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Project Title:	Changes in the Neuroproteome Associated with HZE-Induced Impairment of Cognition		
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	<p>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:</p> <p>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.</p> <p>Aim 2. Identify changes in the neuroproteome that are associated with susceptibility or resistance to developing HISMI and HIASSI following exposure to 56Fe particles.</p> <p>Aim 3. Determine the mechanism of HISMI and HIASSI induced by HZE particles of differing LET.</p> <p>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.</p> <p>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.</p> <p>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.</p>
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	<p>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.</p>
	<p>Project Objective</p> <ol style="list-style-type: none"> 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. <p>Project Approach</p> <p>Adult (proven breeder) male rats are used in this study. These rats have a comparable chronological age to young astronauts, but are often overweight and “cage weary.” Thus the rats used in our study are placed on an exercise regimen (30 min treadmill sessions, 2-3 times a week) for the duration of the study. The rats are “vetted” for good attentional set shifting (ATSET) performance, and then exposed (single exposure) to <15 cGy of HZE ions (incident energy <600 MeV/n). ATSET performance is re-established at 3 months post exposure, using a reconfigured ATSET test that necessitates that the rats have to “relearn” the associative clues, which are non-olfactory dependent.</p> <p>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.</p> <p>Research Highlights</p> <p>256 “vetted” rats have been irradiated at Brookhaven National Laboratory (BNL) with 5, 10, or 15 cGy of 600 MeV/n 56Fe (2 batches), 400 MeV/n 28Si (2 batches), or 1 GeV/n 48Ti (1 batch), and their ATSET performance assessed. ATSET performance was impaired at all doses studied. At 5 cGy, there are significant (>2 fold) increases in the percentage of rats that failed to successfully complete (on two occasions) one of the first 4 paradigms of the ATSET test. Twelve percent of Sham rats failed at least one stage of testing, whereas 25, 32, and 60% of rats irradiated with 5 cGy Ti, Fe, or Si ions failed at least one stage (on two occasions).</p> <p>There appears to be some ion (perhaps LET) specific changes in the level and nature of cognitive impairment induced. Silicon (with the lowest LET) is the most potent at impairing the overall performance in the ATSET test, with 60% of rats failing a paradigm (on 2 separate occasions).</p> <p>There are also marked differences in how the irradiated rats perform in the various paradigms. Silicon induced failures in Food Foraging (FF), Simple Discrimination (SD), and Compound Discrimination Reversal (CDR). Ti exposure induces significant changes in SD performance, while Fe induces changes in Compound Discrimination (CD) and CDR</p>

	<p>performance.</p> <p>Potential implications for astronaut performance</p> <p>The HZE-induced changes in ATSET performance could have some profound impacts on crew performance IF similar changes were induced in astronauts.</p> <p>The failure to complete the FF paradigm appears to be attributable to an inability of the irradiated rats to maintain focus on that task. The irradiated rats started to dig for the food (suggesting that they encoded and retrieved the procedural memories of food retrieval necessary to perform ATSET), but stopped digging after 5-10 s. All the rats that failed the FF task in the present study showed no obvious signs of anhedonia (sucrose preference test, or general appearance and activity in the cage), and vigorously ate “rat chow” when returned to an unrestricted diet. Further experimentation is needed to determine if these rats truly have an impaired ability to maintain focus on task, but if this proves to be the case, HZE-exposed astronauts could have problems focusing on tasks/activities.</p> <p>Task Progress:</p> <p>Impaired SD performance will result in a reduced ability to establish an attentional set (propensity) to the relevant dimension for the successful completion of a task, in this study identifying the associative clue for a food reward. CD is a reflection of the ability to maintain that attentional set, when there were distracting, irrelevant stimuli present. Astronauts will obviously not use attentional set shifting to find food rewards, but if astronauts were to experience HZE-induced SD impairments, this would result in a decreased ability to multi-task successfully. An HZE-induced impairment of CD performance, would result in a decreased ability to identify and focus on relevant aspects of the task being conducted. Such decrements would be undesirable in any work scenario.</p> <p>These data suggest that the functionality of multiple brain regions may be impaired by these low HZE doses. SD is regulated by the mPFC (Bissonette et al., 2008); CD is probably regulated by perirhinal cortical region (Eacott et al., 2001; Norman et al., 2004; Lindquist et al., 2004; Feinberg et al., 2012), and requires optimal dopamine D2 receptor activation in pre-frontal cortex (Glickstein et al., 2005); and “reversal” tasks are regulated by the basal forebrain (Tait et al., 2008) and the orbital frontal cortex (McAlonan et al., 2003).