Fiscal Year:	FY 2015	**Task Last Updated:**	FY 11/30/2015
PI Name:	Hienz, Robert D. Ph.D.		
Project Title:	Detection & Prevention of Neurobehavioral Vulnerability 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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City:	Baltimore	**State:**	MD
Zip Code:	21224-6823	**Congressional District:**	7
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2011 Crew Health NNJ11ZSA002NA
Start Date:	07/01/2012	**End Date:**	06/30/2015
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:	5	**Monitoring Center:**	NSBRI
Contact Monitor:		**Contact Phone:**	
Contact Email:			
Flight Program:			
Flight Assignment:	NOTE: Sensorimotor Risk added per IRP Rev E (Ed., 3/19/14) NOTE: change in period of performance per July 2013 NSBRI report submission (Ed., 7/12/13) NOTE: End date change to 5/31/2015 per NSBRI (Ed., 8/23/2012)		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Roma, Peter (Institutes for Behavior Resources, Inc.)		
Grant/Contract No.:	NCC 9-58-NBPF02802		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The present research employs an innovative animal model to determine central nervous system (CNS) vulnerabilities leading to functional neurobehavioral changes during long-duration missions, and the mechanisms underlying such changes. The model assesses the short- and long-term effects of radiation exposure on cognitive neurobehavioral function and the likely mechanisms of damage to the CNS following radiation exposure. Neuro-cognitive functions relevant to astronaut performances are assessed via a rodent analog of the human Psychomotor Vigilance Test (PVT) currently used by astronauts aboard the International Space Station (ISS), which assesses general motor function and speed, vigilance, inhibitory control ('impulsivity'), and lapses in attention. Animals are trained on the rodent PVT (the rPVT), exposed to protons and high-energy particle radiation, and tested for up to 12 months post-exposure to measure short- and long-term performance deficits. Mechanisms of CNS damage following radiation exposure are examined via both pre-radiation and post-radiation behavioral pharmacology studies, and via neurochemical assessments of the CNS relevant to neurotransmitter function. Key aims of the study are to determine whether 1) pre-existing individual differences in neurotransmitter function are predictive of the observed differential neurobehavioral susceptibility of individuals to radiation; 2) the observed neurotransmitter changes are restricted to specific neurotransmitter systems and/or brain regions, and 3) differential neurobehavioral susceptibility occurs following exposure to other ion species. Key Findings: • Head-only exposure to space radiation particles at mission-relevant doses of protons (p), iron (Fe), or silicon (Si) ¬ions significantly impairs neurobehavioral function (e.g., decreases accuracy, increases impulsivity, increases lapses in attention, slows reaction times). • Individual rats show a differential susceptibility to radiation, i.e., some rats show an increased sensitivity to radiation while others appear more resistant to radiation effects. Such findings suggest the need for an individualized approach to the measurement and treatment of radiation-induced CNS deficits. • Radiation-induced differential susceptibility to neurobehavioral dysfunction correlates with increased DA protein levels in radiation-sensitive subjects. Specific findings from the past year include: Pre-Radiation DA System Status & Neurocognitive Deficits • Prior to irradiation, the sensitivity of individual animals' to DA compounds was examined via evaluations of the DA agonist d-amphetamine and a DA D2 receptor agonist quinpirole on lever pressing. Post-irradiation tests of the rPVT performances revealed ~30% of the animals were classified as radiation-sensitive (i.e., showing neurocognitive deficits). When the pre-exposure pharmacological data were then re-analyzed as a function of post-exposure radiation sensitivity, rats that eventually showed a sensitivity to radiation exposure also showed an increased sensitivity to d-amphetamine prior to exposure, relative to radiation-insensitive and unexposed control rats, indicating that neurocognitive changes may be linked to individual differences in the pre-radiation DA system status (e.g., increased DA system sensitivity may be predictive of subsequent radiation sensitivity). Dopaminergic Modulation of Radiation-Induced Neurocognitive Deficits • Radiation-induced deficits in rPVT performances are mitigated by injections of the DA agonist d-amphetamine. Following proton irradiation, radiation-sensitive animals show decreased performance accuracy and slowed reaction times, while sham-irradiated controls and radiation-insensitive animals do not. Administrations of d-amphetamine (0.56, 1.0, 1.8, or 3.2 mg/kg) produce dose-dependent recovery of both accuracy and reaction time speed in radiation-sensitive animals. Additional pharmacological evaluations of the norepinephrine reuptake inhibitor atomoxetine showed no differential effects on rPVT performance on radiation-sensitive vs. insensitive rats. Taken together, these data provide additional evidence of the specific involvement of the DA system in radiation-induced neurobehavioral deficits. Changes in Dopaminergic Modulation following Radiation • Drug-induced yawning is a sensitive metric for determining subtle changes in the DA system. Administration of a DA D2/D3 receptor agonist results in a predictable pattern of drug-induced yawning in which yawning frequency first increases as the drug dose is increased, and then decreases at successively higher doses. This rising and falling pattern results from activation of the yawning reflex by D3 receptors on the ascending limb, and by inhibition of yawning by D2 receptors on the descending limb. Following 100 cGy proton exposures, differential shifts in the ascending limbs of these curves have been observed: 1) yawning is reduced in radiation sensitive rats and is unchanged following administration of a D2 antagonist, suggesting continued D2 receptor hypersensitivity and possibly increased D2 receptor levels; 2) yawning is greatest in radiation-insensitive rats and increases dose-dependently following administration of a D2 antagonist, which suggests a faster decrease in D2 hypersensitivity, in addition to altered D3 receptor levels. In sum, the results suggest altered DA signaling in radiation-sensitive rats. A new publication describes the effects of proton irradiation on rodents' performance of an automated intra-dimensional set-shifting task. Results showed decreased responding and elevated numbers of omitted trials during the first two performance stages; when tested on an added social recognition memory test, the same animals showed no significant memory effects. Plans for the Coming Year: This was the last year of the project.
