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The effects of heavy particle irradiation on exploration and response to environmental change

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Abstract

Free radicals produced by exposure to heavy particles have been found to produce motor and cognitive behavioral toxicity effects in rats similar to those found during aging. The present research was designed to investigate the effects of exposure to ^{56}Fe particles on the ability of male Sprague-Dawley rats to detect novel arrangements in a given environment. Using a test of spatial memory previously demonstrated to be sensitive to aging, open field activity and reaction to spatial and non-spatial changes were measured in a group that received a dose of 1.5 Gy ($n = 10$) of ^{56}Fe heavy particle radiation or in non-radiated controls ($n = 10$). Animals irradiated with 1.5 Gy of ^{56}Fe particles exhibited some age-like effects in rats tested, even though they were, for the most part, subtle. Animals took longer to enter, visited less and spent significantly less time in the middle and the center portions of the open field, independently of total frequency and duration of activity of both groups. Likewise, irradiated subjects spend significantly more time exploring novel objects placed in the open field than did controls. However, irradiated subjects did not vary from controls in their exploration patterns when objects in the open field were spatially rearranged. Thus, irradiation with a dose of 1.5 Gy of ^{56}Fe high-energy particle radiation elicited age-like effects in general open field exploratory behavior, but did not elicit age-like effects during the spatial and non-spatial rearrangement tasks.
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Keywords: Free radicals; Irradiation; Spatial memory; Aging; Exploratory behavior

1. Introduction

There is a long history of experiments which have reported the parallels between aging and radiation, specifically those produced by high-energy charged particles (HZEs, particles derived from cosmic irradiation that might be encountered by astronauts on future flights outside the magnetic field of the earth), with respect to behavioral and neuronal functions (Joseph et al., 1998, 2000). Research from our laboratories has shown that exposure of rats to HZE particles, primarily 600 MeV or 1 GeV ^{56}Fe, disrupts the functioning of the dopaminergic system and behaviors mediated by this system, such as motor performance (Joseph et al., 1992), spatial learning and memory (Shukitt-Hale et al., 2000, 2003), amphetamine-induced conditioned taste aversion learning (Rabin et al., 1998, 2000, 2002a), conditioned place preference (Rabin et al., 2001, 2003), and operant conditioning (fixed-ratio bar pressing) (Rabin et al., 2002b).

More specifically, studies using the Morris water maze test (a test of spatial ability) indicate that cognition is affected by ionizing radiation in a similar fashion to that of aging (Shukitt-Hale et al., 2000). The Morris water maze paradigm requires that the subjects utilize spatial learning to find the hidden platform submerged just below the surface of a circular pool of water. Subjects irradiated with 1.5 Gy of ^{56}Fe radiation showed increased latencies to find the hidden platform compared to non-radiated controls, particularly on the fourth day when the platform was moved to the opposite quadrant

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from the one where the platform was originally placed at the beginning of the test. Similarly, rats exposed to 1.0 Gy of ^{56}Fe radiation tested nine months after exposure showed decreased performance in the radial arm maze (RAM) task, another test of spatial memory (Shukitt-Hale et al., 2003).

Based on both the behavioral and neuronal studies mentioned above, there is evidence to suggest that exposure to heavy particles produces an aging-like effect. Currently there is limited information on how this type of radiation, specifically HZEs, affects cognition and exploratory behavior, and if these changes resemble those seen in aging. Therefore, the purpose of this study is to examine the effects of 1.5 Gy of ^{56}Fe particles on a test of object exploration, habituation and response to spatial and non-spatial change, a test which has been previously shown to be sensitive to aging (Shukitt-Hale et al., 2001). Understanding the effects and the mechanism of action of HZEs on behavioral and brain function will not only enable us to evaluate the validity of radiation damage as an appropriate model to study cognitive and motor impairment in aging individuals, but it will also ensure the safety of the astronauts assigned to future long-term missions outside the magnetic field of the Earth.

2. Methods

2.1. Animals

The subjects in this study, male Sprague-Dawley rats (400–500 g) obtained from Taconic Farms (Germantown, NY) ($n = 20$), were irradiated at 3 months and tested at 6 months of age. They were individually housed in hanging cages in a colony maintained at constant temperature (21 ± 1 °C), on a 12-hour light/dark cycle. All subjects had free access to food and water.

