Interaction between age of irradiation and age of testing in the disruption of operant performance using a ground-based model for exposure to cosmic rays

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Abstract Previous research has shown a progressive deterioration in cognitive performance in rats exposed to ^{56}Fe particles as a function of age. The present experiment was designed to evaluate the effects of age of irradiation independently of the age of testing. Male Fischer-344 rats, 2, 7, 12, and 16 months of age, were exposed to 25–200 cGy of ^{56}Fe particles (1,000 MeV/n). Following irradiation, the rats were trained to make an operant response on an ascending fixed-ratio reinforcement schedule. When performance was evaluated as a function of both age of irradiation and testing, the results showed a significant effect of age on the dose needed to produce a performance decrement, such that older rats exposed to lower doses of ^{56}Fe particles showed a performance decrement compared to younger rats. When performance was evaluated as a function of age of irradiation with the age of testing held constant, the results indicated that age of irradiation was a significant factor influencing operant responding,

such that older rats tested at similar ages and exposed to similar doses of ^{56}Fe particles showed similar performance decrements. The results are interpreted as indicating that the performance decrement is not a function of age per se, but instead is dependent upon an interaction between the age of irradiation, the age of testing, and exposure to HZE particles. The nature of these effects and how age of irradiation affects cognitive performance after an interval of 15 to 16 months remains to be established.

Keywords ^{56}Fe particles · Aging · Cognitive · Behavior · Cosmic rays

Introduction

Exposure to particles of high energy and charge (HZE particles) such as ^{56}Fe , a ground-based model for exposure to cosmic rays, produces deficits in neuronal and behavioral functioning. These deficits are similar to those that are characteristic of the aged organism, including deficits in signal transduction (Joseph et al. 1992, 1993, 2000; Casadesus et al. 2005; Denisova et al. 2002), amphetamine-induced taste aversion learning (Rabin et al. 1998), spatial learning and memory using the Morris water maze (Shukitt-Hale et al. 2000, 2003, 2007; Carey et al. 2007), and operant responding (Rabin et al. 2002). Previous research has shown that rats exposed to ^{56}Fe particles at a young age (2 months) show a progressive deterioration in

In memory of James A. Joseph who passed away while the paper was in preparation. He was a valued colleague and friend.

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operant responding on an ascending fixed-ratio (FR) reinforcement schedule as a function of time following irradiation such that doses of particles that did not affect the responding of younger animals did affect their responding as they aged (Rabin et al. 2002, 2005a, b).

In addition to a progressive, age-related deterioration in performance, older animals seem to be more sensitive to the debilitating effects of exposure to HZE particles. Older animals show changes in elevated plus-maze performance (Rabin et al. 2007) and in amphetamine-induced taste aversion learning (Carrhill-Knoll et al. 2005) at lower doses of ^{56}Fe particles than younger animals. However, a limitation of these endpoints is that performance can be measured at only a single point in time. As such, these studies confound age of irradiation with the age of testing, and they do not permit an evaluation of the interaction between age of irradiation and the age of testing. In contrast, operant responding which can be tested repeatedly across the lifespan can provide more detailed information about the nature of the relationship between age of irradiation and age of testing and cognitive performance.

The specific task utilized in these experiments, performance on an ascending FR operant task, is dependent upon the integrity of the striatum and dopaminergic system (Salamone et al. 2003, 2007). This system mediates both appetitive and aversive motivation (Salamone 1992); specifically the motivational aspects of motivation (Salamone and Correa 2002) and decision-making as it relates to the expenditure of energy by the organism to achieve a specific goal (Salamone et al. 2007). As such, it is a measure of the organism's ability and willingness to respond changes in environmental contingencies: to change its pattern of responding as a function of changes in task requirements.

The present experiments were designed to evaluate the effects of exposure to HZE particles on operant responding as a function of both the age of irradiation and age of testing. Specifically, the experiments were designed to determine: (1) whether the dose of ^{56}Fe particles needed to disrupt operant performance varied as a function of the age of the subject at the time of irradiation and to track changes in performance as a function of the age of subsequent testing; and (2) whether there were differences in the effects of exposure to ^{56}Fe particles on the performance of

rats irradiated at different ages but tested at the same age. To evaluate the interaction between age of irradiation and age of testing, rats were exposed to ^{56}Fe particles at four ages and then tested at intervals up to 16 months following irradiation.

