Fiscal Year:	FY 2022	**Task Last Updated:**	FY 12/29/2021
PI Name:	Britten, Richard Ph.D.		
Project Title:	Changes in the Neuroproteome 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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Zip Code:	23507-1607	**Congressional District:**	3
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2013 Space Radiobiology NNJ13ZSA001N
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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:	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 4/30/2023 per NSSC information (Ed., 12/30/2020) 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 2021 report: Dr. Jessica Burket at Christopher Newport University has been added to the project to conduct the social interaction studies. Dr Ashley Blackwell at Eastern Virginia Medical School has been added to the project to conduct the string pulling and neural network cohesiveness studies. 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) Blackwell, Ashley Ph.D. (Eastern Virginia Medical School) Burket, Jessica Ph.D. (Christopher Newport University)		
Grant/Contract No.:	NNX14AE73G		

Performance Goal No.:	
Performance Goal Text:	
Task Description:	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. Our studies will thus address CNS (Central Nervous System) Gaps 1, 2, and 6, [Ed. note February 2022: Human Research Program risks and gaps have changed since this project was initiated--see Human Research Roadmap for updated gaps: https://] and we shall specifically focus on the following aims: 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. Aim 2. Identify changes in the neuroproteome that are associated with susceptibility or resistance to developing HISMI and HIASSI following exposure to 56Fe particles. Aim 3. Determine the mechanism of HISMI and HIASSI induced by HZE particles of differing LET (linear energy transfer). 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. 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. 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. Supplemental studies (in December 2019 report) 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 SR exposure will result in more severe neurocognitive deficits than single, or multiple daily SR doses. In addition, this study will be a robust (akin to a pHase III clinical trial) concurrent validation of the effect of a single dose of 10 cGy simplified 6-ion GCRSim versus a single dose of 10 cGy 250 MeV/n He ions on ATSET/UCFlex performance using the same batch of rats, laboratory personal, transport and environmental conditions. This study will utilize both male and female rats, and two different radiation regimens incorporating 4He ions and the 6-ion GCRsim beam. Executive function performance (ATSET) will be assessed after a single exposure (He or GCRsim) and after a second exposure (~6 months later) to the 6-ion GCRsim beam. To maximize the amount of data obtained from these expensive studies, where possible (dependent upon volunteers in the Britten lab) the impact of these radiations on sensorimotor (string pulling activity), social interaction and switch task performance will also be established.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	These studies will give considerable insight into the underlying cause for Space radiation (SR)-induced neurocognitive impairment (SICI). 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. 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.

Task Progress:

Project Objectives
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.

Supplemental studies

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.

Project Approach

To better simulate the “clinical reality”, adult rats that have been pre-selected for good ATSET performance and who have been maintained on an exercise regimen are used in this study. The first radiation exposures will occur when the rats are ~7 months old. While the biological equivalent age of these 7-month-old rats is closer to that of a 30-year-old human, which is currently younger than most astronauts, the use of such rats allows for the long-term monitoring of cognitive decline, which is less likely to be impacted by age-related cognitive decline.

Rats are exposed to 10 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 Unconstrained Cognitive flexibility (UCFlex) assay, which requires the rats to complete a new task, where the food reward is no longer present in either reward bowl, 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 rats to develop a novel solution to obtain the food reward. Thus, the UCFlex version of the ATSET task interrogates both constrained and unconstrained cognitive flexibility performance within individual rats. Importantly both cognitive flexibility tasks are homologs of tasks used in clinical testing of humans.

Executive functions also regulate social interactions and mood; should SR-exposure alter these executive functions as it does cognitive flexibility, there is the possibility of altered inter-crew interactions and team cooperativity during prolonged space exploration. We have previously reported that exposure to 5 cGy He ions leads to social withdrawal (within freely interacting dyads) in male Wistar rats (Burket et al., 2021). Dr. Burket and her students will determine the relative impact that GCRSim and He ions have on social withdrawal.

We have shown that rats that have no significant loss of ATSET performance after SR (Si) exposure can have significant loss of fine motor skills (Blackwell et al., 2021). Dr. Blackwell has now joined the Britten laboratory and will characterize the impact that He and GCRsim exposure has on fine motor skill performance. Importantly, these studies will be conducted in close temporal proximity (2-3 days) to radiation exposure as well as our traditional 3 month time point.

Brain regions (that regulated certain paradigms within the ATSET and UCFlex tasks) are recovered and subjected to proteomic analysis to identify some of the processes that may be responsible for the SR-induced impairment of cognitive and sensorimotor function.

The supplemental studies involve returning the rats that have maintained good ATSET performance after SR (10 cGy 4He ions or the 6-ion GCRsim beam) to Brookhaven National Laboratory (BNL) where they receive a second dose of 10 cGy of the 6-ion GCRsim. Cognitive and sensorimotor performance is then reassessed at 3 months after the second exposure.

Research Highlights from this reporting period.

