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PI Name:	Lemere, Cynthia Ph.D.		
Project Title:	Impact of Space Radiation on Cognition, Synapses and Biomarkers in Aging and Alzheimer's Disease		
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Human Research Program Risks:	(1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders		
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Space Biology Cross-Element Discipline:	None		
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No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
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Key Personnel Changes/Previous PI:			
COI Name (Institution):	O'Banion, Kerry M.D., Ph.D. (University of Rochester)		
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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 utilize normal, wildtype (WT) mice and genetic mouse models of Alzheimer's disease. Female and male 4 month-old mice will be irradiated once with varying doses of heavy ions (iron) and examined for 2 (early) or 8 (late) months later. A similar study paradigm is being used to look at the late effects of protons in female and male mice. 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:	In our initial study, Aim 1a (early effects of 56Fe iron radiation), we found that deep space radiation had different effects in young female vs. male mice. In general, 6 month-old female Alzheimer's transgenic mice that were irradiated at 4 months of age 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. Irradiated male Alzheimer's transgenic mice showed a trend for cognitive decline but no difference in cerebral amyloid load, neuroinflammation, strength, or motor learning. In our second study, Aim 1c (late effects of 56Fe iron radiation), we found even more robust gender-specific differences in the response to radiation. Twelve month-old male Alzheimer's transgenic mice that were irradiated at 4 months of age had a higher cerebral amyloid burden, more inflammation in the brain, and a strong trend for cognitive deficits compared to non-irradiated male transgenic mice. Radiation with 50 cGy 56Fe also caused cognitive impairment in male wildtype mice. Radiation of female Alzheimer's mice had no effect on amyloid levels, inflammation, or cognition. Thus, it appears that there are gender-specific responses to iron irradiation in mice. Whether these gender (and genotype) specific effects are particular to iron irradiation remains to be determined as we are in the midst of determining the late effects of protons in mice. We will also expand this work by comparing a single dose versus 6 smaller doses of 56Fe in a new Alzheimer's mouse model. Gaining a better understanding of why female Alzheimer's mice seem resistant while male mice seem more vulnerable to the late effects of radiation on cognition might help determine factors underlying learning and memory, and potentially lead to new therapies and/or gender-specific treatments for Alzheimer's disease.
	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 were irradiated once at Brookhaven National Laboratory (NBL) with varying doses of heavy ions (56Fe; iron) or protons and examined 2 or 8 months later. In our upcoming 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 Brookhaven National Laboratory (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 1-2 months post-irradiation to examine general health, locomotion, anxiety, depression, strength, motor learning and fatigue, and cognition. Our findings suggested 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 more active. Unlike other mice in the study, 56Fe-irradiated female Alzheimer's mice had reduced neuroinflammation (PET scans), reduced amyloid-ß burden, 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 radiation had some beneficial short-term effects in female Alzheimer's mice, but not in males. Instead, high dose iron irradiation led to slight memory impairment in male Alzheimer's mice but not in female Alzheimer's mice nor in any of the wildtype mice. During Year 3 of our grant, we re-analyzed our 18F-GE180 PET scan images for inflammation in the short-term effects study described above to distinguish uptake of the tracer versus stable binding within the brain. We determined that the early effect of radiation-related reduction in brain inflammation that we observed by PET imaging in 5.5 month-old female mice was mainly due to changes in uptake (1-19 min) but not stable binding of the tracer in brain (20-60 min), indicating that in the short-term, there were no radiation effects on brain inflammation. We hypothesized that the reduced peak uptake in female irradiated mice might be due to differences in cerebral blood flow or blood brain barrier permeability after radiation. However, by PET imaging, we found no differences in cerebral blood flow between pre- and post-irradiation scans in any groups, indicating that a single dose of iron radiation had no early effects on mouse cerebral blood flow in male or female mice. We performed quantitative staining for inflammatory markers on mouse brain sections and found that iron irradiated 6 month-old female Alzheimer's mice, which had reduced amyloid plaques, also had had reduced gliosis (inflammatory cells) compared to non-irradiated females, while no changes were observed in Aß or gliosis in irradiated male Alzheimer's mice. To investigate late effects of 56Fe (iron) irradiation, 4 month-old male and female Alzheimer's and wildtype mice were

	shipped to Brookhaven National Laboratory and received a single dose of 0, 10, or 50 cGy iron radiation in October 2015. Immediately prior to shipping, a subset of mice underwent pre-irradiation PET scanning for neuroinflammation and cerebrovascular blood flow. After irradiation, the mice were shipped back to Boston and were aged until ~12 months of age (May 2016). Neurobehavioral testing, post-irradiation follow-up PET scans, as well as pathological and biochemical brain analyses were performed.