2.2. Dosimetry and irradiation procedures

Irradiated rats ($n = 10$) were exposed to 1.5 Gy whole-body irradiation with high-energy ^{56}Fe heavy particles (1 GeV/n) at the Alternating Generator Synchrotron (AGS) at Brookhaven National Laboratory (BNL) (Upton, NY) at a dose rate of 1 Gy/min one week prior to arrival at the HNRCA facilities (Boston, MA), as described in previous experiments (e.g., Shukitt-Hale et al., 2000). The rats were irradiated one at a time in well-ventilated plastic holders to minimize movement. The rats were positioned in the line of the beam so that their heads were located in the center of the beam. Dosimetry was provided by the staff of the accelerator facility. Non-irradiated animals ($n = 10$) were also taken to the BNL facility but because of beam time considerations we did not place them in the beam-line apparatus in the exposure cave. For a more detailed description of the radiation procedure, see Shukitt-Hale et al. (2000).

2.3. Behavioral test procedure

The apparatus used in this experiment was a white opaque high-density polycarbonate circular open field (1 m in diameter and 45 cm high) (Fig. 1). The base was divided into four side quadrants, two middle locations (north and south) and one center region. For this test, animals are placed in this circular open field with objects, and habituation of activity to this initially novel environment is measured over successive trials. After habituation, processing of the environment is measured by the animals' reaction to either spatial (displacement of familiar objects) or non-spatial (substitution of a familiar object with a new one) change. This paradigm measures the ability of animals to build up spatial representations and determines the nature of spatial parameters so encoded during exploration (Save et al.,

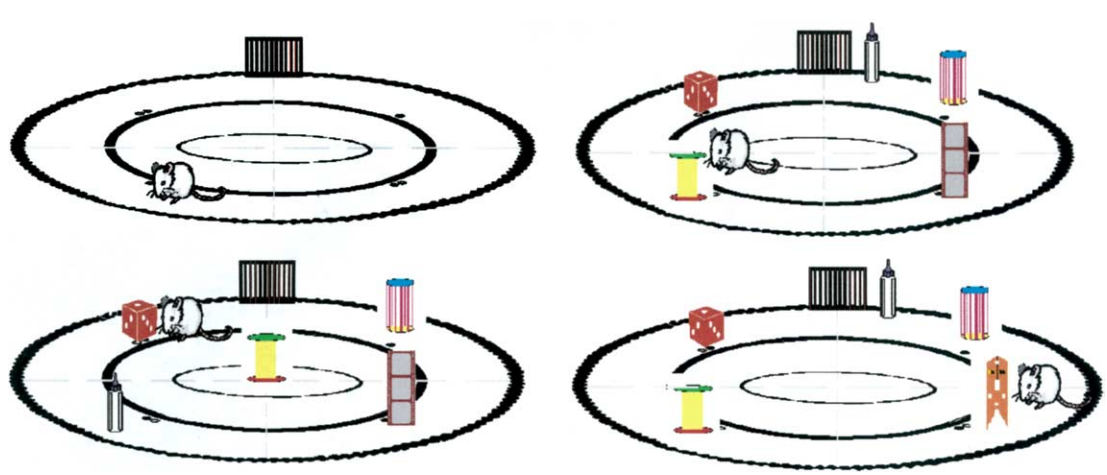

Fig. 1. Diagram of the test apparatus.

1992). Normal, young rats exhibit high levels of initial exploratory activity, which decrease over time (Poucet, 1989). Following a spatial change, these animals reinvestigate the whole set of objects, although they reexplore the displaced objects more than the non-displaced ones (Poucet, 1989). A renewal of exploration requires that some internal representation of the spatial layout of the objects was formed and compared with the new arrangement. Detection of object novelty can also be tested by examining the reactivity to the substitution of a familiar object by a new one at the same location; the novel object induces increased exploration in normal rats (Save et al., 1992). Prior studies which have investigated object exploration, habituation, and spatial recognition and discriminative responses of animals in the same apparatus have attempted to show which areas of the brain (using neural lesions or receptor blockade) are involved in spatial memory acquisition, storage, and use (Poucet, 1989; Roullet et al., 1996; Save et al., 1992; Thinus-Blanc et al., 1996).

