Fiscal Year:	FY 2021	**Task Last Updated:**	FY 08/22/2022
PI Name:	Kiffer, Frederico C. Ph.D.		
Project Title:	Effects of Galactic Cosmic Radiation on Translationally-Relevant Cognitive Behaviors and Response to Social Stress		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	TRISH--TRISH		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	None		
Human Research Program Risks:	None		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
PI Email:	fredkiffer@gmail.com	**Fax:**	FY
PI Organization Type:	NON-PROFIT	**Phone:**	831-419-2676
Organization Name:	Children's Hospital of Philadelphia		
PI Address 1:	3615 Civic Center Blvd		
PI Address 2:	Room 402 F Abramson Pediatric Research Center		
PI Web Page:			
City:	Philadelphia	**State:**	PA
Zip Code:	19104-4318	**Congressional District:**	3
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2019 TRISH RFA-1901-PD Translational Research Institute for Space Health (TRISH) Postdoctoral Fellowships
Start Date:	08/01/2019	**End Date:**	07/31/2022
No. of Post Docs:	1	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**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:**	TRISH
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: End date changed to 7/31/2022 per E. Urquieta/TRISH (Ed., 7/1/21)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):			
Grant/Contract No.:	NNX16AO69A-P0402		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	POSTDOCTORAL FELLOWSHIP Astronauts on a Mars mission will be exposed to potentially harmful levels of charged-particle radiation. Thirty years of basic research with ground-based charged-particle radiation has provided overwhelming evidence that the rodent Central Nervous System (CNS) and behavior are negatively affected by charged-particles, suggesting this is a concern for astronaut health. However, the current literature has several caveats, including using young rather than fully-adult rodents, lack of studies focused on the female rodent CNS, unrealistic single-particle radiation simulations, lack of feasible therapeutic countermeasures, and behavioral tests with low translational potential and high handling- or experimenter-induced variability. Additionally, no published CNS study has yet assessed the effects of charged-particle radiation in combination with spaceflight-relevant stressors. We will address these limitations by exposing male and female mice of astronaut age to a novel, complex, but realistic Galactic Cosmic Ray simulation (GCR) then examining network-dependent behavioral performance on a highly-translational, appetitive touch-screen platform, including a behavioral test battery that can be viewed as analogous to the tests currently used on astronauts aboard the International Space Station. A separate group of mice will be examined for the influence of GCR on their ability to cope with social and physical stress in a validated mouse model of depression. Finally, we will test a promising anti-inflammatory drug and its ability to prevent GCR-induced deficits in cognition and social defeat stress. This proposal will address a wide range of NASA-defined knowledge gaps in its Human Research Roadmap. Specifically, we strive to provide a model basis for identifying individuals who are resilient to the extreme spaceflight conditions, validate a measure for monitoring behavioral health, determine radiation dose thresholds for behavioral measures in a domain basis and in combination with social defeat stress, all of which will help inform NASA's risk models for a crewed mission to Mars.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	We have demonstrated that GCR remains a pressing concern for the behavioral health of mice due to observed behavioral deficits following exposure in male and female mice. These observations in a mouse model suggest that astronauts on a mission to Mars, who are expected to receive similar doses of GCR might be at risk of similar behavioral endpoints. Our work also demonstrates that CDDO-EA might be a promising dietary countermeasure to prevent radiation-induced cognitive deficits in female mice. However, CDDO-EA was not effective in preventing radiation-induced social memory deficits in male mice. In both male and female mice, CDDO-EA in combination with ground-based GCR exposure resulted in sociability deficits as compared to control mice. Further inquiry into CDDO-EA is warranted. [Ed. Note: CDDO-EA is a chemical compound. For more information about CDDO-EA, visit the National Library of Medicine website: https:// .
