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| **Fiscal Year:** | FY 2019 | **Task Last Updated:** | FY 12/30/2018 |
| **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<br>(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 |
| **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 |
| **Contact Monitor:** | Simonsen, Lisa | **Contact Phone:** | |
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| **Flight Program:** | | | |
| **Flight Assignment:** | NOTE: Extended to 12/31/2020 per NSSC information (Ed., 3/12/19)<br>NOTE: Extended to 12/31/2018 per S. Monk/SR/LaRC (Ed., 1/11/18) | | |
| **Key Personnel Changes/Previous PI:** | 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):** | | | |
| **Grant/Contract No.:** | NNX14AE73G | | |
| **Performance Goal No.:** | | | |
| **Performance Goal Text:** | | | |

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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.<br>Our studies will thus address CNS (Central Nervous System) Gaps 1, 2, and 6, and we shall specifically focus on the following aims:<br><br>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.<br><br>Aim 2. Identify changes in the neuroproteome that are associated with susceptibility or resistance to developing HISMI and HIASSI following exposure to 56Fe particles.<br><br>Aim 3. Determine the mechanism of HISMI and HIASSI induced by HZE particles of differing LET (linear energy transfer).<br><br>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.<br><br>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.<br><br>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<br>1. Identify the lowest dose of space radiation (SR) that results in Attentional Set Shifting (ATSET) impairment<br><br>2. Determine if there are LET-specific mechanisms of ATSET Impairment.<br><br>3. Identify changes in the neuroproteome that reflect the cognitive performance status of SR-exposed animals.<br><br>Project Approach: To better simulate the “clinical reality,” adult (proven breeder) male rats that have been pre-selected for good ATSET performance, and who have been maintained on an exercise regimen are used in this study. These “vetted” 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. Typically 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 six paradigms that are “media”-based and not olfactory-based. These changes eliminate memory retention issues and also SR-induced changes in olfaction. However, in some instances, rats are presented with the pre-screening ATSET protocol to determine if SR exposure impairs the rats’ memory of the test.<br><br>After completion of the ATSET test, the rats are then tested in the Unrestrained Cognitive flexibility (UCFlex) assay, which requires that the rats have 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, requiring 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. Unconstrained cognitive flexibility is frequently used by humans to solve complex problems (insightful problem solving).<br><br>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.<br><br>Work conducted to date:<br><br>To date ~550 “vetted” rats have been used to assess the ATSET performance after exposure to <10 cGy of 400 MeV/n 4He, 400 MeV/n 16O, 600 MeV/n 28Si, 600 MeV/n 48Ti, and 600 MeV/n 56Fe ions. Approximately 250 of these rats have also been characterized for their performance in the UCFlex assay. |

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| | Furthermore, our studies have focused on presenting our data in a format that can be readily used to calculate a Probabilistic Risk Analysis (PRA) for cognitive impairment, i.e., establishing the severity and frequency of severe ATSET impairment. |
| **Task Progress:** | Research Highlights<br>• 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.<br>• 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).<br>• 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.<br>• SR doses as low as 1 cGy impair insightful problem solving.<br>• 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.<br>• 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 Si, 36% following 18 cGy protracted neutron (data from NSCOR--NASA Specialized Center of Research--studies).<br>Brain regions impacted by SR exposure. 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.<br>Changes in the Neuroproteome associated with changes in ATSET performance. The first batch of pre-frontal cortex samples were run over the summer of 2017, and Dr. Britten continues to sort through the vast amount of data generated. Preliminary data suggest that SR exposure induces marked differences in the neuroproteome and that Beta-adrenergic signaling and GABAergic signaling pathways may be preferentially altered by SR exposure.<br>Reference:<br>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. |
| **Bibliography Type:** | Description: (Last Updated: 02/21/2024) |
| **Articles in Peer-reviewed Journals** | Jewell JS, Duncan VD, Fesshaye A, Tondin A, Macadat E, Britten RA. "Exposure to < or =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 Dec;190(6):565-75. Epub 2018 Nov 8. https://doi.org/10.1667/RR15085.1 ; PMID: 30407900 , Dec-2018 |
| **Articles in Peer-reviewed Journals** | Britten RA, Jewell JS, Duncan VD, Hadley MM, Macadat E, Musto AE, La Tessa C. "Impaired attentional set-shifting performance after exposure to 5 cGy of 600 MeV/n (28)Si particles." Radiat Res. 2018 Mar;189(3):273-82. Epub 2018 Jan 8. https://doi.org/10.1667/RR14627.1 ; PubMed PMID: 29309264 , Mar-2018 |
| **Articles in Peer-reviewed Journals** | Dutta SM, Hadley MM, Peterman S, Jewell JS, Duncan VD, Britten RA. "Quantitative proteomic analysis of the hippocampus of rats with GCR-induced spatial memory impairment." Radiat Res. 2018 Feb;189(2):136-45. Epub 2017 Dec 5. https://doi.org/10.1667/RR14822.1 ; PubMed PMID: 29206597 , Feb-2018 |