Fiscal Year:	FY 2023	**Task Last Updated:**	FY 12/29/2022
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		
PI Email:	Brittera@evms.edu	**Fax:**	FY
PI Organization Type:	NON-PROFIT	**Phone:**	757-446-5038
Organization Name:	Eastern Virginia Medical School		
PI Address 1:	Radiation Oncology		
PI Address 2:	700 W Olney Rd		
PI Web Page:			
City:	Norfolk	**State:**	VA
Zip Code:	23507-1607	**Congressional District:**	3
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2013 Space Radiobiology NNJ13ZSA001N
Start Date:	02/27/2014	**End Date:**	06/30/2024
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
Contact Monitor:	Whitmire, Alexandra	**Contact Phone:**	
Contact Email:	alexandra.m.whitmire@nasa.gov		
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 6/30/2024 per NSSC information (Ed., 8/3/23) 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 2022 report: Dr. Dorela Shuboni-Mulligan of Eastern Virginia Medical School has been added to the project to determine if the SR-induced cognitive decrements are related to changes in the retina, specifically the loss of intrinsically photosensitive retinal ganglion cells (ipRGCs). December 2022 report: Dr. Biswajit Maharathi from the Illinois Brain Analytics Institute (University of Illinois Chicago) has been added to the project to assist in applying AI-assisted learning algorithms to determine neural network cohesiveness. 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) Shuboni-Mulligan, Dorela (Eastern Virginia Medical School) Maharathi, Biswajit (University of Illinois Chicago)
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.

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 re-irradiation with 10 cGy of simplified (5-ion) Galactic Cosmic Ray Simulation (GCRsim) 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.

[Ed. Note: For references cited below, see Cumulative Bibliography.]

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, that is less likely to be impacted by age-related cognitive decline.

Rats are exposed to 10 cGy of SR ions 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, that 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). The impact that He and GCRsim exposure have on fine motor skill performance in close temporal proximity (2-3 days) to radiation exposure, as well as our traditional 3 month time point is now being determined.

Task Progress:

Brain regions (that regulate 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 5-ion GCRsim beam) to Brookhaven National Laboratory (BNL) where they receive a second dose of 10 cGy n 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 GCRSim impair cognitive flexibility performance in both male and female rats. However, the stage of the ATSET task where SR-induced deficits were observed differed, with males having performance deficits in the Simple Discrimination (SD) task, while female rats had deficits in the Compound Discrimination (CD) stages. Thus, while GCRSim exposure primarily impairs rule learning in the SD stage in males, in female rats GCRSim exposure results in a decreased ability to resolve contextual influences on discrimination learning. • In addition to the loss of CD performance, SR-exposed female rats had performance decrements in the CDR stage, where the previously unrewarded cue from CD is switched to the rewarded cue (and vice versa). Consideration of this data and our published female Associative Recognition Memory and Interference Touchscreen (ARMIT) data suggests that SR-exposed female rats are preferentially susceptible to anterograde interference, and/or an inability or unwillingness to switch attention to a new rule. • 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. This was observed in both male and female rats, but the stage that was impacted differed in a sex-dependent manner. • Both male and female rats exposed to GCRSim have significant problems in completing high cognitive task load assays. • In both male and female rats, GCRSim-exposure (but not He-exposed rats) leads to a significantly decreased ability to switch attention in a task that mimics those used to assess pilot response times. However, the nature of those decrements differed in a sex dependent manner: in males, an increased switch cost (response time) was the primary decrement observed, while in the females an increased switch cost (accuracy) was observed. • The doubly irradiated rat study has shown that the second SR dose induces decrements in ATSET performance in both male and female rats that had retained a high level of performance after a single SR exposure. Thus, these rats are not inherently radiation resistant. Furthermore, the second SR dose impaired performance in the more complex ATSET stages. • The second exposure also led to the loss of performance savings in both male and female rats. However, the nature of those decrements differed in a sex dependent manner, with males taking more time to solve the problem in the intra-dimensional shifting reversal (IDR) and extra-dimensional set shifting (EDS) stages, while the female rats had problems identifying the cue for the reward in the SD stage. • We identified unique protein signatures in the proteome of the medial prefrontal cortex (mPFC) from: 1) sham rats, 2) Si-exposed rats, 3) Si-exposed rats that had sham-like spatial memory performance, and 4) Si-exposed rats that ATSET performance (Laiakis et al, 2022).

