Fiscal Year:	FY 2017	**Task Last Updated:**	FY 02/05/2018
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		
PI Email:	bhienz@jhmi.edu	**Fax:**	FY 410-550-2780
PI Organization Type:	UNIVERSITY	**Phone:**	410-550-2788
Organization Name:	The Johns Hopkins University School of Medicine		
PI Address 1:	Department of Psychiatry & Behavioral Sciences		
PI Address 2:	5510 Nathan Shock Drive		
PI Web Page:			
City:	Baltimore	**State:**	MD
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		
Performance Goal No.:			
Performance Goal Text:			

Task Description:

This research determined the effectiveness of biomedical countermeasures to mitigate the effects of space radiation on central nervous system (CNS) function. Using an animal analog of the human Psychomotor Vigilance Test (PVT) that is used for human risk assessment, the studies assessed 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) in rats. Rats were trained in a rodent version of the human PVT, exposed to proton irradiation at NASA's Space Radiation Laboratory at Brookhaven National Laboratory, and returned to Johns Hopkins for post-exposure testing to 1) identify long-term neurobehavioral deficits, and 2) assess the effectiveness of pharmacologic compounds to mitigate the deficits. Mechanisms of action were evaluated by employing different types of potential mitigating compounds (i.e., given after radiation exposure), such as those that directly alter dopaminergic (DA) signaling by binding to the DA transporter protein (DAT; e.g., methylphenidate), those that directly alter DA signaling by binding to receptors from the D2 receptor family (e.g., aripiprazole), and those that indirectly alter DA and other monoamine levels (e.g., NE reuptake inhibition, atomoxetine). Two FDA-approved compounds – the putative DNA repair targeting drug cholorquine (CLQ), and the hemopoietic growth factor erythropoietin (EPO) – were also assessed for their potential radioprotective effects (i.e., given prior to radiation exposure) and their alternative mechanisms of action. Key Findings from this 2-year project 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 in radiation-sensitive animals, but produced performance decrements in radiation-insensitive animals.

• The DA/NE reuptake inhibitor methylphenidate also produced dose-dependent recovery of performance in radiation-sensitive animals, but did not impair performances in radiation-insensitive animals.

• 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.

• Both pramipexole (a D3 agonist) and aripiprazole (a partial D2 agonist) produced dose-dependent recovery of radiation-induced slowing of reaction times, suggesting that altered dopamine D2-like receptor signaling is involved in these deficits. Further, the improvements following aripiprazole suggest that DA tone could differ in various brain regions, with this partial agonist acting like an antagonist in areas of high DA tone and acting like an agonist in areas of low DA tone.

• The data provide evidence of the specific involvement of both D1-like and D2-like dopamine receptor systems in radiation-induced neurobehavioral deficits. Studies of potential radiation-protective compounds

• EPO – a compound involved in the brain's response to various insults, including radiation – did not improve the radiation-induced deficits in performance in radiation-sensitive rats at any doses tested.

• CLQ – a drug that improves clinical outcomes following whole-brain radiotherapy – also did not lessen radiation-induced deficits in rPVT performance; fine-grain analyses of these data are still ongoing.

Changes in Dopaminergic Modulation following Radiation

• 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.

Predicting an individual's sensitivity via analyses of pre-exposure rPVT performances

• Prior to irradiation, rats that were to subsequently show sensitivity to radiation were found to be more prone to exhibit higher levels of premature responding and lower levels of lapses in attention, thus suggesting a potential method for predicting pre-exposure individual sensitivity to radiation (see Main Findings in Task Progress section).

Two new publications during this reporting period:

• The rodent psychomotor vigilance test (rPVT): A method for assessing neurobehavioral performance in rats and mice is both a publication and a video demonstrating the procedure and documenting that rats show a high degree of similarity to human PVT performances, including similarities in lapses in attention, reaction times, decrements across a session (i.e., human time-on-task effects), and the human response-stimulus interval (RSI) effect.