Task Progress:	Iron irradiation at 4 months of age had no long-term effects on basic health, motor and sensory function, grip strength, fatigue resistance, sensorimotor reactions or anxiety in Alzheimer's or wildtype mice at ~12 months of age. Long-term radiation effects were observed mostly in male mice. Irradiated male Alzheimer's mice were less active but more coordinated, and had worse short-term spatial memory. Irradiated male wildtype mice had improved motor learning but significantly worse cognition than non-irradiated male wildtype mice. Radiation had no long-term effects on cognition in female mice, including both Alzheimer's and wildtype mice, suggesting that the long-term cognitive effects of iron irradiation are gender-specific. Interestingly, although female Alzheimer's mice have more Aß in brain than males, radiation at 4 months of age increased Aß levels and plaques in 12 month-old male Alzheimer's mice but had no effect in females. Biochemical detection of synaptic markers showed no radiation effect in male or female Alzheimer's or wildtype mice. Further analysis of individual synapses is ongoing. PET scan imaging and staining of mouse brain sections were performed to assess the long-term effects of a single dose of iron irradiation on inflammation in the brain. Neuroinflammation (detected by PET scan) was elevated in 12 month-old non-irradiated male and female Alzheimer's mice due to the presence of amyloid plaques compared to plaque-free wildtype control mice. However, a single dose of iron irradiation further increased neuroinflammation in male but not female Alzheimer's mice. As stated above, radiation also increased Aß levels and plaques only in male Alzheimer's mice. Staining of brain sections revealed that 50 cGy iron irradiation increased immune cell activation (i.e., gliosis) in both male and female Alzheimer's mice. Radiation had no effect on cerebral blood flow in any group as assessed by pre- vs. post-irradiation PET scans using a radio-labeled oxygenated water tracer. Taken together, our results suggest that a single exposure of 56Fe (iron) radiation produced long-term changes in mouse behaviors that vary by gender, genotype (wildtype vs. Alzheimer's mice), and dose. Late radiation effects were more predominant in male mice compared with female mice. In particular, iron radiation reduced motor activity, improved motor coordination, impaired short-term spatial memory, increased Aß burden and brain inflammation (GE180 PET scan), and up-regulated microglia activation in male Alzheimer's mice compared with non-irradiated male control mice. Radiation had long-term effects on locomotor activities in female mice, but had no effect on memory, brain inflammation (PET), or Aß burden. Further analyses are ongoing to quantify pathologically and biochemically individual synapses, neuronal health, vascular integrity and Aß production. In order to compare proton irradiation effects with those we have observed for iron irradiation, female and male wildtype and Alzheimer's mice were shipped to Brookhaven National Laboratory in October 2016 for a single dose of proton radiation (0, 50, or 200 cGy). The mice were shipped back to Boston shortly thereafter and are currently aging. Behavioral testing will begin in May 2017 when the mice are almost 1 year of age. Following behavioral testing, all mice will be sacrificed in June 2017 and brains analyzed. Next, we will compare the long-term effects of single vs. fractionated, chronic dosing of iron irradiation in a new Alzheimer's mouse model and wildtype mice. We have bred and aged male mice to almost one year. Currently, a subset of these mice are in the midst of undergoing pre-irradiation MRI scans for brain structure and PET imaging for brain inflammation. In early April, we will ship the entire cohort of 12 month-old male APP knock-in and wildtype mice to BNL for iron irradiation. Alzheimer's and wildtype mice will be irradiated once with 50 cGy iron (single dose) or with an equivalent dose divided into 6 radiation sessions over 2 weeks (fractionated dose). Control non-irradiated mice will be shipped and handled in the same way as the irradiated mice. Follow-up imaging and behavioral testing will be performed in September/October 2017. Upon completion, all mice will be sacrificed and their brains analyzed. In addition to comparing single vs. fractionated dosing, this study will also provide new information regarding the effects of radiation exposure during middle-age as 12 month-old mice correspond approximately to 40-45 human years. We expect to complete the analyses of these mice by the end of our grant period, May 31, 2018. To date, our studies suggest that female mice are somewhat resistant to 56Fe radiation while male mice appear to be more vulnerable, especially to the long-term effects. Our proton studies will reveal whether these gender-specific effects are consistent across different types of radiation. Our next step is to identify which factors contribute to resistance in the females and vulnerability in the males.

Bibliography Type:	Description: (Last Updated: 11/20/2024)
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