Task Progress:	1. Original Project Aims Aim 1. Define GCR effects on translationally-relevant cognitive tests in mice. Aim 2. Define the outcomes of GCR on adaptive, social-stress-mediated behavior. 2. Key Findings To accomplish aim 1, we have exposed 6-month-old male and female mice to an acute, whole-body 750mGy dose of the NSRL's 33-GCR. To assess CDDO-EA as a GCR countermeasure, we gave a subset in mice receiving either Sham or GCR ad libitum access to a CDDO-EA-containing diet (400mg/kg); whereas, non-countermeasure mice received a vehicle (Veh) diet of the same excipient preparation omitting CDDO-EA. Four months after radiation, male mice were tested for locomotor activity with activity chambers, anxiety with open field (OF) and elevated-plus mazes (EPM), sociability and social memory with the 3 chamber social interaction (3-CSI) test and object memory, with the novel object recognition (NOR) test. We observed no effects of diet on weights among the four groups of male mice for the duration of the experiment. We similarly did not observe significant differences in mouse survival between groups. Following suit, behavioral analyses revealed no major differences in gross locomotion, anxiety, or object memory following radiation. However, in 3-CSI CDDO-EA/33-GCR, mice failed to spend more time exploring a stranger mouse vs. nothing, suggesting sociability deficits, and Veh/33-GCR and CDDO-EA/Sham mice failed to discriminate between a stranger vs. familiar mouse, suggesting social memory deficits. CDDO-EA did not attenuate the 33-GCR-induced social memory deficits. Our findings suggest that radiation poses a risk to socio-cognitive behavior, and that CDDO-EA was not an effective GCR countermeasure in male mice. Future elucidation of the mechanisms underlying 33-GCR-induced social memory deficits will improve risk analysis for astronauts which may, in turn, improve countermeasures. Female mice similarly maintained similar weights among groups for the duration of the experiment. They were next trained for a touchscreen-based appetitive behavioral platform (ABET II, Lafayette Neuroscience) for one month. Mice were next tested for visuo-spatial pattern separation, by the Location Discrimination task. For both the "easy" and "hard" separation settings, Veh/33-GCR completed fewer daily trials throughout the three month-long testing period. Mice were next tested for a rule-based acquisition test, and subsequently for extinction learning. Veh/33-GCR took nearly three times longer to reach acquisition criteria than the other groups. However, we observed no differences among groups in extinction learning. Touchscreen testing was followed by arena testing for anxiety (EPM, OF), sociability and social memory (3-CSI), object memory (NOR), and compulsive-like behavior (marble-burying and nestlet-digging). We observed no differences in social, cognitive, or compulsive behavior; however, Veh/33-GCR and CDDO-EA/33-GCR mice explored the center of the OF for shorter durations than non-33-GCR mice. Overall, 33-GCR exposure resulted in pattern separation and rule-based acquisition deficits in mice, which was prevented by CDDO-EA. 33-GCR also caused lowered open field exploration, which was not prevented by CDDO-EA. To fulfill aim 2, we exposed six-month-old male and female mice to 3 x 6.7 cGy of 56Fe (600MeV/n) every other day for five days. Six months after exposure, mice were tested for social hierarchy and dominance behavior via the tube dominance test across 16 days. Next, mice were tested for anxious behavior (OF), sociability and social memory (3-CSI), and despair response with the Forced Swim Test. We observed sex-specific responses to social hierarchy and dominance behavior. Radiation lowered rank attainment, and lowered rank stability in males, but improved these measures in females. Rank and other behavioral and histological analyses are ongoing.

	3. Impact of Key Findings on Hypotheses Guided by a literature of simple GCR models, it was hypothesized that a complex ground-based GCR simulation would result in numerous behavioral deficits in male and female mice of astronaut-equivalent age. Overall, we did not observe the commonly reported behavioral deficits described in the literature, such as anxious behavior and object memory. However, male mice nevertheless displayed social memory deficits, and female mice displayed lowered pattern separation, rule-based acquisition, and increased anxious behavior, suggesting our hypothesis that radiation would result in behavioral deficits is accepted. Contrary to our hypotheses, CDDO-EA was an ineffective countermeasure for radiation-induced social memory deficits in male mice, and when given in combination with 33-GCR, appeared to induce sociability deficits. However, in female mice, CDDO-EA prevented radiation-induced deficits to cognitive behaviors (pattern separation and rule-based acquisition). CDDO-EA did not, however, prevent 33-GCR-induced OF anxiety in females, suggesting partial success as a radiation countermeasure in female, but not male mice. 4. Proposed Research Plan for the Coming Year Early analyses of tube test data indicate sex-specific responses to hierarchy and stress-mediated social conflict resolution. To understand what might give rise to these differences, we will extrapolate individual mouse behaviors across the testing period using deep learning-based automated ethograms to quantify within-tube behaviors such as conflict lengths, methods of resolution (passive vs. conflict-based), number of pushes, retreats, etc. To investigate the brain regions involved in tube-based conflicts we will process collected brain tissues from behaviorally naive, but acutely tube-tested mice. Tissues will be stained for immediate early genes for insight into the neuronal ensembles involved in this task, and quantified to understand if there are radiation differences in the regions involved in tube testing between sham and irradiated mice, and whether these vary by sex, or social rank.
Bibliography Type:	Description: (Last Updated: 08/21/2023)
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 ; PMCID: 34707486; PMC8543003 , Oct-2021
Awards	Kiffer et al. "Learning and Memory - Editor's Pick 2021 for "Late effects of 1H + 16O on short-term and object memory, hippocampal dendritic morphology and mutagenesis", Frontiers in Behavioral Neuroscience, June 2021." Jun-2021