Fiscal Year:	FY 2014	**Task Last Updated:**	FY 08/21/2014
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:	2	**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:	Assessing the biological consequences of living in the space radiation environment represents one of the highest priority areas of NASA research. Of critical importance is the need for an assessment of the vulnerabilities of the central nervous system (CNS) leading to functional neurobehavioral changes during long-term space missions, and the development of effective countermeasures to such risks. The present research addresses this need via the application of an innovative animal model to determine 1) the short- and long-term effects of radiation exposure on cognitive neurobehavioral function; and 2) the likely mechanisms of damage to the CNS following radiation exposure. Cognitive neurobehavioral functions relevant to astronaut mission performance effectiveness are being assessed with a rodent analog of the human Psychomotor Vigilance Test (PVT) currently used in space analog environments and by astronauts aboard ISS, which includes assessments of general motor function and speed, vigilance, inhibitory control ('impulsivity'), timing, motivation, and basic sensory function. Animals trained on the rodent version of the PVT (the rPVT) are subsequently exposed to protons and high-energy particle radiation and then tested for up to 12 months post-exposure to assess potential short- and long-term performance deficits. Likely mechanisms of damage to the CNS following radiation exposure are examined via pre-radiation behavioral pharmacology studies as well as post-radiation behavioral pharmacology studies and neurochemical assessments of CNS proteins relevant to neurotransmitter function and inflammation. Key aims of the study are to determine 1) whether pre-existing individual differences in neurotransmitter function may be predictive of the observed differential neurobehavioral susceptibility of individuals following proton radiation; 2) whether the observed neurotransmitter changes are restricted to specific brain regions; and 3) whether differential neurobehavioral susceptibility occurs following exposure to other ion species. Key Findings: Results from the project have demonstrated that head-only exposure to space radiation (protons, 56Fe, 28Si) significantly impairs neurobehavioral function (e.g., decrease accuracy, increase impulsivity, increase lapses in attention) and slows motor function. These findings support the success of the rPVT as a rodent model for studying the risks of living in the space radiation environment due to changes in neurobehavioral function. Specific findings from the past year include: 1. Pre-exposure evaluations of a DA agonist and antagonist on FR/FI performance were completed. Following radiation, retests on the rPVT performances revealed ~30% of the animals to be classified as radiation-sensitive. Post-exposure pharmacological challenges with a DA agonist and antagonist are underway to determine whether radiation-induced changes in the DA system are linked to pre-radiation DA system changes (i.e., whether pre-radiation DA system sensitivities may be predictive of subsequent radiation sensitivity). 2. Drug-induced yawning is being used as a sensitive metric for determining subtle changes in D2 and D3 activity in rodents. A rising and falling pattern of DA-induced yawning in rodents is induced by activation of the D3 receptor on the ascending limb, and by inhibition by the D2 receptor on the descending limb. This differential modulation by D3 and D2 antagonists results in D3-preferring antagonists producing selective rightward shifts of the ascending limb, and D2-preferring antagonists producing selective shifts of the descending limb. Following 25-100 cGy proton exposures, differential shifts in the ascending limbs of these curves have been observed, suggesting that D3 receptor activity and/or tissue levels are altered by radiation. 3. A study (part of Catherine Davis' NSBRI Postdoctoral Fellowship) determined the degree to which radiation-induced deficits in neurobehavioral function differ as a function of changes in cytokine protein expression. Brain tissue of both F344 and LEW rPVT-trained rats were found to have differential changes in frontal cortex cytokine levels; several neurotrophic and putative pro-cognitive cytokines were significantly elevated in the LEW rats, which could underlie the lack of radiation-induced rPVT deficits in this strain. Western blot analyses of several different proteins important for dopamine neurotransmission (e.g., dopamine transporter, D2 receptor, tyrosine hydroxylase) and cell survival (e.g., Akt, p-Akt, CREB), in addition to various cytokines (e.g., TNF-a, Il-1a, Il-6, GM-CSF, CNTF, VEGF) in the frontal and parietal cortices of the F344 and LEW rats were found to be differentially altered following proton exposure. 4. Two new publications have appeared that demonstrate 1) Exposure to head-only proton irradiation differentially disrupts rPVT performance in a subgroup of radiation-sensitive animals, and that these deficits are correlated with changes in the levels of the dopamine transporter and the D2 receptor in this subgroup; and 2) following proton irradiation, rats performing an automated intra-dimensional set shifting task respond less and have elevated numbers of omitted trials during the first two performance stages, but show no effects of radiation on social recognition memory. Plans for the Coming Year: Plans include completing 1) behavioral pharmacology studies to determine the degree to which pre-existing individual differences in neurotransmitter function may be predictive of the observed differential neurobehavioral susceptibility of individuals following radiation, 2) neurotransmitter protein level studies to determine the degree to which the observed neurotransmitter changes are restricted to specific brain regions, and 3) continued support of Dr. Catherine Davis' NSBRI Postdoctoral Fellowship studies designed to assess neurochemical changes in the brain following radiation.
