Fiscal Year:	FY 2017	**Task Last Updated:**	FY 03/21/2017
PI Name:	Limoli, Charles Ph.D.		
Project Title:	Charged Particle Effects on Neuronal Injury, Plasticity and Neurodegeneration		
Division Name:	Human Research		
Program/Discipline:	HUMAN RESEARCH		
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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Zip Code:	92697-2695	**Congressional District:**	45
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2012 Space Radiobiology NNJ12ZSA001N
Start Date:	01/01/2013	**End Date:**	12/30/2016
No. of Post Docs:	1	**No. of PhD Degrees:**	1
No. of PhD Candidates:	1	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	4
No. of Bachelor's Candidates:	4	**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 12/30/2016 per S. Monk/LaRC (Ed., 12/11/15)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Hughes, Christopher (University of California, Irvine)		
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Performance Goal No.:			
Performance Goal Text:			
	The space radiation environment poses unique hazards to astronauts since a range of potential complications can result from exposure of the central nervous system (CNS) to these dangerous radiation fields. Damage caused by the traversal of charged particles in space through the brain is likely to elicit alterations to the structure and function of neurons and perturb the critical interactions between multiple cell types in the CNS. Irradiation also elicits a persistent increase in free radicals or “oxidative stress” that will complicate further the recovery of the CNS after exposure. Thus, we believe that exposure to the charged particles in space will cause acute and chronic alterations to the cell types in the brain that are critical for learning and memory, thereby having an adverse effect on the functionality of the CNS. To address the foregoing problems we will measure the impact of charged particle irradiation on neuronal anatomy and function using cultures of human neurons grown in the presence and absence of additional cell types known to be		

Task Description:	critical for proper neuronal function. Studies will also be performed in the presence of antioxidants that can minimize damage from reactive species, providing a useful strategy for gauging the importance of radiation-induced oxidative stress. These cell-based studies will be complemented by animal studies in which similar endpoints will be measured in brain tissue isolated from irradiated mice. One animal model genetically modified to express a neuronal fluorescent marker will be used to measure the subtle structural changes to neurons after irradiation. Another animal model genetically modified to exhibit early onset dementia will be used to gauge how exposure to charged particles found in space might impact the onset and/or severity of neurodegenerative phenotypes. Collectively, these studies will provide new data regarding the consequences of charged particle irradiation in the CNS, data that will be useful in estimating the uncertainties and risks associated with space travel.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	In general, work will characterize adverse effects of ionizing radiation on the CNS and help define potential causes and consequences of radiation-induced dementia.
Task Progress:	FINAL REPORTING--MARCH 2017 Overall accomplishments We have now defined many of the underlying causes of charged particle-induced cognitive dysfunction in mice. Mice (6 months of age) have been subjected to an extensive series of cognitive testing 6, 12, and 24 weeks following low dose exposure (5 - 50cGy) to 1H, 4He, 16O, 28Si, and 48Ti HZE (high energy) ions. Behavioral tasks administered at these times reveal marked if not stunning decrements in behavior using 6 different testing paradigms. Each of these paradigms, including Novel Object Recognition (NOR), Object in Place (OiP), Temporal Order (TO), Elevated Plus Maze (EPM), Forced Swim Test (FST), Fear Extinction (FE) tasks interrogate hippocampal and select cortical regions of the brain and have conclusively indicated that deficits and learning and memory along with increased anxiety- and depression-like behavior are associated with exposure to space relevant fluences of these charged particles. Temporally coincident with these decrements are significant reductions in dendritic complexity and spine density along the very neurons that mediate neurotransmission important for each of the selected behavioral tasks. These measurements have also facilitated efforts at defining the relationship between individual performance and specific alterations in structural and/or synaptic integrity. The adverse effects of space radiation are certainly not limited to the structural alterations measured in neurons throughout different regions of the brain, but can also be linked to elevated neuroinflammation and oxidative stress that persist long after exposure. Collectively, our findings have been derived from roughly 2 NASA Space Radiation Laboratory (NSRL) campaigns/year spanning the years of 2013-2016. Results obtained from this funding have laid the groundwork for a deeper understanding of CNS (central nervous system) space radiation effects, and in many respects have been paradigm shifting. Previously very little (if any) information was known concerning the short or long term effects of cosmic radiation exposure on neuronal structure, and these data along with the inclusion of additional behavioral paradigms introduced during this funding cycle have established many of the underlying mechanisms that compromise CNS functionality after radiation exposure. Data derived from this grant has also been instrumental in moving forward with additional mechanistic studies focused on elucidating further how cosmic radiation exposure alters neurotramsmission to adversely impact cognition. We firmly believe that we are now well poised