• Whole-Body Oxygen Ion Exposure-Induced Impairments in Social Odor Recognition Memory in Rats are Dose and Time Dependent demonstrated that at 1 month post-exposure, irradiated rats display a memory deficit for recall of a conspecific odor experienced 24 hours prior. At 6 months post-exposure, 25 cGy-exposed rats show persistent deficits in 24-hr recognition memory, while the 5 cGy-exposed rats show recovery of recognition memory, demonstrating that space-relevant 16O ion exposure has deleterious effects on the central nervous system related to exposure dose and time post-exposure.

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 220 male Long-Evans rats were used. In April 2016, N=60 rats were trained in the rPVT and exposed to protons (100 & 25 cGy, 150 MeV/n), and subsequently tested with DA compounds (atomoxetine, memantine, pramipexole, aripiprazole). June 2016, N=80 rats were trained in the rPVT and exposed to protons (100 cGy, 150 MeV/n). Prior to exposure, subgroups were treated with 5,000, 3,000, 1,000, and 0 U/kg EPO. In October 2016, N=80 rats were trained in the rPVT and exposed to protons (100 cGy @ 150 MeV/n). Prior to exposure, subgroups were treated with 7.0, 3.5, 1.0, and 0 mg/kg chloroquine. Specific findings from the past year include: Psychostimulants as potential countermeasures for proton-induced deficits in neurobehavioral function • Both pramipexole (a D3 agonist) and aripiprazole (a partial D2 agonist) produced dose-dependent recovery of radiation-induced slowing of reaction times in the rPVT procedure, thus suggesting that altered dopamine D2-like receptor signaling is involved in radiation-induced deficits. Further, the improvements following aripiprazole suggest that dopaminergic tone could differ in various brain regions, with this partial agonist acting like an antagonist in areas of high dopaminergic tone and acting like an agonist in areas of low dopaminergic tone. The data provide evidence of the specific involvement of the DA system in radiation-induced neurobehavioral deficits. Studies of potential radiation-protective compounds • EPO – a compound involved in the brain's response to various insults, including radiation – did not improve the radiation-induced deficits in performance in radiation-sensitive rats at any doses tested. • CLQ – a drug that improves clinical outcomes following whole-brain radiotherapy – also did not lessen radiation-induced deficits in rPVT performance; fine-grain analyses of these data are still ongoing. • Both EPO and CLQ rats were tested for intact 24-hr recognition memory using the social odor recognition memory test at 6-months post-radiation. Preliminary analyses of the EPO data suggest no benefit of EPO treatment proton-induced deficits in recognition memory. Analysis of the CLQ data is ongoing. Predicting an individual's sensitivity via analyses of pre-exposure rPVT performances • A database was developed for over 400 rats subsequently exposed to proton radiation by rating each animal's rPVT performance efficiency relative to all other animals. Efficiency ratings for rats later categorized as radiation-sensitive were compared to those later categorized as radiation-insensitive. Rats that subsequently showed radiation sensitivity were more prone to exhibit high levels of premature responding and low levels of lapses in attention. Further analyses are underway to accurately pinpoint the differences in pre-exposure performances that may predict future sensitivity to radiation exposure, and whether these differences may be related to DA system tone.
Bibliography Type:	Description: (Last Updated: 01/12/2021)
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
Articles in Peer-reviewed Journals	Mange A, Cao Y, Zhang S, Hienz RD, Davis CM. "Whole-body oxygen (16O) ion-exposure-induced impairments in social odor recognition memory in rats are dose and time dependent." Radiat Res. 2018 Mar;189(3):292-9. Epub 2018 Jan 13. https://doi.org/10.1667/RR14849.1 ; PubMed PMID: 29332539 , Mar-2018
Articles in Peer-reviewed Journals	Johnson D, Lawrence SE, Livingston EW, Hienz RD, Davis CM, Lau AG. "Modeling space radiation induced bone changes in rat femurs through finite element analysis." Conf Proc IEEE Eng Med Biol Soc. 2018 Jul;2018:1763-6. https://doi.org/10.1109/EMBC.2018.8512620 ; PubMed PMID: 30440736 , Jul-2018
Awards	Davis C. "Johns Hopkins Venture Discovery Award, January 2017." Jan-2017
Awards	Hienz R, Davis C. "Seed grant from the new Space@Hopkins Institute, July 2016." Jul-2016