• Low doses (10 cGy) of simplified GCRSim significantly impairs ATSET performance, specifically in the Simple Discrimination task. These data extend the range of space radiation ions that have a significant impact upon SD performance to include He (Burket et al., 2021), Si (Britten et al., 2020), Ti (Parihar et al., 2016), Fe (Jewell et al., 2018), protracted mixed neutrons (Britten et al., 2021), and now GCRSim. Impairment of SD performance would thus appear to be the common consequence of exposure to every SR ion studied to date. SR-exposed rats take between 1.5 (Si (Britten et al., 2020)) to 2.6 (neutron (Britten et al., 2021))-fold more attempts to reach criterion (Impairment ratio) than sham rats.

• An assessment of performance savings (a concept widely used in many fields to define the faster response to a situation that has been previously encountered than when it was initially encountered) revealed that both He and GCRSim exposure eliminated performance savings in the ATSET task.

• Low doses (10 cGy) of simplified GCRSim significantly impair UCFlex (creative problem solving) performance.

• We conducted a robust (akin to a phase III clinical trial) concurrent validation of the effect of a single dose of 10 cGy simplified 6-ion GCRSim versus a single dose of 10 cGy 250 MeV/n He ions on ATSET/UCFlex performance using the same batch of rats, laboratory personal, transport, and environmental conditions. While both He ions and GCRsim significantly impaired ATSET performance, there was no obvious difference in the incidence nor severity of the ATSET performance. Similarly, there were no obvious differences in the severity of UCFlex impairment induced by He and GCRSim.

• Exposure to low (10 cGy) doses of He ions led to significant impairment of string pulling (fine motor skill) performance within 72 hours of exposure. He-exposed rats took longer to approach the string and to start the recovery of the string, indicating disruptions in motivation, attention, or sensorimotor function. By 3 months both He and GCRSim exposed rats exhibited longer approach and recovery times.

• Both He and GCRSim exposed rats had significant problems in completing a high cognitive task load assay. When the task was compartmentalized, so that the rats were presented with incremental changes instead of simultaneous changes, over 90% of the SR-exposed rats that previously failed the high cognitive task load assay were able to complete it after the incremental “remedial” training.

• GCRSim-exposed, but not He-exposed rats that completed the high cognitive task load assay, had a significantly decreased ability to switch attention (higher switch cost) in a task that mimics those used to assess pilot response times. The magnitude of this deficit would nearly double the rate of errors in flight simulator exercises.

	• The doubly irradiated rat study has shown that there are further decrements in ATSET and UCFlex performance induced in rats that retained a high level of performance after a single SR exposure. The most notable feature of the performance decrements induced after the second exposure is the lack of any performance savings. While it is reassuring that no further losses in performance (completion percentage) occurred, the inability to improve performance with practice (MCL) is problematic. • We identified unique protein signatures in the hippocampal proteome of: 1) sham rats, 2) Ti-exposed rats, 3) Ti-exposed rats that had sham-like spatial memory performance, and 4) Ti-exposed rats that impaired spatial memory performance (Tidmore et al., 2021). SR-exposure was also associated with a switch towards increased pro-ubiquitination proteins from that seen in shams. These data suggest that the role of the ubiquitin-proteome system as a determinant of SR-induced neurocognitive deficits needs to be more thoroughly investigated. References Burket JA, Matar M, Fesshaye A, Pickle JC, Britten RA. Exposure to low (=10 cGy) doses of 4He particles leads to increased social withdrawal and loss of executive function performance. Radiat Res. 2021, 196:345-354. Blackwell AA, Schell BR, Osterlund Oltmanns JR, Whishaw IQ, Ton ST, Adamczyk NS, Kartje GL, Britten RA, Wallace DG. Skilled movement and posture deficits in rat string-pulling behavior following low dose space radiation (28Si) exposure. Behav Brain Res. 2021;400:113010. Britten RA, Duncan VD, Fesshaye A, Rudobek E, Nelson GA, Vlkolinsky R. Altered cognitive flexibility and synaptic plasticity in the rat prefrontal cortex after exposure to low (< or =15 cGy) doses of 28Si radiation. Radiat Res. 2020 Mar;193(3):223-35. Parihar V, Allen B, Caressi C, Kwok S, Chu E, Tran K, Chmielewski N, Giedzinski E, Acharya M, Britten RA, Baulch J, Limoli CL. Cosmic radiation exposure and persistent cognitive dysfunction. Sci Reports 2016, 6: 34774. 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. Britten RA, Duncan VD, Fesshaye AS, Wellman LL, Fallgren CM, Sanford LD. Sleep fragmentation exacerbates executive function impairments induced by protracted low dose rate neutron exposure. Int J Radiat Biol. 2021;97(8):1077-1087. Tidmore A, Dutta SM, Fesshaye AS, Russell W, Duncan VD, Britten RA. Space radiation induced alterations in the hippocampal ubiquitin-proteome system. Int J Mol Sciences 2021;22: 7713.
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