

Fiscal Year:	FY 2020	Task Last Updated:	FY 12/30/2019
PI Name:	Britten, Richard Ph.D.		
Project Title:	Changes in the Neuropoteome Associated with HZE-Induced Impairment of Cognition		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline-- Element/Subdiscipline:			
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 (2) Sensorimotor :Risk of Altered Sensorimotor/Vestibular Function Impacting Critical Mission Tasks		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Comments:			
Project Type:	GROUND	Solicitation / Funding Source:	2013 Space Radiobiology NNJ13ZSA001N
Start Date:	02/27/2014	End Date:	12/31/2020
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:	0	Monitoring Center:	NASA JSC
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Flight Program:			
Flight Assignment:	NOTE: Element change from SR to HFBP per Human Research Roadmap information dtd July 2019 (Ed., 1/6/2020) NOTE: Extended to 12/31/2020 per NSSC information (Ed., 3/12/19) NOTE: Extended to 12/31/2018 per S. Monk/SR/LaRC (Ed., 1/11/18)		
Key Personnel Changes/Previous PI:	December 2019 report: Dr. Douglas Wallace at Northern Illinois University (NIU) is now a CoInvestigator. Dec 2016: Drs. Semmes and Dutta were removed from the project; proteomic analysis is now being conducted at UTMB (University of Texas Medical Branch) as contract work.		
COI Name (Institution):	Wallace, Douglas Ph.D. (Northern Illinois University)		
Grant/Contract No.:	NNX14AE73G		
Performance Goal No.:			
Performance Goal Text:			

	<p>One of NASA's biggest concerns about the long-term health of astronauts who go on deep space missions is the impact that High Z, High Energy (HZE) particles have on brain function (neurocognition). Data from our laboratory and others suggests that there is significant impairment of certain neurocognitive tasks (spatial memory and Executive function-attentional set shifting) following exposure to low HZE doses. The goal of this application is to determine the Threshold dose for the induction of HZE-induced spatial memory impairments (HISMI) or Attentional Set Shifting Impairments (HIASSI) following exposure to ⁵⁶Fe, ⁴⁸Ti, and ²⁸Si particles. The proposed studies will also identify the changes in the proteome of the brain (neuroproteome) of rats that differ in their susceptibility to HISMI and HIASSI, which will provide further insight into the factors that lead to HISMI/HIASSI and perhaps more importantly, that prevent its emergence. Our underlying hypothesis is that HISMI and HIASSI arise as the direct result of HZE-induced changes in the neuroproteome. We also hypothesize that exposure to HZE species that have different track structures will result in different mechanisms of HZE-induced cognitive impairment (HICI). Collectively, these studies will give some insight into the underlying cause for HISMI and HIASSI.</p> <p>Our studies will thus address CNS (Central Nervous System) Gaps 1, 2, and 6, and we shall specifically focus on the following aims:</p> <p>Aim 1. Determine the Threshold dose for the induction of HISMI and HIASSI following exposure to ⁵⁶Fe, ⁴⁸Ti, and ²⁸Si particles when delivered as a single dose.</p> <p>Aim 2. Identify changes in the neuroproteome that are associated with susceptibility or resistance to developing HISMI and HIASSI following exposure to ⁵⁶Fe particles.</p> <p>Aim 3. Determine the mechanism of HISMI and HIASSI induced by HZE particles of differing LET (linear energy transfer).</p> <p>In Aim 1, socially mature (~6 month old) male Wistar rats will be irradiated with ⁵⁶Fe, ⁴⁸Ti, and ²⁸Si particles (with incident energies of 600 MeV/nucleon). Rats will receive whole body HZE irradiation (< 15 cGy), and HISMI and HIASSI will be assessed at 3 months post irradiation.</p> <p>In Aim 2 and 3, the composition of the neuroproteome (hippocampus and selected regions of the prefrontal cortex) of irradiated rats that have “normal” cognitive performance or have developed HISMI or HIASSI will be established using an unbiased proteomic profiling approach. We shall use a label free differential protein profiling workflow on the Q-Exactive Orbitrap mass spectrometer.</p> <p>These studies will give considerable insight into the underlying cause for HZE-induced neurocognitive failure. The proposed studies will continue to define the minimum dose of HZE particles that will induce HISMI and HIASSI. Moreover, our studies will provide considerable insight into the underlying mechanism of HICI, and will identify prognostic biomarkers that could be translated to human studies to monitor the emergence of HICI. These studies may also help to develop appropriate countermeasures and help identify sensitive individuals, so that NASA’s medical staff can implement appropriate countermeasures to protect these at risk individuals.</p> <p>Supplemental studies (in December 2019 report)</p> <p>This study will provide information on the robustness of single-exposure experiments to predict the impact of repeated episodic radiation exposures (such as will be encountered on the mission to Mars) on neurocognition. This study will test the hypothesis that episodic space radiation (SR) exposure will result in more severe neurocognitive deficits than single, or multiple daily SR doses. This study will utilize both male and female rats, and two different radiation regimens incorporating 4He ions and the 5-ion GCRsim beam. Performance in one executive function task (Attentional Set shifting-ATSET) will be assessed after a single exposure (He or GCRsim) and after a second exposure (~6 months later) to the 5-ion GCRsim beam.</p>
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	<p>These studies will give considerable insight into the underlying cause for Space radiation (SR)-induced neurocognitive impairment (SICI).</p> <p>The proposed studies will continue to define the minimum dose of SR particles that will impair cognitive flexibility (Attentional Set shifting and Unconstrained cognitive flexibility) performance. Importantly both of our cognitive flexibility tasks are homologs of tasks used in clinical testing of humans. Our studies will model the impact that single and repeated episodic exposure to SR has on neurocognitive performance and fine motor skills.</p> <p>Moreover, our studies will provide considerable insight into the underlying mechanism of SICI, and will identify prognostic biomarkers that could be translated to human studies to monitor the emergence of SICI. These studies may also help to develop appropriate countermeasures and help identify sensitive individuals, so that NASA’s medical staff can implement appropriate countermeasures to protect these at risk individuals.</p>
	<p>Project Objectives</p> <ol style="list-style-type: none"> 1. Identify the lowest dose of space radiation (SR) that results in Attentional Set Shifting (ATSET) impairment. 2. Determine if there are LET-specific mechanisms of ATSET impairment. 3. Identify changes in the neuroproteome that reflect the cognitive performance status of SR-exposed animals. <p>Supplemental studies</p> <ol style="list-style-type: none"> 4. Establish the impact that that re-irradiation with 10 cGy of simplified (5-ion) CGRsim beam has on the ATSET performance of male and female Wistar rats that maintained a functional ATSET performance after exposure to 10 cGy of either He or GCRsim. <p>Project Approach</p> <p>To better simulate the “clinical reality,” adult (proven breeder) rats that have been pre-selected for good attentional set shifting (ATSET) performance, and who have been maintained on an exercise regimen are used in this study.</p>