</p> <p>The Basal Forebrain, Infra-limbic Prefrontal cortex and hippocampus have been recovered from each irradiated rat and will be subjected to proteomic analysis in the near future. These studies will give considerable insight into the underlying cause for HZE-induced neurocognitive failure.</p> <p>Project Summary</p> <p>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 16O. Currently studies are underway to contrast the efficacy with which isofluences of the various HZE ions impair ATSET.</p> <p>References</p> <p>Bissonette GB, Martins GJ, Franz TM, Harper ES, Schoenbaum G, Powell EM. Double dissociation of the effects of medial and orbital prefrontal cortical lesions on attentional and affective shifts in mice. <i>J Neurosci</i> 2008; 28:11124-30.</p> <p>Eacott MJ, Machin PE, Gaffan EA. Elemental and configural visual discrimination learning following lesions to perirhinal cortex in the rat. <i>Behav Brain Res</i> 2001; 124:55–70.</p> <p>Norman G, Eacott MJ. Impaired object recognition with increasing levels of feature ambiguity in rats with perirhinal cortex lesions. <i>Behav Brain Res</i> 2004; 148:79–91.</p> <p>Lindquist DH, Jarrard LE, Brown TH. Perirhinal cortex supports delay fear conditioning to rat ultrasonic social signals. <i>J Neurosci</i> 2004; 24:3610–17.</p> <p>Feinberg LM, Allen TA, Ly D, Fortin NJ. Recognition memory for social and non-social odors: differential effects of neurotoxic lesions to the hippocampus and perirhinal cortex. <i>Neurobiol Learn Mem</i> 2012; 97:7–16.</p> <p>Glickstein SB, Desteno DA, Hof PR, Schmauss C. Mice lacking dopamine D2 and D3 receptors exhibit differential activation of prefrontal cortical neurons during tasks requiring attention. <i>Cereb Cortex</i> 2005; 15:1016-24.</p> <p>McAlonan K, Brown VJ. Orbital prefrontal cortex mediates reversal learning and not attentional set shifting in the rat. <i>Behav Brain Res</i> 2003; 146:97-103.</p> <p>Tait DS, Brown VJ. Lesions of the basal forebrain impair reversal learning but not shifting of attentional set in rats. <i>Behav Brain Res</i> 2008; 187:100-8.</p>
Bibliography Type:	Description: (Last Updated: 02/21/2024)
Abstracts for Journals and Proceedings	<p>Britten RA. "Potential impact of space radiation on crew performance on deep space mission." NASA Blue Sky meeting: Biological Countermeasures (BCMs) Against Space Radiation Risks. Institute of Human and Machine Cognition, Pensacola, FL, August 18-19, 2015.</p> <p>NASA Blue Sky meeting: Biological Countermeasures (BCMs) Against Space Radiation Risks. Institute of Human and Machine Cognition, Pensacola, FL, August 18-19, 2015. , Aug-2015</p>
Abstracts for Journals and Proceedings	<p>Britten RA. "Impact of space radiation exposure on cognitive performance, neuronal physiology and psychology." Neurobehavioral Resilience during Prolonged Space Flight. National Space Biomedical Research Institute, Houston, TX, July 28-29, 2015.</p> <p>Neurobehavioral Resilience during Prolonged Space Flight. National Space Biomedical Research Institute, Houston, TX, July 28-29, 2015. , Jul-2015</p>
Abstracts for Journals and Proceedings	<p>Britten RA, Jewell J, Hadley M, Miller M, Macadat E. "Executive Function in Socially-Mature Rats Is Significantly Impaired by Low (Space Radiation and Heavy Ions in Therapy Symposium 2015, Osaka, Japan, May 22-24, 2015. , May-2015</p>

Abstracts for Journals and Proceedings	Britten RA, Machida M, Wellman L, Sanford LD. "A pilot study on the impact that exposure to 20 cGy 1 GeV/nucleon ⁵⁶ Fe particles has on Delta and Theta wave activity and sleep homeostasis." 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. , Jan-2015
Abstracts for Journals and Proceedings	Hadley M, Jewell J, Macadat E, Miller V, Britten RA. "Executive function is significantly impaired following exposure to low (2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. , Jan-2015
Abstracts for Journals and Proceedings	Jewell J, Macadat E, Miller V, Hadley M, Dutta S, Britten RA. "Changes in the Hippocampal proteome associated with the induction of spatial memory impairment by mission relevant HZE doses." 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. , Jan-2015
Abstracts for Journals and Proceedings	Macadat E, Miller V, Jewell J, Hadley M, Britten RA. "Executive function is significantly impaired following exposure to mission relevant (10 cGy) doses of 600 MeV/u ⁵⁶ Fe particles." 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. , Jan-2015
Abstracts for Journals and Proceedings	Miller V, Jewell J, Hadley M, Macadat E, Britten RA. "Executive function is significantly impaired following exposure to low (15 cGy) doses of 600 MeV/u ²⁸ Si particles." 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. 2015 NASA Human Research Program Investigators' Workshop, Galveston, TX, January 13-15, 2015. , Jan-2015
Articles in Peer-reviewed Journals	Hadley MM, Davis LK, Jewell JS, Miller VD, Britten RA. "Exposure to mission relevant doses of 1 GeV/n ⁴⁸ Ti particles impairs attentional set-shifting performance in retired breeder rats." Radiation Research. In press, January 2016. Online ahead of print: http://dx.doi.org/10.1667/RR14086.1 , Jan-2016