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. In addition, the development of a comprehensive and experimentally flexible animal model of neurobehavioral performance provides a useful tool for preclinical research and development in other domains such as sleep/chronobiology, neuropsychiatric disorders, aging, and cognitive enhancement. Moreover, the human

	Psychomotor Vigilance Test (PVT) is a standardized and widely validated objective measure of neurobehavioral status not only employed by NASA, but also utilized in a variety of settings such as clinical neuropsychiatric assessment, military, shiftwork, and aviation. As such, 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:	57 new rats were trained in the rPVT and tested with multiple DA compounds to determine the susceptibility of individual rats to DA agonists and antagonists prior to and following irradiation. 49 new rats were used to examine the effects of protons (10-100 cGy at 150 MeV/n) on the behavior, neuropharmacology, and neurochemistry underlying differential susceptibility to low-dose irradiation. Specific findings from the past year include: Prior to irradiation, the sensitivity of individual animals' to DA compounds was examined via evaluations of the DA agonist d-amphetamine and a DA D2 receptor agonist quinpirole on lever pressing. Post-irradiation tests of the rPVT performances revealed ~30% of the animals were classified as radiation-sensitive (i.e., showing neurocognitive deficits). When the pre-exposure pharmacological data were then re-analyzed as a function of post-exposure radiation sensitivity, rats that eventually showed sensitivity to radiation exposure also showed an increased sensitivity to the DA agonist prior to exposure, indicating that neurocognitive changes may be linked to increased DA system sensitivity prior to radiation. Dopaminergic Modulation of Radiation-Induced Neurocognitive Deficits: Radiation-induced deficits in rPVT performances are mitigated by injections of the DA agonist d-amphetamine. Radiation-sensitive animals show decreases in performance accuracy and slowed reaction times; administration of d-amphetamine, however, produces dose-dependent recovery of both performance accuracy and reaction time speed in radiation-sensitive animals. The norepinephrine reuptake inhibitor atomoxetine shows no differential effects on rPVT performance on radiation-sensitive vs. insensitive rats, which suggests the specific involvement of the DA system in these neurobehavioral deficits. Changes in Dopaminergic Modulation following Radiation: Drug-induced yawning is a sensitive metric for determining subtle changes in the DA system. Administration of a DA agonist produces predictable rising and falling pattern of drug-induced yawning in which yawning first increases as the drug dose is increased, and then decreases at successively higher doses. This pattern results from activation of yawning by D3 receptors on the ascending limb, and by inhibition of yawning by D2 receptors on the descending limb. Proton exposures produce differential shifts in the ascending limbs of these curves: 1) yawning is reduced in radiation sensitive rats and is unchanged following administration of a D2 receptor antagonist, which suggests continued D2 receptor hypersensitivity and possibly increased D2 receptor levels; 2) yawning is greatest in the radiation insensitive rats and dose-dependently increases following administration of a D2 receptor antagonist, which suggests a faster decrease in D2 hypersensitivity in addition to altered D3 receptor levels and/or function. In sum, the results suggest altered DA signaling in radiation-sensitive rats.
Bibliography Type:	Description: (Last Updated: 01/12/2021)
Articles in Peer-reviewed Journals	Davis CM, Roma PG, Hienz RD. "A rodent model of the human psychomotor vigilance test: Performance comparisons." Journal of Neuroscience Methods. 2016 Feb 1;259:57-71. Epub 2015 Nov 27. http://dx.doi.org/10.1016/j.jneumeth.2015.11.014 ; PubMed PMID: 26639896 (originally reported in August 2015 as "Submitted") , Feb-2016
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Articles in Peer-reviewed Journals	Davis CM, Roma PG, Hienz RD. "The Rodent Psychomotor Vigilance Test (rPVT): A method for assessing neurobehavioral performance in rats and mice." J Vis Exp. 2016 Dec 29;(118). https://doi.org/10.3791/54629 ; PubMed PMID: 28060276 , Dec-2016
Awards	Davis CM. "NSBRI Career Development Award, November 2014." Nov-2014
Awards	Gupta SR. "1st Place, Undergraduate Poster Contest, American Society for Pharmacology and Experimental Therapeutics Division for Behavioral Pharmacology, March 2015." Mar-2015