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Performance in hippocampus- and PFC-dependent cognitive domains are not concomitantly impaired in rats exposed to 20 cGy of 1 GeV/n ^{56}Fe particles

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ABSTRACT

NASA is currently conducting ground based experiments to determine whether the radiation environment that astronauts will encounter on deep space missions will have an impact on their long-term health and their ability to complete the various tasks during the mission. Emerging data suggest that exposure of rodents to mission-relevant HZE radiation doses does result in the impairment of various neurocognitive processes. An essential part of mission planning is a probabilistic risk assessment process that takes into account the likely incidence and severity of a problem. To date few studies have reported the impact of space radiation in a format that is amenable to PRA, and those that have only reported data for a single cognitive process. This study has established the ability of individual male Wistar rats to conduct a hippocampus-dependent (spatial memory) task and a cortex-dependent (attentional set shifting task) 90 days after exposure to 20 cGy 1 GeV/n ^{56}Fe particles. Radiation-induced impairment of performance in one cognitive domain was not consistently associated with impaired performance in the other domain. Thus sole reliance upon a single measure of cognitive performance may substantially under-estimate the risk of cognitive impairment, and ultimately it may be necessary to establish the likelihood that mission-relevant HZE doses will impair performance in the three or four cognitive domains that NASA considers to be most critical for mission success, and build a PRA using the composite data from such studies.

1. Introduction

The deep space exploratory missions to planets, such as Mars, that NASA is committed to will be very different in multiple aspects from its previous missions. NASA utilizes Probabilistic Risk Assessments (PRA) when planning space flights (NASA, 2004), where risk is characterized by two quantities: (1) the magnitude (severity) of possible adverse event(s), and (2) the likelihood (probability) that such an event will occur during the mission. Currently NASA lists 33 risks in its Human Research Roadmap,[1] one of which is the Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure. The prolonged duration of a mission to Mars, coupled with the deep space radiation environment, will result in astronauts being exposed to much greater (potentially 10 fold higher) radiation exposure than astronauts have previously experienced on ISS missions (Nelson, 2016). It is predicted that astronauts on a mission to Mars will receive a cumulative dose of ~20 cGy Galactic Cosmic Radiation, with ~50% of the dose accruing from High Z and Charge (HZE) particles, the remaining being from high-energy protons (Cucinotta et al., 2014).

Ground based studies using rodent model systems have demonstrated that mission-relevant (10–30 cGy) HZE doses impairs multiple cognitive domains regulated by the hippocampus (Britten et al., 2012; Cherry et al., 2012; Haley et al., 2013; Tseng et al., 2014; Rabin et al., 2014; Parihar et al., 2015; Britten et al., 2016),

Abbreviations: AO, Attentional Set Shifting Only; ATSET, Attentional Set Shifting; BMO, Barnes Maze only; CD, Compound discrimination; CompRate, Completion rate; DA, Dual-assay; ESL, Escape latency; FF, Food Foraging; GABA, gamma-aminobutyric acid; HZE, High Z and Charge; IDR, Intra-dimensional shift reversal; PFC, Prefrontal Cortex; PRA, Probabilistic Risk Assessment; REL, Relative Escape Latency; RRP, Readily Releasable Pool.

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[1] http://humanresearchroadmap.nasa.gov.

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amygdala (Rabin et al., 2014), striatum (Rabin et al., 2007) and frontal lobes (Lonart et al., 2012; Britten et al., 2014; Davis et al., 2014; Hadley et al., 2016). Most studies have reported the impact of HZE on a single cognitive domain. In a few studies, two or more cognitive domains have been assessed in the irradiated cohorts (Cherry et al., 2012; Rabin et al., 2014, 2007; Parihar et al., 2015; Davis et al., 2014). In some instances, there are significant impairments of one cognitive domain but not the other(s) (Cherry et al., 2012; Haley et al., 2013; Rabin et al., 2014; Parihar et al., 2015; Davis et al., 2014), and in some cases both domains are impaired (Cherry et al., 2012; Parihar et al., 2015; Rabin et al., 2007). However, in no instance has the data been presented for individual animals in both behavioral tests, but a few studies have presented data from individual animals in a single cognitive domain in a manner where it would be possible to determine the two quantities required for a PRA: (1) the severity of the neurocognitive deficit, and (2) the frequency that significant neurocognitive impairment is induced following HZE exposure. These studies suggest that there is considerable inter-individual variation in the susceptibility of rats to develop impaired performance in attentional set shifting (ATSET) (Lonart et al., 2012; Britten et al., 2014; Hadley et al., 2016), spatial memory (Britten et al., 2016) and the rat psychomotor vigilance (rPVT) test (Davis et al., 2014). While it appears that spatial memory and ATSET performance are impaired at similar HZE doses, there is a paucity of data on whether individual animals experience impaired performance in both domains, i.e., a generalized panoramic impairment, or in just one domain. It is convenient to classify behavioral paradigms as being primarily regulated by a certain brain region, but few cognitive processes are truly regulated by just one brain region. Attentional set shifting is considered to be a PFC-dependent cognitive task, but PFC-mediated cognitive processes in rodents are modulated by a distributed neural system involving multiple forebrain regions including the ventral hippocampus, nucleus accumbens, basal forebrain, and the mediodorsal nucleus of the thalamus (Brooks et al., 2011; Floresco et al., 2009; Tseng et al., 2009; Hasselmo and Sarter, 2011). Indeed, transient inactivation of the ventral hippocampus leads to impaired attentional set shifting behavior (Hasselmo and Sarter, 2011). Conversely, alterations to the cholinergic pathways in the basal forebrain (a brain region that regulates reversal behavior in ATSET, and has been shown to have impaired GABA RRP following HZE exposure (Britten et al., 2014)) leads to changes in hippocampus-dependent behavior (Hernandez et al., 2010). Current modeling suggests that there is little variation in the HZE dose delivered to the front, mid or rear brain (Cucinotta et al., 2014), thus the PFC and hippocampus are likely to receive the same HZE dose, so it is conceivable that there will be a concomitant impairment of attentional set shifting in those individuals that exhibit HZE-induced spatial memory impairment. However, there are differences in the antioxidant response of the hippocampus and cortex (Todorovic et al., 2005) so it could also be argued that there would not necessarily be collateral impairment of ATSET and spatial memory. Should that be the case then PRA could not use data from a single cognitive domain as an indicator of all neurocognitive performance, and it would be necessary to construct a PRA for each cognitive domain that NASA deems critical for mission success.