Rats were individually submitted to seven successive 6-min trials, each of these separated by 3 min during which the subjects were returned to their home cage. On the first trial, the rats were placed (north–west quadrant) into an empty open field in order to allow for baseline measurements of locomotor activity (Fig. 1, top left). During trials 2–4, the animals were left to habituate to an environment where four objects were placed in a square arrangement and the fifth object was in the center of the field (Fig. 1, bottom left). Trials 5 and 6 were used to measure response to spatial change by moving around two of the objects in the open field (Fig. 1, top right).

In the last trial, response to non-spatial change was measured by replacing one of the familiar, non-displaced objects with a new one, very different in shape, at the same location (Fig. 1, bottom right) (for a more detailed description of the test, see Shukitt-Hale et al., 2001). All experiments were taped and subsequently analyzed by an experimenter blind to the treatment.

Data analysis was performed by scoring the videotapes of the trials with the help of a computerized program for the sequential analysis of behavior. In trial 1, locomotor activity and inactivity was recorded by counting the frequency and duration of these behaviors in the seven different sectors. In addition to locomotor behavior, other exploratory behaviors such as rearing and grooming (frequency and duration) were also measured. For trials 2 through 7, object exploration (divided into old, changed, and new objects) was evaluated by recording the time the animal spent in contact with the particular objects and latency to begin exploration of the objects. A contact was defined as the subject's snout actually touching the object.

Analyses of variance (ANOVA) comparing the two radiation groups were used for each behavioral measure using the statistical analysis software Systat (SPSS, Inc., Chicago, IL). Statistical significance was determined at the $p < 0.05$ level. Trials were included as a within-subjects variable when appropriate. Post-hoc analyses were performed using t-tests to determine which trials were different between the two groups, when a significant overall group difference or a group × trial interaction was found.

3. Results

Overall, radiation produced a pattern of decreased activity and increased reactivity to change. The effects of 1.5 Gy of ^{56}Fe radiation on exploratory behavior in an open field, and on reactivity to both spatial and non-spatial change, were subtle.

Even though the overall pattern of locomotor activity did not differ between groups, statistical analysis for trials 1–7 illustrated that irradiated animals overall spent significantly less time in the center portion of the open

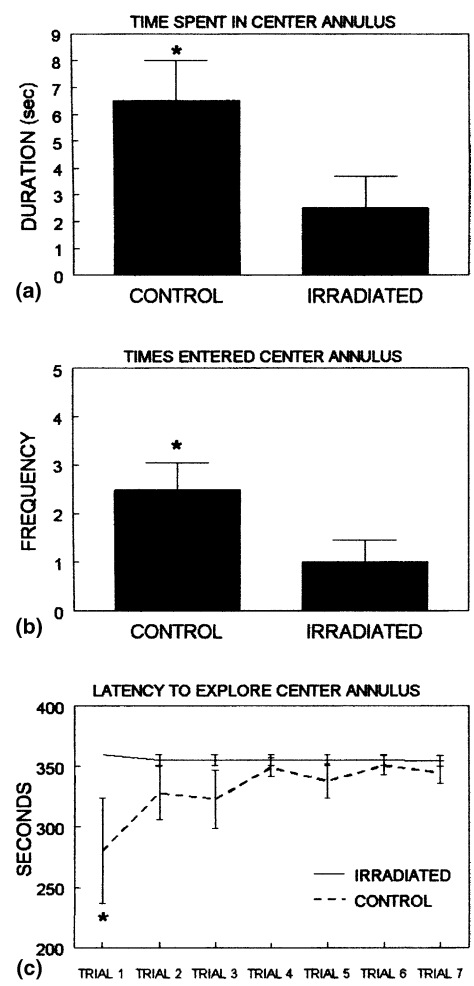

Fig. 2. Effects of 1.5 Gy of ^{56}Fe radiation on: (a) duration (time spent, s); (b) frequency (number of times entered) and (c) latency to explore the center annulus during a 7-trial test (mean ± SEM). Asterisks indicate significant differences between the groups ($^{*} = p < 0.05$).

