Fiscal Year:	FY 2017	**Task Last Updated:**	FY 01/03/2017
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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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Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2013 Space Radiobiology NNJ13ZSA001N
Start Date:	02/27/2014	**End Date:**	02/26/2018
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:			
Key Personnel Changes/Previous PI:	November 2012 report: Dr. Sucharita Dutta, a proteomics expert, has been added to the team.		
COI Name (Institution):	Dutta, Sucharita (Eastern Virginia Medical School) Semmes, Oliver (Eastern Virginia Medical School) Lonart, Gyorgy Ph.D. (Eastern Virginia Medical School)		
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, 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.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	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.
	Project Objectives 1. Identify the lowest HZE dose 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 HZE-exposed animals. Project Approach: To better simulate the “clinical reality,” adult (proven breeder) male 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. Rats are exposed (primarily a single exposure) to <15 cGy of HZE ions (incident energy <600 MeV/n) and ATSET performance re-established at 3 months post exposure. The post-exposure ATSET test is reconfigured from the pre-exposure ATSET test, so that the rats have to “relearn” the associative clues, and importantly the post-exposure test uses associative clues in the first 6 paradigms that are “media”-based and not olfactory-based. These changes eliminate memory retention issues and also HZE-induced changes in olfaction. A novel aspect of the current study is to characterize the “motivational” status of the rats to perform the ATSET test, i.e., whether they are motivated to perform the task, give up easily, etc. Regions of the cortex and basal forebrain (that regulated certain paradigms with the ATSET test) will be recovered and subjected to proteomic analysis to identify some of the processes that may be responsible for the HZE-induced impairment of ATSET. Work conducted to date: To date a total of 683 rats have been pre-screened for ATSET performance, and 407 (59.7%) “vetted” rats had adequate ATSET performance to be used to assess the impact of HZE on ATSET performance. These “vetted” rats were exposed to 600 MeV/n 56Fe or 600 MeV/n 28Si during NASA Space Radiation Laboratory (NSRL) 15A, to 600 MeV/n 48Ti, 600 MeV/n 56Fe, 600 MeV/n 28Si, or 400 MeV/n 16O during NSRL15C, and to 600 MeV/n 28Si or 400 MeV/n 4He during NRSRL16C. Research Highlights No impairment of ATSET performance was observed in the 1 batch of rats exposed to 400 MeV/n 16O (1.5, 5 and 10 cGy). However, significant impairments in ATSET performance were observed after exposure to the other ions. The lowest dose where ATSET performance was impaired was:

Task Progress:	600 MeV/n 48Ti, 5 cGy (lowest studied); 600 MeV/n 56Fe, 3 cGy (NS changes at 1 cGy) 600 MeV/n 28Si, 5 cGy (lowest studied); 400 MeV/n 4He, Rats not screened for ATSET performance yet. Marked inter-individual differences in level of impairment. Some irradiated individuals retain “normal” ATSET, while others fail the paradigm. Brain regions impacted by HZE exposure. The paradigms impaired after exposure to 5 cGy (of all ions studied) were Simple Discrimination (SD) and Compound Discrimination (CD). These data suggest that the functionality of multiple brain regions may be impaired by these low HZE doses. 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. Probabilistic Risk Assessments: In recent years we have started to present our data in a format that is more amenable to the Probabilistic Risk Assessments that NASA uses to evaluate mission risks. Such data analysis requires that the percentage of individuals impacted as well as the severity of the impairments be considered. We have established that 5-15% of Sham rats failed to pass the SD and CD paradigms on their first attempt, but <5% of Sham rats could not pass these stages when given 2 attempts to do so. In contrast 15-40% of the irradiated rats had problems completing SD and CD on their first attempt. Many of these rats managed to pass SD on the second attempt, but a significantly higher percentage failed to complete CD even after 2 attempts. Overall, 8% of Sham rats failed (on two occasions) at least one stage of testing; in contrast 43, 41, and 63% of rats irradiated with 5 cGy 600 MeV/n Fe, Si, or Ti ions failed at least one stage. Re-irradiation studies. As mentioned earlier, some irradiated rats exhibited an ATSET performance that was indistinguishable from that of the Shams. We determined whether these “resistant” individuals maintained their good performance status when exposed to episodic multi-ion exposures. In a pilot study “resistant” (that had good ATSET performance) rats from NSRL14C were returned to Brookhaven National Laboratory (BNL) during NSRL15A (~270 days later) and re-irradiated. In some cases, rats received Si, O, or Ti during NSRL14C and some received Fe. All received 600 MeV/n 56Fe during NSRL15A. A few conclusions can be drawn from this study: 1. Resistant rats are not always resistant, and that repeated exposures can changed their ATSET performance. 2. The failures in the episodic exposed rats occur in paradigms that are rarely impacted after a single exposure (IDS and IDR) as well as CDR. Changes in the Neuroproteome associated with changes in ATSET performance. Now that our studies have come close to the lowest dose of HZE particles that resulted in significant impairment of ATSET performance and the regions of the brain most frequently impacted (mPFC, perirhinal and basal forebrain (Reversal behavior), it is appropriate to start establishing how HZE exposures impaired ATSET performance. In light of our recent paper (Britten et al, 2016; LSSR) where it appears that hippocampal and PFC-dependent cognitive domains are not similarly impaired in individual rats, the Basal Forebrain, Infra-limbic Prefrontal cortex, and hippocampus have been recovered from each rat exposed to 5 cGy 600 MeV/n Fe and Si and subjected to proteomic analysis. We have established that it is feasible to characterize the composition of the neuroproteome within defined (4 x 3 x 1 mm) areas of the brain from irradiated rats. Preliminary data suggest that there are marked differences in the neuroproteome in response to HZE exposure within each brain region, and that such changes may be very specific to the HZE ion. Project Summary We have demonstrated that low (5 cGy) doses of various HZE species results in significant impairment of ATSET performance. There appears to be quantitative and qualitative differences in the manner how Si, Ti, and Fe impair ATSET performance. Further batches of rats will be exposed to <5 cGy of these ions species and to 400 MeV/n 4He and 16O. Currently studies are underway to contrast the efficacy with which isofluences of the various HZE ions impair ATSET. Preliminary data suggest that there are marked differences in the neuroproteome in response to HZE exposure within each brain region, and that such changes may be very specific to the HZE ion.
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