Methods

Subjects

The subjects were 140 male Fischer 344 (F-344) rats obtained from the N.I.A. supported contract colonies. The initial sample sizes were 10 rats/age/dose. Throughout the course of the experiment, animals were euthanized because they developed large tumors (>5 cm diameter) or because they became debilitated. With the exception of the rats irradiated at 16 months of age, in which there was the loss of most rats exposed to 150 cGy, the loss of animals was similar for all ages and doses.

The ages of the rats at the time of irradiation were 2 ($n=40$), 7 ($n=30$), 12 ($n=40$), and 16 ($n=30$) months. The rats were maintained at AAALAC-accredited facilities at Brookhaven National Laboratory (BNL) for irradiation. Following irradiation, they were shipped to the University of Maryland, Baltimore County (UMBC). The animal facilities at UMBC are supervised by Veterinary Medicine Resources of the University Of Maryland School Of Medicine. At both facilities, the rats were maintained on a 12:12 h light: dark cycle with food and water continuously available except as required by the experimental protocol. While at BNL, the rats were tested for the effects of irradiation on the acquisition of an amphetamine-induced conditioned taste aversion (Carrhill-Knoll et al. 2005). Operant responding was tested at UMBC. All procedures were approved by the IACUC of both BNL and UMBC.

Radiation

The rats were exposed to ^{56}Fe particles (1000 MeV/n) at the NASA Space Radiation Laboratory at BNL. For irradiation, the rats were placed in well-ventilated plastic tubes which were located perpendicular to the beam with the head of the rat placed in the center of the beam. As a consequence of this placement, the shoulders of the rats received some exposure to the

particles. The 7- and 16-month-old rats were irradiated first, 8 months before the 2- and 12-month-old rats. The doses ($n=10/\text{dose}$) to which the rats were exposed varied as a function of the age of the rats. The 7- and 16-month-old rats were exposed to 50 and 150 cGy; the 2-month-old rats were exposed to 50, 150, and 200 cGy; and the 12-month-old rats were exposed to 25, 50, and 150 cGy. All exposures were at a nominal dose rate of 50 to 100 cGy/min. The control rats (0 cGy) were taken to the NSRL but were not irradiated.

The doses to which the rats were exposed were selected on the basis of previous research in which young (2-month-old) Sprague–Dawley (S–D) rats were exposed to different doses of ^{56}Fe particles. This research showed that a dose of 200 cGy was needed to disrupt operant responding in young rats exposed to ^{56}Fe (1,000 MeV/n) particles, but that as the rats aged, there were performance deficits in those rats exposed to lower doses of ^{56}Fe particles (Rabin et al. 2005c, 2007). Specifically, at 7 months post-irradiation (9 months of age), the rats that had been exposed 150 cGy of ^{56}Fe particles showed a significant disruption of operant responding; at 11 months post-irradiation (13 months of age), a significant disruption in operant responding was seen in the rats that had been exposed to 100 cGy, which was the lowest dose tested. Because the current experiments were designed to determine whether or not there would be a decrease in the threshold dose needed to disrupt operant performance as a function of the age of irradiation/testing and whether there would be a progressive decrease in the dose needed to produce a performance decrement, the doses were selected that were equal to or lower than the threshold dose obtained in the prior experiments (Rabin et al. 2005a, b, c). Because previous research had established doses that were likely to produce a deficit in performance as a function of increasing age (Rabin et al. 2007; Carrihill-Knoll et al. 2005), not all subjects were tested at all doses.

Operant responding

The rats were trained to make a lever-pressing response in order to obtain a 45-mg food pellet. The training procedure involved placing the rats on a mild food deprivation schedule to maintain their body weight at approximately 90% of their weight prior to

the start of the deprivation protocol. The rats were placed on the food deprivation schedule for the duration of the 3-week testing period. Throughout the training and testing periods, the rats were weighed daily and the amount of food obtained in the operant chamber was supplemented by food provided by the experimenter as needed to maintain this body weight. Following each test of operant responding, the rats were returned to an ad lib feeding schedule. Prior to each retest, the rats were again weighed and then placed on a deprivation schedule to reduce their body weight to approximately 90% of their current weight at the time of testing.

