Fiscal Year:	FY 2021	**Task Last Updated:**	FY 09/27/2021
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		
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Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Flight Assignment:	NOTE: End date changed to 2/28/2021 per NSSC information (Ed., 7/31/2020)		
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Performance Goal No.:			
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Task Description:	ED. NOTE: New grant number 80NSSC17K0060--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. 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 Sciences 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:	January 2022: We have published that mice irradiated at "astronaut-age" show improved hippocampal-dependent performance in an aversive task (context discrimination fear conditioning, CDFC). Notably, we have found that mature mice (of equivalent age to astronauts) exposed to either 28Si or 56Fe HZE particle irradiation (IRR) actually show improved performance on a difficult hippocampal task (discrimination of 2 similar contexts) without influencing performance on an easier hippocampal task or other behaviors. For NASA Space Research Laboratory (NSRL)16B, we found that males have improved pattern separation (location discrimination, LD). This extended our findings on IRR-induced improvement in pattern separation from an aversive task (CDFC) to an appetitive task (LD). These ground-based studies on the cognitive impact of space radiation show male rodents exposed to a single high-energy particle unexpectedly have enhanced discrimination learning with similar stimuli. However, far less work has been done in female rodents. It was specifically unknown how space radiation influences cognition of female rodents when assessed via touchscreen testing, a translationally-relevant approach that reveals integrity of many cognitive domains. In mice run in NSRL17B and 18A, we showed mature female mice exposed to a mission-relevant dose of a space radiation particle have a) improved performance on a hippocampal-dependent task, b) no change in performance on a prefrontal cortex-dependent task, and c) impaired performance on a striatum-dependent behavior task. These data support the idea of competition between hippocampal and striatal memory systems, and fill a key knowledge gap on the influence of space radiation on female cognition. September 2021: Using mice irradiated at astronaut-age and multiple time points post-irradiation, we have found that mice of astronaut age show improved pattern separation in both appetitive and aversive tasks. Our ongoing work is revealing the sex- and task-dependency of this result, which is being prepared for publications. In addition to our ongoing work on how the translationome of genetically-defined dentate gyrus granule cells is altered after radiation, we are collaborating with other investigators to determine the efficacy of key countermeasures that may prevent irradiation-induced behavioral changes. This grant (NNX15AE09G/80NSSC17K0060) has funded progress on the following publications (19): Latchney SE*, Jiang Y*, Petrik DP, Eisch AJ^, Hsieh J^. Inducible knockout of Mef2A/C/D from nestin-expressing stem/progentior cells and their progeny unexpectedly uncouples neurogenesis and dendritogenesis in vivo. The Journal of the Federation of American Societies for Experimental Biology (The FASEB Journal). 29(12):5059-5071 (2015). PMID 26286136, PMC 4653059. *equal contribution ^co-corresponding authors Petrik D, Latchney SE*, Masiulis I*, Yun S*, Zhang Z*, Wu JI^, Eisch AJ^. 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Bibliography Type:	Description: (Last Updated: 10/26/2023)
Articles in Peer-reviewed Journals	Soler I, Yun S, Reynolds RP, Whoolery CW, Tran FH, Kumar PL, Rong Y, DeSalle MJ, Gibson AD, Stowe AM, Kiffer FC, Eisch AJ. "Multi-domain touchscreen-based cognitive assessment of C57BL/6J female mice shows whole-body exposure to 56Fe particle space radiation in maturity improves discrimination learning yet impairs stimulus-response rule-based habit learning." Front Behav Neurosci. 2021 Oct 11;15:722780. https://doi.org/10.3389/fnbeh.2021.722780 ; PMID: 34707486; PMCID: PMC8543003 , Oct-2021
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