field than did control subjects ($F_{1,18} = 4.52$, $p < 0.05$; Fig. 2(a)) and visited the center less frequently than controls ($F_{1,18} = 4.14$, $p \leqslant 0.05$; Fig. 2(b)). Likewise, irradiated animals showed impairments in initiating and continuing visits to the center annulus of the open field when compared to controls ($F_{1,18} = 7.04$, $p < 0.05$; Fig. 2(c)). Irradiated subjects also took significantly longer to enter and explore the middle portion of the open field than controls, i.e., they spent less time in the middle annulus of the open field ($F_{6,108} = 3.50$, $p < 0.01$; Fig. 3(a)), significantly so on trial 1 ($t_{18} = 2.38$, $p < 0.05$) and trial 2 ($t_{18} = 2.79$, $p < 0.05$) of testing, but there was no difference between the groups on subsequent trials. Additionally, irradiated rats entered the middle portion of the open field significantly less times than did controls ($F_{6,108} = 3.44$, $p < 0.05$; Fig. 3(b)), particularly during the initial trials, trial 1 ($t_{1,18} = 2.69$, $p < 0.05$), and trial 2 of testing ($t_{1,18} = 2.69$, $p < 0.05$). Repeated measures analysis also showed a significant trial-dependent decrease in exploration duration ($F_{6,108} = 14.69$, $p < 0.001$) and frequency ($F_{6,108} = 10.07$, $p < 0.001$) of the side portion of the open field, and duration ($F_{6,108} = 2.20$, $p < 0.05$) and frequency ($F_{6,108} = 4.14$, $p < 0.01$) of visits to the middle portions of the open field, for both groups. We did not find any significant differences between groups when rearing and grooming behaviors were examined.

Statistical analysis on object exploration revealed very subtle differences between groups, as most variables

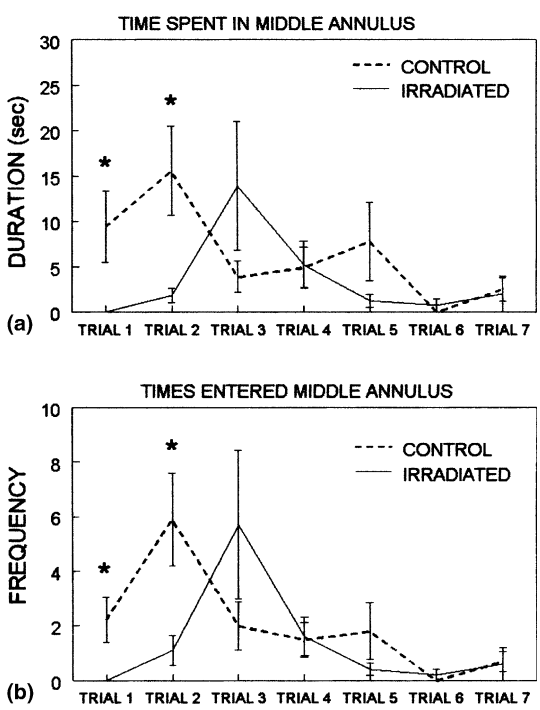

Fig. 3. Effects of 1.5 Gy of ^{56}Fe radiation on: (a) duration (time spent) and (b) frequency (number of times entered) of exploration of the middle annulus during a 7-trial test (mean ± SEM). Asterisks indicate significant differences between the groups ($^{*} = p < 0.05$).

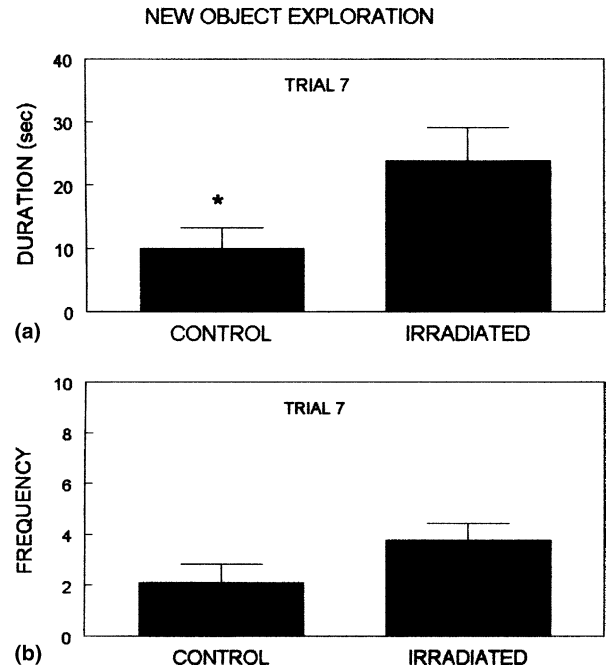

Fig. 4. Effects of 1.5 Gy of ^{56}Fe radiation on: (a) duration (time spent) and (b) frequency (number of physical contacts with the object) of exploration of a new object placed in the field during trial 7 (non-spatial change) (mean ± SEM). Asterisks indicate significant differences between the groups ($^{*} = p < 0.05$).

