Fiscal Year:	FY 2016	**Task Last Updated:**	FY 04/11/2016
PI Name:	Lemere, Cynthia Ph.D.		
Project Title:	Impact of Space Radiation on Cognition, Synapses and Biomarkers in Aging and Alzheimer's Disease		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
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:			
Project Type:	Ground	**Solicitation / Funding Source:**	2013 Space Radiobiology NNJ13ZSA001N
Start Date:	06/01/2014	**End Date:**	05/31/2018
No. of Post Docs:	1	**No. of PhD Degrees:**	1
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: change in period of performance to 6/1/2014-5/31/2018 (from 4/29/14-4/28/18) per PI and NSSC information (Ed., 3/17/2015)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	O'Banion, Kerry M.D., Ph.D. (University of Rochester)		
Grant/Contract No.:	NNX14AI07G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The goal of our work is to identify early and late effects of space radiation on the connections between nerve cells in the brain (i.e., synapses), inflammation, and cognition so that one can assess the central nervous system (CNS) risk to future astronauts involved in long-duration lunar missions and/or a mission to Mars. These early changes, along with changes in brain inflammation that may relay signals between cells in the brain and blood flow, may help define those individuals at risk for developing long-term learning and memory problems. Our studies will utilize normal, wildtype (WT) mice and a genetic mouse model of Alzheimer's disease. Female and male 4 month-old mice will be irradiated once with varying doses of heavy ions or protons and examined 2 or 8 months later. Chronic dosing will be compared with a single dose for long-term effects as well. A subset of mice will undergo positron emission tomography (PET) imaging for brain inflammation and blood flow, and behavioral testing before being sacrificed. We will perform a close-up inspection of synapses, Alzheimer's amyloid plaques, neuron loss, and inflammation in the brain.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our initial study, Aim 1a (early effects of 56Fe radiation), suggests that deep space radiation may have different effects in young female vs. male mice. In general, irradiated female Alzheimer's transgenic mice had less cerebral amyloid accumulation, less neuroinflammation, and no cognitive deficits compared to non-irradiated female transgenic mice. Irradiated female mice had reduced grip strength but increased motor learning. Male Alzheimer's transgenic mice showed a trend for cognitive decline but no difference in cerebral amyloid load, neuroinflammation, strength, or motor learning. Thus, there appear to be gender-specific responses to iron irradiation. Further studies are underway to investigate late effects of irradiation with iron and protons. Whether these gender (and genotype) specific effects are long-lasting remains to be determined.
Task Progress:	The goal of our work is to identify early and late effects of space radiation on the connections between nerve cells in the brain (i.e., synapses), inflammation, and cognition so that one can assess the Central Nervous System (CNS) risk to future astronauts involved in long-duration lunar missions and/or a mission to Mars. These early synaptic changes, along with changes in brain inflammation that may relay signals between cells in the brain, and blood flow, may help define those individuals at risk for developing long-term learning and memory problems. Our studies utilize normal wildtype mice and two genetic mouse models of Alzheimer's disease that develop some of the same lesions in the brain and cognitive changes seen in people with Alzheimer's disease. In our first series of experiments, female and male 4 month-old wildtype and Alzheimer's mice are to be irradiated once at Brookhaven National Laboratory (BNL) with varying doses of heavy ions (56Fe; iron) or protons and examined 2 or 10 months later. In our second set of experiments, 12 month-old male Alzheimer's (a second genetic model) and wildtype mice will be exposed to either a single dose or six fractionated doses of smaller amounts of radioactivity over a two-week period. For the iron irradiation studies, a subset of mice will undergo microPET imaging for cerebral blood flow and brain inflammation immediately prior to transfer to BNL and again after behavioral testing, just before being sacrificed at the end of study. In addition, structural MRIs will be performed both pre- and post-irradiation in a subset of single vs. fractionated iron-irradiated Alzheimer's and wildtype mice. Changes in synapses, Alzheimer's amyloid plaques, neuron loss, and inflammation in the brain will be determined by pathological and biochemical examination of mouse brain tissues. We began our project in July 2014. In our first study (Aim 1a), we investigated the early effects of single-dose 56Fe (iron) irradiation in four month-old female and male wildtype (non-genetically manipulated) and Alzheimer's transgenic (genetically manipulated) mice. These animals were shipped to Brookhaven National Laboratory (BNL) in April 2015 and exposed to a single dose of 0, 10 (low dose), or 50 (high dose) cGy 56Fe (iron heavy ions; 1000 MeV/n). Mouse neurobehavioral tests were conducted 1 month post-irradiation to examine general health, locomotion, anxiety, depression, strength, motor learning and fatigue, and cognition. We found that iron irradiation in young adult mice had no short-term effects on general health, including basic motor and sensory function, body weight, anxiety, or depression 1 month later. We confirmed that male Alzheimer's Tg mice were more active than WT mice, as previously observed, and male mice were stronger than females. Importantly, we found significant interactions between gender (male vs. female), genotype (Alzheimer's mice vs. wildtype), and dose (non-irradiated vs. low and high dose 56Fe iron) in motor activity. Female Alzheimer's mice treated with low dose iron and male Alzheimer's mice treated with high dose iron were significantly more active than non-irradiated female and male Alzheimer's mice. Notably, both low and high dose iron radiation resulted in significant weakness in female Alzheimer's Tg mice, while high dose iron irradiation improved motor learning in female Tg mice. Iron irradiation had no effect on strength or motor learning in male mice, further highlighting gender differences. High dose iron irradiation led to slight memory impairment in male Alzheimer's mice but not in female Alzheimer mice or any of the wildtype mice. Early iron irradiation effects on brain inflammation and cerebral blood flow (CBF) were assessed by microPET imaging before and after 0 or high dose iron irradiation. We observed reduced uptake of the PET tracer for neuroinflammation in the brains of female Alzheimer's and wildtype mice when comparing the pre- vs. post-irradiation PET scans. This may reflect reduced inflammation; pathological studies are underway to confirm this interpretation. No changes were observed in male mice. Quantification of cerebral blood flow is underway. Aggregates of amyloid-ß protein (Aß) accumulate in Alzheimer's disease brain many years prior to the onset of clinical symptoms. Many genetic mouse models of Alzheimer's disease develop Aß aggregates, including extracellular plaques, which are often associated with inflammation and a loss of connections (i.e. synapses) between neurons. Early radiation effects on brain amyloid-ß (Aß) levels were assessed. We found that a single exposure of either the low dose or the high dose of iron irradiation reduced Aß levels in female Alzheimer's mice but had no effect on Aß in male Alzheimer's mice at 6 months of age. The lowering of amyloid in iron-irradiated Alzhiemer's female mice correlates with the reduced inflammation observed in this mouse group using PET imaging. We also examined microhemorrhages in mouse brain and found preliminary evidence suggesting that high dose iron irradiation may be associated with a slight increase in microhemorrhages in male wildtype mice; further analysis is underway. Using biochemical methods, we have observed no early effects of radiation on synaptic markers thus far except for a small, radiation-associated elevation of one postsynaptic marker in low dose irradiated female Alzheimer's mice. Taken together, our Aim 1a study suggests that a single exposure of 56Fe (iron) radiation produced early changes in mouse behaviors that vary by gender, genotype, and dose; low dose irradiated female Alzheimer's mice and high dose irradiated male Alzheimer's mice were particularly susceptible. Unlike other mice in the study, 56Fe-irradiated female

	Alzheimer's mice had reduced neuroinflammation (PET scans), reduced amyloid-ß burden and increased levels of a post-synaptic marker in brain, and reduced grip strength but higher motor learning, compared to non-irradiated female Alzheimer's mice, suggesting that female Alzheimer's mice were, in general, more affected by a single dose of iron radiation than other mice. Further analyses are ongoing to quantify pathologically and biochemically the early effects of deep space radiation on brain inflammation, synapses, neuronal health, and vascular integrity. To investigate late effects of 56Fe irradiation in mice (Aim 1c), male and female Alzheimer's and wildtype mice were shipped to Brookhaven National Laboratory for 56Fe irradiation in October 2015. Immediately prior to shipping, a subset of mice underwent pre-irradiation PET scanning for neuroinflammation and cerebovascular blood flow. After irradiation, the mice were shipped back to Boston and are currently aging until they reach 11-12 months of age in mid-May, 2016 at which time they will undergo behavioral testing and post-irradiation PET scanning followed by pathological and biochemical brain analyses.
Bibliography Type:	Description: (Last Updated: 11/20/2024)