to extend our work and provide NASA more definitive data that quantify the uncertainties and unique risks associated with deep space travel. Lastly, much of this funding will likely prove instrumental in our efforts to develop interventions using mitigating agents, aimed at ameliorating the adverse effects of cosmic radiation exposure on the CNS. The summation of our published work contains much the critical details outlined above. See Cumulative Bibliography. ANNUAL REPORTING--NOVEMBER 2016 Scope of Work – General We have now defined many of the underlying causes of charged particle-induced cognitive dysfunction in mice. Mice (6 months of age) have been subjected to an extensive series of cognitive testing 6, 12, and 24 weeks following low dose exposure (5, 30 cGy) to 16O and 48Ti HZE (high energy) ions. Behavioral tasks administered at these times reveal marked if not stunning decrements in behavior using 5 different testing paradigms that persist 6 months following a single acute dose. Temporally coincident with these decrements are significant reductions in dendritic complexity and spine density along the very neurons that mediate neurotransmission important for each of the selected behavioral tasks. These measurements have also facilitated efforts at defining the relationship between individual performance and specific alterations in structural and/or synaptic integrity. Much of this data has been highlighted in our past progress report and has now resulted in a major manuscript entitled “Cosmic radiation exposure and persistent cognitive dysfunction” published in Scientific Reports in October 2016. Collectively, our findings indicate that HZE ion irradiation elicits significant structural deterioration of neurons that persists and contributes to the progressive dementia found long after exposure. We have many follow up studies that corroborate these findings, extending our work showing that charged particle exposure constitutes a unique risk for developing behavioral decrements and CNS dysfunction. Recent experimental highlights are detailed below: Experimental highlights: 1. The Tg (Thy1-EGFP)MJrs/J transgenic mouse strain expresses eGFP in specific subsets of neurons, thereby providing brightly fluorescent neurons for morphometric analyses. Cohorts of 6-month old animals have now been irradiated with 16O and 48Ti ions (600 MeV) at doses of 0, 5, and 30 cGy (NASA Space Radiation Laboratory-NSRL 15B, 15C, 16A). Animals have been analyzed for behavioral deficits at 6, 12, and 24 weeks after exposure. Data sets for 6 weeks are published and data for the 12 & 24 wk time points are provided in this report. Data has now confirmed the presence of significant behavioral deficits for each ion at weeks 12 and 24 using the Novel Object Recognition (NOR), Object in Place (OiP), Temporal Order (TO), Elevated Plus Maze (EPM), Fear Extinction (FE) tasks. 2. All animals described above (i.e., eGFP expressing transgenic mice subjected to 16O and 48Ti ion irradiation) have now been analyzed for alterations in neuronal structure (see data below). These studies highlight persistent and significant reductions in the complexity of the dendritic tree and density of dendritic spines along neurons of the medial prefrontal cortex (mPFC) and within the hippocampal CA1 and dentate gyrus. The majority of this data has now been published and extends our earlier studies demonstrating qualitatively similar findings 6 weeks after exposure.

	3. Additional structural and synaptic parameters collected from HZE ion irradiated animals have again been used to provide quantitative readouts of developing behavioral decrements. Discrimination indices routinely decrease with reduced spine density and elevated PSD95 puncta, and validate the utility of our experimental approach for quantifying parameters relevant to the estimation of risk for developing various forms of dementia. 4. We now completed some follow up studies demonstrating the beneficial effects of MCAT expression in the subiculum region of the hippocampus. One month following irradiation of WT and MCAT mice, a range of morphometric parameters were quantified along Golgi-Cox impregnated neurons. Compared to WT mice, subiculum neurons from MCAT mice exhibited increased trends (albeit not statistically significant) toward increased dendritic complexity in both control and irradiated cohorts. However, Sholl analysis of MCAT mice revealed significantly increased arborization of the distal dendritic tree, indicating a protective effect on secondary and tertiary branching. Interestingly, radiation-induced increases in postsynaptic density protein (PSD-95) puncta were not as pronounced in MCAT compared to WT mice, and were significantly lower after the 0.5 Gy dose. As past data has linked radiation exposure to reduced dendritic complexity, elevated PSD-95 and impaired cognition, reductions in mitochondrial oxidative stress have proven useful in ameliorating many of these radiation-induced sequelae. 5. We have started a new line of investigation to extend our structural studies to the level of electron microscopy. In this work, mice subjected to low dose charged particle exposure were analyzed for changes in synapse density and myelination. One month following exposure, mice showed significant decreases in each of these endpoints, demonstrating for the first time that space relevant exposure to charged particles elicits ultrastructural changes detectable by electron microscopy.
Bibliography Type:	Description: (Last Updated: 12/13/2023)
Articles in Peer-reviewed Journals	Chmielewski NN, Caressi C, Giedzinski E, Parihar VK, Limoli CL. "Contrasting the effects of proton irradiation on dendritic complexity of subiculum neurons in wild type and MCAT mice." Environ Mol Mutagen. 2016 Jun;57(5):364-71. http://dx.doi.org/10.1002/em.22006 ; PubMed PMID: 26996825 , Jun-2016
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