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:	During this year, 108 rats were trained and exposed to proton radiation (doses of 10-100 cGy at 150 MeV/n) in studies that examined the effects of proton radiation on the behavior, neuropharmacology, and neurochemistry underlying differential susceptibility to low-dose irradiation. 1. Neurotransmitter studies are assessing levels of neurotransmitter protein, terminal degradation (via changes in related protein levels), and inflammatory proteins commonly active following brain trauma. Tissue has been collected at 1 and 5 months post-radiation, and neurochemical cytokine analyses are ongoing. 2. Behavioral pharmacology studies are examining radiation effects on the integrity of the DA system in trained rats via comparison of pre- and post-radiation assessments of their sensitivity to neurotransmitter receptor indirect agonists, agonists, and antagonists via 3 procedures: the rPVT procedure, a mixed FR-30/FI-2 min operant schedule, and a drug-induced yawning procedure. A. Pre-exposure evaluations of a DA agonist and antagonist on FR/FI performance were completed and the animals subsequently irradiated. Post-exposure challenges with a these same drugs are underway to assess whether radiation-induced changes in the DA system are linked to pre-radiation DA system changes (i.e., whether pre-radiation DA system sensitivities may be predictive of subsequent radiation sensitivity). B. Drug-induced yawning is a sensitive metric for determining subtle changes in D2 and D3 activity in rodents. A rising and falling pattern of DA-induced yawning in rodents is induced by activation of the D3 receptor on the ascending limb, while inhibition of yawning is observed at higher doses (descending limb) via concomitant activation of the D2 receptor. Following 25-100 cGy proton exposures, differential shifts in these curves have been observed, suggesting that activity of these receptors is altered following exposure. 3. A study (part of Catherine Davis' NSBRI Postdoctoral Fellowship) determined the degree to which radiation-induced deficits in neurobehavioral function differ as a function of changes in cytokine protein expression. Brain tissue of both F344 and LEW rPVT-trained rats were found to have differential changes in frontal cortex cytokine levels; several neurotrophic cytokines were significantly elevated in the LEW rats, which could underlie the lack of radiation-induced rPVT deficits in this strain. Many of these same cytokines were significantly decreased in the irradiated F344 rats, the strain displaying rPVT deficits following radiation. Analyses of several different proteins important for dopamine neurotransmission (e.g., dopamine transporter, D2 receptor, tyrosine hydroxylase) and cell survival (e.g., Akt, p-Akt, CREB), in addition to various cytokines (e.g., TNF-a, Il-1a, Il-6, GM-CSF, CNTF, VEGF) in the frontal and parietal cortices of the F344 and LEW rats have been found to be differentially altered following proton exposure.
Bibliography Type:	Description: (Last Updated: 01/12/2021)
Articles in Peer-reviewed Journals	Davis CM, Roma PG, Armour E, Gooden VL, Brady JV, Weed MR, Hienz RD. "Effects of x-ray radiation on complex visual discrimination learning and social recognition memory in rats." PLoS One. 2014 Aug 6;9(8):e104393. eCollection 2014. http://dx.doi.org/10.1371/journal.pone.0104393 ; PubMed PMID: 25099152; PubMed Central PMCID: PMC4123910 , Aug-2014
Articles in Peer-reviewed Journals	Davis CM, DeCicco-Skinner KL, Roma PG, Hienz RD. "Individual differences in attentional deficits and dopaminergic protein levels following exposure to proton radiation." Radiation Research. 2014 Mar;181(3):258-71. http://dx.doi.org/10.1667/RR13359.1 ; PubMed PMID: 24611657 , Mar-2014
Awards	Davis CM. "1st Place, Best Abstract Competition, Behavioral Pharmacology Division of ASPET, April 2014." Apr-2014