	<p>Rats are exposed (primarily a single exposure) to <15 cGy of SR ions (incident energy <1000 MeV/n) and ATSET performance re-established at 3 months post exposure. After completion of the ATSET test, the rats are then tested in the Unrestrained Cognitive flexibility (UCFlex) assay, that requires the rats to complete a new task (where the food reward is no longer present in either reward pot, as it was for all seven stages of the ATSET; instead the reward is located in a third location that the rat had limited experience with) that requires the rat to develop a novel solution to obtain the food reward. Thus, the UCFlex version of the ATSET provides the ability to measure both constrained and unconstrained cognitive flexibility within individual rats. Importantly, both of our cognitive flexibility tasks are homologs of tasks used in clinical testing of humans.</p> <p>Through a new collaboration with Dr. Wallace at Northern Illinois University (NIU), we have shipped our rats to NIU, where Dr. Wallace’s team has determined whether there are sensorimotor defects induced by SR, and if any observed changes are co-incidental with changes in ATSET/UCF performance. Specifically, fine motor skills have been assessed using the string-pull assay.</p> <p>Regions of the cortex, basal forebrain, hippocampus (that regulated certain paradigms with the ATSET test), and temporal lobe (that probably regulates UCFlex performance) are recovered and subjected to proteomic analysis to identify some of the processes that may be responsible for the SR-induced impairment of ATSET.</p> <p>The supplemental studies involve returning the rats that have maintained good ATSET performance after SR (10 cGy 4He ions or the 5-ion GCRsim beam) to Brookhaven National Laboratory (BNL) where they receive a second dose of 10 cGy of the 5-ion GCRsim. ATSET performance is then reassessed at 3 months after the second exposure.</p> <p>Research Highlights</p> <ul style="list-style-type: none">• SR doses as low as 1 cGy lead to the impairment of ATSET performance, particularly in the tasks regulated by the mPFC and perirhinal regions.• However, imprinted memories are preserved following SR exposure, suggesting that highly “entrained” skill sets may not be affected by SR exposure [Jewell et al., 2018].• The addition of the UCFlex test not only increases the spectrum of executive functions studied, but provides information on the impact of SR exposure on insightful problem solving, and by default on the functionality of the temporal lobe.• SR doses as low as 1 cGy impair insightful problem solving.• SR doses as low as 5 cGy impair fine motor skills, even when the rats have no apparent loss of ATSET performance.• These data suggest that a wide range of executive functions are impaired by mission pertinent SR doses, which raises concerns about whether other executive functions that regulate risk decision making and impulsivity are also affected.• The use of Kernel Density Estimation to interrogate the distribution of ATSET performance metrics in sham and irradiated rats facilitates the quantification of severely impaired individuals. Substitution of the percentage of severely impaired individuals into the Numbers Needed to Harm (NNH) algorithm provides an estimation of the absolute risk increase on cognitive performance by SR: 34% following 3 cGy Fe, 36% following 18 cGy protracted neutron (data from NSCOR--NASA Specialized Center of Research--studies). <p>Brain regions impacted by SR exposure.</p> <p>The tasks most frequently impaired after SR exposure were Simple Discrimination (SD) and Compound Discrimination (CD). SD is regulated by the mPFC; CD is probably regulated by perirhinal cortical region, and requires optimal dopamine D2 receptor activation in pre-frontal cortex. The impairment of UCFlex performance is indicative of changes in the functionality of the temporal lobe.</p> <p>Changes in the Neuroproteome associated with changes in ATSET performance.</p> <p>The first batch of pre-frontal cortex samples were run over the summer of 2017, and Dr. Britten has analyzed the vast amount of proteomic data generated. It is clear that there are proteins whose expression changes as a result of radiation exposure, and other proteins whose expression differs in relationship to the ability of the rats to perform ATSET, including GABAergic signaling pathways.</p> <p>Reference:</p> <p>Jewell JS, Duncan VD, Fesshaye A, Tondin A, Macadat E, Britten RA. Exposure to <15 cGy of 600 MeV/n 56Fe particles impairs rule acquisition but not long-term memory in the attentional set-shifting assay. Radiat Res. 2018; 190: 565-575.</p>
Task Progress:	
Bibliography Type:	Description: (Last Updated: 02/21/2024)