Fiscal Year:	FY 2016	**Task Last Updated:**	FY 06/10/2016
PI Name:	Hienz, Robert D. Ph.D.		
Project Title:	Countermeasures for 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) **HFBP**:Human Factors & Behavioral Performance (IRP Rev H)		
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:	21224-6823	**Congressional District:**	7
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2013 HERO NNJ13ZSA002N-Crew Health (FLAGSHIP & NSBRI)
Start Date:	06/01/2015	**End Date:**	05/31/2017
No. of Post Docs:	0	**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: Element change to Human Factors & Behavioral Performance; previously Behavioral Health & Performance (Ed., 1/18/17) NOTE: Change in period of performance per NSBRI (formerly 7/1/15-6/30/17)--Ed., 7/7/15		
Key Personnel Changes/Previous PI:			
COI Name (Institution):	Davis, Catherine Ph.D. (Johns Hopkins Medical School) Roma, Peter Ph.D. (Institutes for Behavior Resources, Inc.)		
Grant/Contract No.:	NCC 9-58-NBPF04201		
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Task Description:

As spelled out in NASA's Integrated Research Plan, it is essential that methods are developed to detect behavioral changes induced by radiation exposures and that potential countermeasures are developed for mitigating radiation damage. To this end, this research focuses on determining the effectiveness of biomedical countermeasures for mitigating the effects of space radiation on human central nervous system (CNS) function. Specifically, the studies assess the effectiveness of a number of Food and Drug Administration (FDA)-approved compounds to lessen the deleterious effects of radiation exposure on CNS function (sustained attention). This work provides data in an animal analog of the human Psychomotor Vigilance Test (PVT) that is used for human risk assessments. Rats are trained in a rodent version of the human PVT, exposed to proton irradiation at NASA's Space Radiation Laboratory at Brookhaven National Laboratory, and then returned to Johns Hopkins for extended post-exposure testing to identify long-term neurobehavioral deficits and assess the effectiveness of pharmacologic compounds to mitigate the deficits. Mechanisms of action are evaluated by employing different types of potential mitigating compounds (i.e., when administered after radiation exposure), including those that directly alter dopaminergic (DA) signaling by binding to the DA transporter protein (DAT; e.g., methylphenidate), compounds that directly alter DA signaling by binding to receptors from the D2 receptor family (e.g., aripiprazole), and compounds that otherwise indirectly alter DA levels (e.g., NE reuptake inhibition, atomoxetine). Two additional FDA-approved compounds – the putative DNA repair targeting drug cholorquine, and the hemopoietic growth factor erythropoietin (EPO)– will also be assessed for their potential radioprotective effects (i.e., when administered prior to radiation exposure) as well as their alternative mechanisms of action.
Key Findings from the past year include: Psychostimulants as potential countermeasures for proton-induced deficits in neurobehavioral function

• The psychostimulant d-amphetamine (DA releaser, indirect DA agonist) produced dose-dependent recovery of both accuracy and reaction time speed in radiation-sensitive animals; in radiation-insensitive animals, d-amphetamine produced decrements in performances.

• The DA/NE reuptake inhibitor methylphenidate also produced dose-dependent recovery of performance in radiation-sensitive animals, but had no effect in radiation-insensitive animals (i.e., unlike d-amphetamine, it did not impair performances in this latter group).

• The NE reuptake inhibitor atomoxetine showed no differential effects on rPVT performance in radiation-sensitive or radiation-insensitive rats.

• SCH 39166, a D1 receptor antagonist, blocked amphetamine's effects on percent correct responding, indicating that D1 receptors are responsible for amphetamine-induced changes in rPVT performance.

• L-741,626, a D2 receptor antagonist, did not block amphetamine's effects, indicating that D2 receptors are not involved in the amphetamine-induced changes in rPVT performance. The data provide 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. DA D2/D3 receptor agonists produce 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. The rising/falling pattern results from reflex activation by D3 receptors on the ascending limb, and by inhibition by D2 receptors on the descending limb.

• Differences in dopamine-agonist induced yawning and its antagonism by a dopamine D2 receptor antagonist (L-741,626) were found between radiation-sensitive and radiation-insensitive rats. Greater levels of yawning were found in radiation insensitive rats, whereas radiation sensitive rats displayed reduced levels of induced yawning. ED50 values (the dose effective in 50% of subjects) also significantly differed between the radiation sensitive and insensitive rats. Thus D2 dopamine receptors are altered in radiation sensitive rats, and D3 receptors may be altered in radiation insensitive rats.

