Program:			
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Key Personnel Changes/Previous PI:			
COI Name (Institution):			
Grant/Contract No.:	80NSSC17K0060		
Performance Goal No.:			
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Task Description:	ED. NOTE: Continuation of "HZE Particle Exposure-Induced Improvement of Pattern Separation in Mature Mice: Alterations in Mission-Relevant Behaviors and Neural Circuitry," grant NNX15AE09G, with the same Principal Investigator (PI) Dr. Amelia Eisch; PI moved to Children's Hospital of Philadelphia/Univ Pennsylvania Perelman School of Medicine from University of Texas Southwestern Medical Center at Dallas. The new grant number: 80NSSC17K0060. An unavoidable consequence of deep space missions is exposure to galactic cosmic radiation (GCR), which includes high (H) atomic number (Z) and energy (E) particles particles like Fe, Si, and O. Estimating radiation risks to the central nervous system (CNS) by HZE particles encountered during space missions is a high research priority. Past research has shown that rodents exposed to HZE particles have cognitive and performance deficits in numerous behavioral tasks, including those that rely on the hippocampus, a brain region involved in learning and memory. Notably, we have found that mature mice (of equivalent age to astronauts) exposed to either Si or Fe HZE particles actually show improved performance on a very difficult hippocampal task to assess the ability to discrimination two contexts that differ in discrete ways. Here we propose three aims to understand this improved context “pattern separation” after HZE particle exposure. In Aim 1, we hypothesize that HZE particle exposure-induced improved pattern separation is linked to improved performance on related learning and memory tasks, as well as executive function tasks, in the short-term, but to decreased performance in the long-term. In Aim 2, we hypothesize that HZE particle exposure-induced improved pattern separation is linked in the short-term to diminished stress-induced emergence of anxiety and depression-like behaviors, but to greater emergence in the long-term. In Aim 3, we hypothesize that HZE particle exposure-induced improved pattern separation is associated with disrupted hippocampal-cortical neural networks. All aims will rely on both classic and cutting-edge techniques. In sum, these aims will address whether the HZE particle exposure-induced improvement in pattern separation is beneficial or detrimental to mission success (Aims 1, 2), will indicate the integrity of neural circuitry contributing to mission-relevant behaviors (Aim 3), and will define both the short- and long-term health of neural networks needed to complete deep space missions.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	An unavoidable aspect of manned space flights is exposure to galactic cosmic radiation (GCR), which is made up primarily of protons (87%), followed by helium (11%) and then high atomic number (Z) and high-energy (HZE) particles (2%) like iron, silicon, and oxygen. The energy of HZE particles can be very high (>1000 MeV/u), sufficient in many cases to penetrate the spacecraft hull and interior materials, and they have a complex track structure and high linear energy transfer (LET). Thus, while the greatest physical radiation dose of GCR comes from high-energy protons, the greatest biological radiation dose of GCR comes from HZE particles. With long-duration and exploratory space missions in the near future, we need to understand how GCR influences human health and behavior. Estimation of radiation risks to the central nervous system (CNS) is a high research priority according to both a National Academy of Science report and NASA’s Radiation Health Bioastronautics Roadmap. In rodents, HZE particles induce cognitive domain deficits, including decreased hippocampal learning and memory and cortically based executive function. However, it remains unclear whether the age at irradiation (IRR) influences the outcome of behavioral tests. It is also unclear whether these cognitive decrements extend to other cognitive tests, or to other behavioral domains, such as mood and stress response. Recently, we found that mice exposed at maturity (“astronaut-aged”) to 28Si or 56Fe HZE particle IRR perform better than control mice on a hippocampal-based pattern separation task (context discrimination fear conditioning, CDFC). We want to understand if this behavioral improvement in pattern separation is reflective of other changes in behavior, and whether these changes will be beneficial or detrimental to mission success. We propose a behavioral domain- and brain network-based analysis to understand the HZE particle-induced behavioral improvement shown in our pilot data. These data will have relevance for understanding the risks facing crew members in deep space missions, particularly in regards to the age of crew member at the time of the mission.
Task Progress:	Aim 1: The impact of HZE particles on other tests in the cognitive domain. Using the “flexible battery” of tests offered by the touchscreen operant platform, we will identify a behavioral framework for the HZE particle-induced improvement in pattern separation. We hypothesize HZE particles will improve performance reliant on hippocampal-cortical integrity, but not on striatal-cortical integrity. Aim 2: The impact of HZE particles on behaviors in the affective/social domain. Pattern separation is important not just to contextual discrimination, but also to the resistance to mood and anxiety disorders. Based on this, and with our previous experience with an ethologically-relevant stressor, we will test HZE particle-induced influence in the affective/social domain. We hypothesize that improved pattern separation is linked to resilience to social stressors. Aim 3: Indices of neural network perturbation underlying HZE particle exposure-induced improved pattern separation. While improved pattern separation has been causally linked to increased hippocampal neurogenesis, our data show HZE particle-induced improvement in pattern separation is actually marked by decreased hippocampal neurogenesis. Using classic (stereology of dentate gyrus interneuron counts) as well as cutting-edge techniques (RNAseq), we will test the hypothesis that HZE particles influence the integrity of hippocampal-cortical neural networks. Taken together, these aims will address whether the improved pattern separation seen after 28Si or 56Fe HZE particle IRR is beneficial or detrimental to mission success (Aims 1, 2), will indicate the integrity of neural circuitry contributing to mission-relevant behaviors (Aim 3), and will define both the short- and long-term health of neural networks needed to complete deep space missions. By providing both behavioral and mechanistic insight at numerous time points, these aims are highly relevant to NASA’s goal to gain new understanding using age-appropriate animal models representative of the risks astronauts will face in extended space missions. Using mice irradiated at astronaut-age and multiple time points post-IRR, we have found that mice of astronaut age show improved pattern separation in both appetitive and aversive tasks, work that has been submitted for publication. We are now building an additional manuscript expanding on our novel RNA-seq revealing the translationome of genetically-defined granule cells and identifying key intracellular protein pathways altered after radiation.
Bibliography Type:	Description: (Last Updated: 10/09/2024)

Articles in Peer-reviewed Journals	Yun S, Reynolds RP, Petrof I, White A, Rivera PD, Segev A, Gibson AD, Suarez M, DeSalle MJ, Ito N, Mukherjee S, Richardson DR, Kang CE, Ahrens-Nicklas RC, Soler I, Chetkovich DM, Kourrich S, Coulter DA, Eisch AJ. "Stimulation of entorhinal cortex-dentate gyrus circuitry is antidepressive." Nat Med. 2018 May;24(5):658-66. https://doi.org/10.1038/s41591-018-0002-1 ; PubMed PMID: 29662202 ; PubMed Central PMCID: PMC5948139 , May-2018