Bibliography Type: Description: (Last Updated: 02/21/2024)

Articles in Peer-reviewed Journals	Blackwell AA, Fesshaye A, Tidmore A, I Lake R, Wallace DG, Britten RA. "Rapid loss of fine motor skills after low dose space radiation exposure." Behav Brain Res. 2022 Jul 26;430:113907. https://doi.org/10.1016/j.bbr.2022.113907 ; PMID: 35500721 , Jul-2022
Articles in Peer-reviewed Journals	Ton ST, Laghi JR, Tsai S, Blackwell AA, Adamczyk NS, Osterlund Oltmanns JR, Britten RA, Wallace DG, Kartje GL. "Exposure to 5 cGy 28 Si particles induces long-term microglial activation in the striatum and subventricular zone and concomitant neurogenic suppression." Radiat Res. 2022 Apr 4;198(1):28-39. https://doi.org/10.1667/RADE-21-00021.1 ; PMID: 35377458 , Apr-2022
Articles in Peer-reviewed Journals	Britten RA, Sanford LD, Guo M-L, Krishnan B, Emmett MR, Laiakis EC. "A Sankofian appraisal on how to maximize translatability of rodent space radiation/CNS studies to astronauts." THREE. 2022 Apr 25. https://three.jsc.nasa.gov/articles/Sankofa%20022522.pdf , Apr-2022
Articles in Peer-reviewed Journals	Stephenson S, Britten R. "Simulated space radiation exposure effects on switch task performance in rats." Aerosp Med Hum Perform. 2022 Sep 1;93(9):673-80. https://doi.org/10.3357/AMHP.6017.2022 ; PMID: 36224731 , Sep-2022
Articles in Peer-reviewed Journals	Laiakis EC, Pinheiro M, Nguyen H, Behesti A, Dutta SM, Russell WK, Emmett MR, Britten RA. "Quantitative proteomic analytic approaches to identify metabolic changes in the medial prefrontal cortex of rats exposed to space radiation." Front Physiol. 2022 Aug 26;13:971282. https://doi.org/10.3389/fphys.2022.971282 , Aug-2022
Articles in Peer-reviewed Journals	Zablotska LB, Zupunski L, Leuraud K, Lopes J, Hinkle J, Pugeda T, Delgado T, Olschowka J, Williams J, O'Banion MK, JD Jr, Sarah S. Cohen SS, Mumma MT, Dauer LT, Britten RA, Stephenson S. "Radiation and CNS effects: Summary of evidence from a recent symposium of the Radiation Research Society." Int J Radiat Biol. 2022 Nov 11:1-11. https://doi.org/10.1080/09553002.2023.2142984 , Nov-2022
Articles in Peer-reviewed Journals	Britten RA, Fesshaye A, Tidmore A, Blackwell AA. "Similar loss of executive function performance after exposure to low (10 cGy) doses of single (4He) ions and the multi-ion GCRSim beam." Radiat Res. 2022 Jul 20. Online ahead of print. https://doi.org/10.1667/RADE-22-00022.1 ; PMID: 35857423 , Jul-2022
Articles in Peer-reviewed Journals	Huff JL, Poignant F, Rahmanian S, Khan N, Blakely EA, Britten RA, Chang C, Fornace AJ, Hada H, Kronenberg A, Norman RB, Patel ZS, Shay JW, Weil MM, Simonsen LC, Slaba TC. "Galactic cosmic ray simulation at the NASA Space Radiation Laboratory–Progress, challenges and recommendations on mixed-field effects." Life Sciences in Space Research. 2023 Feb;36:90-104. https://doi.org/10.1016/j.lssr.2022.09.001 ; PMID: 36682835 , Feb-2023
Articles in Peer-reviewed Journals	Blackwell AA, Tracz JA, Fesshaye AS, Tidmore A, Osterlund Oltmanns JR, Schaeffer EA, Lake RI, Wallace DG, Britten RA. "Fine motor deficits exhibited in rat string-pulling behavior following exposure to sleep fragmentation and deep space radiation." Exp Brain Res. 2022 Dec 27. https://doi.org/10.1007/s00221-022-06527-z ; PMID: 36574036 , Dec-2022
Books/Book Chapters	Wellman LL, Adkins AM, Yoon H, Britten RA, Sanford LD. "Telemetry in rats and mice: Methodological considerations and example studies of stress and anxiety in ground-based spaceflight analogs." in "Psychiatric Vulnerability, Mood, and Anxiety Disorders: Tests and Models in Mice and Rats. " Ed. Harro, J. Neuromethods, Vol. 190. New York, NY: Humana, 2023. p. 201-22. https://doi.org/10.1007/978-1-0716-2748-8_11 , Jan-2023