Two new publications during this reporting period:

• "Deficits in Sustained Attention and Changes in Dopaminergic Protein Levels following Exposure to Proton Radiation Are Related to Basal Dopaminergic Function" describes the effects of proton irradiation in inbred adult male Fischer 344 and Lewis rats performing the rPVT. These strains were used to determine if genetic differences in dopaminergic function would impact radiation-induced deficits in sustained attention. Proton irradiation disrupted rPVT performance in a strain-specific manner, with Fischer 344 rats displaying deficits in sustained attention while Lewis rats did not, indicating that basal dopaminergic function impacts the severity of radiation-induced deficits in sustained attention.

• "A rodent model of the human psychomotor vigilance test: Performance comparisons" describes the design and empirical validation of the rPVT, and demonstrates that 1) rats and humans show similar performances on several PVT behavioral measures, 2) the rPVT is an effective task for preclinical studies assessing attention, and 3) the rPVT is extremely sensitive to radiation-induced deficits.

Plans for the Coming Year: Sixty animals were irradiated in April of 2016, and will receive administrations of 5 compounds to assess their potential radiation-mitigating effects on neurocognitive function (modafinil, reboxetine, aripiprazole, pramipexole, memantine). Two additional groups of 80 rats each will be exposed in June and November of 2016 to assess the effects of human EPO and chloroquine, respectively, in preventing radiation-induced deficits in neurocognitive function.

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 funding year 60 male Long-Evans rats were used in the studies. The new rats were trained in the rPVT and exposed to protons (10, 100 cGy at 150 MeV/n) in April of 2016. They will subsequently be tested with multiple DA compounds to determine the susceptibility of individual rats to DA agonists and antagonists prior to and following irradiation. Specific findings from this year include: Psychostimulants as potential countermeasures for proton-induced deficits in neurobehavioral function: • The psychostimulant d-amphetamine (DA releaser, indirect DA agonist) produced dose-dependent recovery of both accuracy and reaction time speed in radiation-sensitive animals; in radiation-insensitive animals, d-amphetamine produced decrements in performances. • The DA/NE reuptake inhibitor methylphenidate also produced dose-dependent recovery of performance in radiation-sensitive animals, but had no effect in radiation-insensitive animals (i.e., unlike d-amphetamine, it did not impair performances in this latter group). • The NE reuptake inhibitor atomoxetine showed no differential effects on rPVT performance in radiation-sensitive or radiation-insensitive rats. • SCH 39166, a D1 receptor antagonist, blocked amphetamine's effects on percent correct responding, indicating that D1 receptors are responsible for amphetamine-induced changes in rPVT performance. • L-741,626, a D2 receptor antagonist, did not block amphetamine's effects, indicating that D2 receptors are not involved in the amphetamine-induced changes in rPVT performance. The data provide 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. DA D2/D3 receptor agonists produce 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. The rising/falling pattern results from reflex activation by D3 receptors on the ascending limb, and by inhibition by D2 receptors on the descending limb. • Differences in dopamine-agonist induced yawning and its antagonism by a dopamine D2 receptor antagonist (L-741,626) were found between radiation-sensitive and radiation-insensitive rats. Greater levels of yawning were found in radiation insensitive rats, whereas radiation sensitive rats displayed reduced levels of induced yawning. ED50 values (the dose effective in 50% of subjects) also differed significantly between the radiation sensitive and insensitive rats. Thus D2 dopamine receptors are altered in radiation sensitive rats, and D3 receptors may be altered in radiation insensitive rats.
Bibliography Type:	Description: (Last Updated: 01/12/2021)
Articles in Peer-reviewed Journals	Davis CM, DeCicco-Skinner KL, Hienz RD. "Deficits in sustained attention and changes in dopaminergic protein levels following exposure to proton radiation are related to basal dopaminergic function." PLoS One. 2015 Dec 10;10(12):e0144556. eCollection 2015. http://dx.doi.org/10.1371/journal.pone.0144556 ; PubMed PMID: 26658810; PubMed Central PMCID: PMC4684339 , Dec-2015
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 , Feb-2016
Awards	King S. (Scott King) "Summer Intern Fellowship awarded by the American Society of Pharmacology and Experimental Therapeutics (mentored by Dr. Davis), April 2016." Apr-2016