In this study, we thus assessed the impact that exposure to 20 cGy of 1 GeV/n ^{56}Fe particles has on the ability of individual adult male Wistar rats (at three months post exposure) to perform in the Barnes Maze (spatial memory) and attentional set shifting. This study was conducted contemporaneously to our previously published studies on spatial memory (Britten et al., 2016) and attentional set shifting (Britten et al., 2014).

2. Materials and methods

2.1. Irradiation procedure

This study was conducted in accordance with the National Research Council's "Guide for the Care and Use of Laboratory Animals (9th Edition)", at facilities of Eastern Virginia Medical School (EVMS) and Brookhaven National Laboratory (BNL), both of which are accredited by the Association for Assessment and Accreditation of Laboratory Animal Care, International. All procedures where approved by the Institutional Animal Care and Use Committees (IACUC) of both EVMS and BNL.

This study was conducted in parallel with our previously published studies (Britten et al., 2016, 2014) but used an additional 49 male Wistar (HSD:WI, Harlan Sprague-Dawley, Inc., Indianapolis, IN, USA) retired breeder rats, weighing on average 612 g at the time of irradiation. Four batches of rats were irradiated during NSRL runs 11A, 11B, 12B and 12C. The rats were delivered directly from the supplier to BNL, where they were group housed, maintained on a 12:12 light/dark cycle and given *ad libitum* access to autoclaved Purina Rodent Chow 5001 and municipal water by bottle. After at least one week of acclimatization, the rats were irradiated with 1 GeV/n ^{56}Fe particles at the NASA Space Radiation Laboratory (NSRL). The number of socially mature rats exposed to each dose point was: Sham-irradiated: 25 and 20 cGy: 24.

On the day of the experiment, the rats were placed in a well-ventilated custom-made irradiation jig that was constructed of black polyacrylic plastic. Two rats were exposed simultaneously to the 1 GeV/n ^{56}Fe beam at a dose rate of 20 cGy/min. Dose calibration was performed as previously described (Vlkolinsky et al., 2007). Control rats were placed in an identical irradiation jig that remained in the preparation room, while their counterparts were taken into the irradiation vault at NSRL. Immediately following irradiation, the rats were implanted with ID-100us RFID transponders (Trovan Ltd., United Kingdom) to facilitate identification of individual animals. One week after irradiation, the rats were transported to EVMS, where they were group housed, maintained on a reversed 12:12 light/dark cycle, and given *ad libitum* access to autoclaved Teklad 2014 chow and municipal water by bottle.

2.2. Behavioral testing

Prior to the commencement of any behavioral testing a proportion of the rats irradiated during a specific run at BNL were randomly selected for testing in both behavioral tests, the remaining rats were allocated to either be tested just the Barnes Maze (Britten et al., 2016) or in the ATSET (Britten et al., 2014). Due to concerns that the large amount of handling and investigator contact during the ATSET testing may diminish the rats' fear of open space (a major aversive stimuli for the Barnes Maze), all rats selected for dual testing were first screened for spatial memory performance then for ATSET performance.

The identity of the rats who were selected for dual testing was withheld from the people conducting the Barnes Maze performance tests. All rats were tested for spatial memory performance at 12±weeks, in accordance with the protocol outlined in our previous study (Britten et al., 2016). Each animal was tested on the Barnes' Maze over a three day period, with two tests per day. A key element of the Barnes Maze is that rats progressively learn and recall the location of the escape box, as measured by the time to find its location i.e., Escape latency (ESL). For each animal we calculated an individualized metric of their relative increase (or decrease) in performance between day 1 and 3 of testing i.e., the Relative Escape Latency (REL3: where the Day 3 ESL for a specific rat is expressed as a decimal fraction of its Day 1 ESL). The REL3 for rats