related to object exploration did not reach statistical significance. However, data analysis did show that the irradiated group spent a significantly greater amount of time exploring the newly replaced object than did the control subjects ($F_{1,18} = 5.10$, $p < 0.05$; Fig. 4(a)), although there was no difference in frequency of new object exploration ($F_{1,18} = 2.86$, $p = 0.11$; Fig. 4(b)). Conversely, no difference between groups was demonstrated for time spent exploring (having contact with) old or the spatially displaced objects. Data analysis also revealed a general decline in visits over time (trials) to the different objects placed in the open field, as well as the time taken to begin exploring those objects in both groups. Specifically, both groups decreased the amount of visits and the amount of time spent with old objects over the seven trials of the test session ($F_{5,90} = 25.56$, $p < 0.001$; $F_{5,90} = 23.67$, $p < 0.001$) and decreased the amount of times and the length of time that they spent with each spatially changed object during trials 5–7 ($F_{2,36} = 3.34$, $p < 0.05$; $F_{2,36} = 9.96$, $p < 0.001$).

4. Discussion

Older animals have been found to generally move less and investigate less than younger animals (Soffie et al., 1992). In addition, it has been shown that older animals tend to become more anxious in novel environments as they age (Frussa-Filho et al., 1991; Imhof et al., 1993).

Thus, it is possible that the decrement in exploration seen in older animals may be, at least partially, related to an age-related increase in anxiety. Given the similarity between behavioral changes induced by exposure to heavy particles and aging (e.g., Joseph et al., 2000; Shukitt-Hale et al., 2000) our initial hypothesis was that animals irradiated with ^{56}Fe radiation would also explore the environment less. Indeed, and in accordance with research done in aged animals (Casadesus et al., 2001), we found that animals irradiated with 1.5 Gy of ^{56}Fe radiation explored the center annulus significantly less than controls, and that this reduced exploration was independent of the amount of locomotor activity. That is, while the overall level of locomotor activity was comparable between groups, the irradiated subjects spent longer periods of time in the annulus closest to the walls as opposed to the center of the open field. Given that exploration around the walls (wall-hugging behavior) has been characterized as fear-provoked behavior (Dellu et al., 1994), it is possible that irradiated animals, like aged animals, show increased amounts of anxiety when exploring an open field. Further evidence to support this hypothesis comes from the fact that the animals that received 1.5 Gy of radiation began exploring the middle annulus of the open field at least one trial later than did controls and also took longer to begin exploring both the middle and center annulus of the open field than did controls across trials. This is illustrated by the fact that there was a phase-shift in the exploration of the middle annulus. Thus, it appears that the irradiated animals took longer to overcome the "anxiety" produced by the novel environment than did control subjects.

Reactivity to novel objects has been shown to decrease in both aged animals (Soffie et al., 1992) and in animals that received various types of ionizing radiation (McDowell et al., 1961). It has been postulated that this lack in reactivity is due to a general decrease in activity and exploration of novel surroundings (Dellu et al., 1994; Gage et al., 1984). Shukitt-Hale et al. (2001) used the same test as that used in the current study to measure aging differences in Fischer 344 rats and demonstrated that senescent subjects have less frequency and duration of contact with old and spatially displaced objects but showed no differences with respect to frequency and duration of new object exploration. Interestingly, our study showed that animals irradiated with the 1.5 Gy dose reacted to a novel object significantly more than did the control animals, which does not agree with the established literature on the behavioral effects of aging. One possible explanation is that irradiated animals were more reactive to the novel object because overall they were less active and spent more time in the quadrant of the open field where the object was located, since this was the quadrant into which they were placed in the open field. The higher amount of time spent in this region of the open field may have increased their familiarity towards the objects in that region and thus may have made them more prone to react to a change.

