Fiscal Year:	FY 2015	**Task Last Updated:**	FY 02/20/2015
PI Name:	Davis, Catherine M. Ph.D.		
Project Title:	Mitigating Neurobehavioral Vulnerabilities to Space Radiation		
Division Name:	Human Research		
Program/Discipline:	NSBRI		
Program/Discipline--Element/Subdiscipline:	NSBRI--Neurobehavioral and Psychosocial Factors Team		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **BHP**:Behavioral Health & Performance (archival in 2017)		
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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PI Organization Type:	NON-PROFIT	**Phone:**	301-400-4596
Organization Name:	Henry M. Jackson Foundation		
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City:	Bethesda	**State:**	MD
Zip Code:	20817-1891	**Congressional District:**	8
Comments:	Campus address (Jan 2022): Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, 4301 Jones Bridge Road, Bethesda, MD 20814. NOTE: PI formerly at Johns Hopkins University; moved to Henry M. Jackson Foundation for the Advancement of Military Medicine in fall 2020.		
Project Type:	Ground	**Solicitation / Funding Source:**	2011 NSBRI-RFA-11-01 Postdoctoral Fellowships
Start Date:	11/01/2011	**End Date:**	10/31/2014
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:**	1
No. of Bachelor's Candidates:	3	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: New end date per NSBRI December 2013 report (Ed., 12/24/13)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Hienz, Robert Ph.D. (MENTOR/ Johns Hopkins University)		
Grant/Contract No.:	NCC 9-58-PF02602		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	POSTDOCTORAL FELLOWSHIP Original Aims/Objectives Aim 1: To determine the degree to which radiation-induced deficits in neurobehavioral function differ as a function of basal dopaminergic tone. Aim 2: To determine the radioprotective effectiveness of dietary flaxseed (FS) to mitigate the deleterious effects of low-dose proton radiation on neurobehavioral function. Aim 3: To determine DAergic and inflammatory protein levels in radiation-induced, neurobehaviorally-impaired Fischer and Lewis rats and in radioprotectant-treated (FS) rats. Aim 4: To assess functional changes in dopaminergic neurotransmission following head-only proton radiation using well-characterized dopamine receptor-mediated behaviors (i.e., DA agonist-induced yawning and hypothermia). To assess the likelihood of space radiation producing changes in the central nervous system (CNS), neurobehavioral functions are being measured in rodents via an animal test analogous to 'vigilance' tests in humans. Cognitive neurobehavioral functions relevant to astronaut mission performance effectiveness are assessed with a rodent analog of the Psychomotor Vigilance Test (PVT) currently used in space analog environments and by astronauts aboard the International Space Station (ISS). Neurobehavioral functions examined include assessments of general motor function and speed, vigilance, memory, inhibitory control ('impulsivity'), timing, and motivation. Groups of PVT-trained animals with inherent differences in dopamine system function were exposed to radiation and then re-tested for up to 5 months post-exposure. In an additional study, separate groups of animals were given an experimental diet supplemented with flaxseed and underwent the same behavioral testing using the rPVT. Likely mechanisms of damage to the CNS following radiation exposure and flaxseed treatment are being examined using Western blotting of proteins relevant to neurotransmitter function and inflammation. Key Findings • Exposure to protons, 56Fe, or 28Si ions produces highly specific effects on vigilance that include a phenotypic individual differences effect in that only a subset of irradiated animals show neurobehavioral deficits (i.e., are radiation sensitive). • Deficits in rPVT performance are associated with changes in several proteins important for dopaminergic neurotransmission, such as tyrosine hydroxylase and the dopamine transporter, in the frontal and parietal cortices, two brain regions thought to regulate PVT performance in humans. • Radiation-insensitive animals appear to have increased density and/or sensitivity of D3 receptors, while radiation-sensitive rats appear to have a decrease in these same receptors or possibly an increase in D2 receptor sensitivity or levels. • d-Amphetamine dose dependently improves rPVT performance in rats displaying proton-induced deficits (i.e., radiation sensitive rats), while these same doses have no impact on sham control performance levels. Impact The key findings during this funding period further support the hypothesis that the dopamine system is sensitive to the effects of radiation exposure and is an important system underlying the behavioral deficits in radiation-sensitive rats. Proposed research for the coming year Behavioral pharmacology studies assessing the effects dopamine receptor agonists in rats pre- and post-exposure will be conducted. In addition, assessments of spontaneous locomotor activity and core body temperature in rPVT-trained rats will be recorded pre- and post-radiation to determine if any behavioral markers related to fatigue and/or inflammation are associated with radiation-induced deficits.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The critically needed research on the effects of ionizing radiation on cognitive/behavioral functions will provide the basis for extrapolating the effects of the space radiation environment on human cognitive function and performance. Earth-based applications of this research will extend to comparing the effects of other types of radiation exposures (e.g., from the workplace, medical environment, home) on neurobehavioral functions. Knowledge of those neurobehavioral functions and related brain areas affected by acute exposure to space radiation is extremely important in not only the development of a biobehavioral risk assessment model of radiation-induced deficits that could compromise operational performance during long-duration space exploration missions, but also in the development of mitigation strategies, countermeasures, as well as appropriate self-administered tests that astronauts can use to gauge their performance readiness for critical tasks. Moreover, the present rodent analog of the PVT provides a direct translational link to performance capacity on Earth. Once validated, the rPVT model developed here may be used as a basic and translational research tool to predict performance deficits induced by radiation or other CNS insults while providing an innovative experimental platform for exploring the bases of individual vulnerability to performance impairments and evaluating potential prophylactics, countermeasures, and treatments.
Task Progress:	Radiation-induced alterations in tyrosine hydroxylase in the frontal and parietal cortices, in addition to changes in the levels of the cytokine vascular endothelial growth factor (VEGF) in the frontal cortex are associated with behavioral deficits in the rPVT and could be involved in the underlying mechanisms of radiation-induced cognitive deficits. Decreases in VEGF are associated with deficits in the rPVT, whereas increases in VEGF are associated with a lack of radiation-induced deficits, when assessed 9-10 months post-radiation, and could be associated with long-term cognitive outcomes following radiation exposure. Dopamine D2 receptor-mediated hypothermia are similar in rats following radiation exposure; however, attenuation of this response via a relatively specific D2 receptor antagonist differs between radiation-sensitive and -insensitive rats, which suggests brain-region specific differences in dopamine D2 receptors or a radiation-induced change in D2 hypersensitivity. Dopamine D3 receptor-mediated yawning behavior is increased in 100 cGy-exposed radiation-sensitive rats, a finding that suggests an increase in function and/or density of

	D3 receptors in these rats. 100 cGy-exposed radiation-sensitive rats display minimal increases in yawning behavior and no attenuation of its inhibition by D2 antagonism, which suggests an increase in D2 receptor density in these animals. This finding supports the increased D2 receptor levels in 100 cGy-exposed radiation-sensitive rats we previously reported. d-Amphetamine appears to dose-dependently attenuate radiation-induced rPVT deficits in proton-exposed radiation-sensitive rats. Following amphetamine administration, radiation-sensitive rats display increased accuracy and decreased reaction times that approach sham-irradiated control performance levels.
Bibliography Type:	Description: (Last Updated: 11/29/2024)
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Awards	Davis CM. "1st Place, Best Abstract Poster Competition, Behavioral Pharmacology Division of American Society for Pharmacology and Experimental Therapeutics (ASPET) meeting, April 2014." Apr-2014
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