Fiscal Year:	FY 2015	**Task Last Updated:**	FY 01/07/2015
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
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Contact Monitor:	Simonsen, Lisa	**Contact Phone:**	
Contact Email:	lisa.c.simonsen@nasa.gov		
Flight Program:			
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Key Personnel Changes/Previous PI:			
COI Name (Institution):	Dutta, Sucharita (Eastern Virginia Medical School) Semmes, Oliver (Eastern Virginia Medical School)		
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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 Gaps 1, 2, and 6, 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. Determine the Threshold dose for the induction of HISMI and HIASSI following exposure to 56Fe, 48Ti, and 28Si particles when delivered in three fractions over a 5-day period. Aim 3. Identify changes in the neuroproteome that are associated with susceptibility or resistance to developing HISMI and HIASSI following exposure to 56Fe particles. Aim 4. Determine the mechanism of HISMI and HIASSI induced by HZE particles of differing LET. 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 and 1000 MeV/nucleon). Rats will receive whole body HZE irradiation (2.5, 5, 10, 15, and 20 cGy), and HISMI and HIASSI will be assessed at 3 months post irradiation. In Aim 2, 6-month old male Wistar rats will be exposed to the 56Fe, 48Ti, and 28Si particle beams using a 5 day, 3 x 5 cGy fraction irradiation scheme with a 48 h inter-fraction time. HISMI and HIASSI will be assessed at 3 months post irradiation and the severity of HISMI and HIASSI compared to that induced when 15 cGy was delivered as a single dose. These studies can be iteratively modified (change in fraction size, number, and inter-fraction time) if warranted so that modelers can extrapolate our findings to a more realistic HZE exposure pattern. In Aims 3 and 4, 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.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	
Task Progress:	During the first year of this study we have pre-screened 184 rats for their ability to complete the first 4 paradigms of the attentional set shifting test (up to Intra-dimensional shifting). Of the first batch of 79 rats, 49 (62%) rats were able to complete the IDS paradigm. These were shipped to BNL for irradiation with 5, 10, and 15 cGy of 1 GeV/n 48Ti or 600 MeV/n 56Fe ions during NSRL14B. Some rats did not survive transit and the remaining rats were exposed to only 48Ti ions. These irradiated rats have now been re-evaluated for their post radiation exposure ability to perform Attentional Set Shifting (up to and including Extra-dimensional Shifting-EDS). 1. The rats were retested using the exact same protocol as used in the prescreening process, i.e. the same associative clues for the food reward were used. It became apparent that the rats remembered the food reward clue (as evidenced by the fact that they did not even investigate the other bowl) from the prescreening stages. 2. The rats were subsequently retested for ATSET performance but with the food reward associative clue being altered from an olfactory one (scent) to a tactile one (digging medium) in the SD, CD, CDR. IDS, and IDR stages (with the opposite changes being implanted in the EDS and EDR stages. 3. An analysis of this second round of data revealed that there was no difference between the ability of the irradiated rats to complete the Attentional Set Shifting task, but that rats exposed to 15 cGy 1 GeV/n Titanium ions took twice as many attempts to complete the EDS paradigm than did the sham-irradiated rats (P=0.041, N=6). A second batch of 105 rats have been pre-screened for their ability to complete the first 4 paradigms of the attentional set shifting test (up to Intra-dimensional shifting); 70 (66.66%) were able to complete the IDS paradigm. These were shipped to BNL for irradiation with 5, 10, and 15 cGy of 600 MeV/n 28Si or 600 MeV/n 56Fe ions during NSRL14C. These rats are scheduled to be re-evaluated for their ATSET performance at the start of Feb 2015, in accordance with the procedures outlined in Item # 2 above.
Bibliography Type:	Description: (Last Updated: 05/16/2025)

Abstracts for Journals and Proceedings	Britten RA. "Interrogating the neuroproteome for clues to the mechanism of HZE-induced neurocognitive impairment." 60th Annual Meeting of the Radiation Research Society, Las Vegas, Nevada, September 21-24, 2014. 60th Annual Meeting of the Radiation Research Society, Las Vegas, Nevada, September 21-24, 2014. , Sep-2014
Abstracts for Journals and Proceedings	Britten RA, Davis L, Jewell J, Miller V, Lonart G. "Executive function in socially - mature rats is significantly impaired by low (2014 NASA Human Research Program Investigators' Workshop, Galveston, TX, February 12-13, 2014. http://www.hou.usra.edu/meetings/hrp2014/pdf/3033.pdf , Feb-2014
Articles in Peer-reviewed Journals	Britten RA, Davis LK, Jewell JS, Miller VD, Hadley MM, Sanford LD, Machida M, Lonart G. "Exposure to mission relevant doses of 1 GeV/nucleon 56Fe particles leads to impairment of attentional set-shifting performance in socially mature rats." Radiat Res. 2014 Sep;182(3):292-8. Epub 2014 Jul 16. http://dx.doi.org/10.1667/RR3766.1 ; PubMed PMID: 25029107; PubMed Central PMCID: PMC4154313 , Sep-2014