When we analyzed the reactivity of the subjects to objects that had been spatially rearranged, we did not find any differences between the radiated and control groups. It is well known that aged animals (Cavoy and Delacour, 1993; Shukitt-Hale et al., 2001; Soffie et al., 1992) and aged humans (Ohta et al., 1981; Barnes, 1987; Raskind and Peskind, 1994) have difficulty in detecting spatial changes in the environment. For this parameter, our findings in irradiated rats would not agree with findings seen in aged animals. However, there are several explanations that may account for these results. The relationship seen between time spent in the quadrant and heightened exploration of the objects in that quadrant suggests the hypothesis that, perhaps, we found only slight differences in the reactivity to spatial changes because both groups were less active over time and that rendered them less capable to encode the original setting well enough to perceive a change later on. However, given that Shukitt-Hale et al. (2001) showed that young controls reinitiated exploration when the objects in the maze were spatially rearranged, it seems more likely that this test was not sensitive enough to detect the subtle changes produced by this dose of radiation exposure (1.5 Gy of ^{56}Fe particles), especially given the fact that irradiated animals do show lower levels of exploration when compared to the non-irradiated subjects' re-initiation of activity during spatial rearrangement of objects (not statistically significant). Moreover, Shukitt-Hale et al. (2000), using the Morris water maze test, and previously Kadar et al. (1989), using the RAM, to establish the effects of ionizing radiation exposure on spatial cognition, found that only when irradiated animals were challenged to use spatial strategies did they show spatial deficits. Therefore it is also possible that we did not find any differences in this type of behavior because the test we used does not require the use of any spatial strategies to find a reward or locate a specific target in an area.

In examining the literature concerned with the behavioral effects produced by exposure to high-energy charged particles, one realizes that: (1) the effects on behavior of this type of radiation are in general subtle, and (2) there is a great degree of variability in the findings reported by different investigators. The results of the present study confirm these statements. On one hand, our results illustrate some degree of decline produced by exposure to ^{56}Fe radiation. For example, irradiated subjects showed an anxiety-provoked pattern of exploration, by not entering the field, spending less time in the annuli farthest from the walls of the open field, and by visiting the sides of the open field more frequently. These findings are in direct accordance with those described in the literature for aged animals in both the RAM (Ammassari-Teule et al., 1994) and other exploration paradigms (Frussa-Filho et al., 1991; Imhof et al., 1993).

Based on these findings, it is possible that both radiation exposure and the aging process may involve the generation of free radicals and oxidative stress (Harman, 1956; Sun et al., 1998). It is well known that radiation induces both oxidative (Brouazin-Jousseaume et al., 2002) and inflammatory (e.g., Brink et al., 2000) stress. Direct evidence for the involvement of free radicals in the deficits produced by exposure to heavy particles is provided by the observation of increased DCF (2′,7′-dichlorofluorescin diacetate) fluorescence in the brain 1–2 months following exposure to 1.5 Gy of ^{56}Fe particles (Denisova et al., 2002). In addition, exposing rats to ^{56}Fe particles produces alterations in signaling proteins (e.g., synaptobrevin, protein kinases) which are correlated with deficits in the performance of tasks requiring spatial memory (Denisova et al., 2002). Similarly, placing rats on antioxidant diets containing blueberry or strawberry extract ameliorates the effects of exposure to heavy particles on dopamine-mediated taste aversion learning (Rabin et al., 2002a). While additional research is needed to determine the degree to which oxidative stress serves as the common factor in the neurochemical and behavioral changes produced by aging and exposure to HZE particles, available research suggests that age may exacerbate the effects of exposure to galactic cosmic rays on exploratory class missions outside the magnetosphere (Rabin et al., 2002c).

However, as stated previously, some of the parameters measured in this study did not confirm our hypothesis that animals irradiated with ^{56}Fe radiation would explore spatially rearranged objects less than controls, similar to aged animals. One possible explanation for the partial number of age-like-radiation comparisons attained in this study may involve a lack of sensitivity of the test at the chosen irradiation dose. Therefore we feel that although a 1.5-Gy dose may be sufficient to induce some age-like changes, more complex behavioral tests may be needed to study this dose of irradiation. Future studies will focus on examining the behavior of the irradiated and control animals on these tests and attempting to characterize the mechanisms (e.g., oxidative stress) involved.

Acknowledgements

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