For the initial acquisition of the response, an autoshaping procedure was utilized, which involved placing the rats in the operant chamber for 12 h. During this phase of the training, the rats were rewarded with a pellet every time the lever was pressed. Once the rats learned to press the lever to obtain food, they were trained to respond on an FR reinforcement schedule. With a FR schedule, the rat is rewarded with a food pellet after a specific number of lever presses: on an FR-1 schedule, every response is rewarded; whereas on an FR-20 schedule, 20 lever presses are required in order to obtain a single pellet; and on an FR-35 schedule, the rat must press the lever 35 times in order to obtain a single pellet. After the initial acquisition of the response, typically within a single session, the rats were introduced to the FR procedure. The training protocol for the acquisition of fixed-ratio responding involved two daily 30-min sessions at FR-1, followed on consecutive days by sessions at FR-5, FR-10, and FR-20. For testing, an ascending fixed-ratio reinforcement schedule from FR-1 to FR-35 was used. On consecutive days, the rats were run on FR-1, FR-5, FR-10, FR-15, FR-20, FR-25, FR-30, FR-35 reinforcement schedules. Each daily session was 30 min in duration and included only a single reinforcement schedule.

The initial evaluation of the effects of exposure to ^{56}Fe particles on operant responding was done within 2–4 months following irradiation. Subsequent evaluations were done at 4–6-month intervals. The number of replications was dependent upon the initial age of the rats because particularly for the rats exposed to the higher doses of ^{56}Fe particles, there was the loss of animals due to the development of tumors or physiological debilitation resulting in sample sizes that were too small to provide statistically meaningful

data. For all tests following the initial run, the rats were food-deprived as above. In order to maintain identical patterns for all tests, the rats were first run using the FR training protocol which was then immediately followed by testing on the ascending FR schedule. This procedure also minimized the unlikely possibility that the differences in performance reflected differences in task memory.

Data and data analysis

The data were collected as the total number of responses (bar presses) at each reinforcement schedule. The same data set was analyzed in two separate ways. For the first analysis, operant performance was evaluated as a function of both age of irradiation and testing. Performance was initially evaluated 2–4 months following exposure at 2, 7, 12, and 16 months of age. Subsequent tests of operant responding were performed at 4–6-month intervals. The data were analyzed using a three-way mixed analysis of variance (ANOVA) in which the main effects were radiation dose, age at testing, and reinforcement schedule. The dose of ^{56}Fe particles to which the rats were exposed and the age at testing were the between subject variables; the reinforcement schedule was the within subject variable. For the second analysis, age of testing (11–14 months or 17 to 18 months of age) was held constant and the age at the time of exposure was varied. This analysis also utilized a three-way mixed ANOVA, in which the main effects were age at exposure, radiation dose, and reinforcement schedule. Dose and age were between subject variables; reinforcement schedule was the within subject variable. Simple effects analyses were performed using mixed two-way ANOVAs as necessary.

Results

Age of irradiation/testing

The first series of analyses was concerned with the effects of exposure to different doses of ^{56}Fe particles on the operant performance of rats irradiated at different ages and tested sequentially at different times (ages) following exposure in order to determine the interactions between the age of irradiation and the age of testing. These analyses were designed to determine whether the overall pattern of responding varied as a function of age and dose of irradiation. A summary of the results of the initial three-way ANOVAs is presented in Table 1. Further analysis of the pattern of responding was done using two-way ANOVAs in order to determine whether the pattern of responding varied as a function of dose.

The effects of exposure to ^{56}Fe particles on operant performance on an ascending FR schedule as a function of the age of irradiation/testing are shown in Figs. 1, 2, 3, and 4. Overall, the results indicate that there was a significant interaction between age of irradiation/age of testing and performance for the subjects irradiated at 2, 7, 12, and 16 months of age. Figure 1 presents the results of the first test of operant responding (run 2–4 months following exposure). The ANOVA for the first test showed that the main effect for age of irradiation/testing (2, 7, 12, 16 months/4, 11, 14, 20 months) was significant ($F[3,70]=9.19$, $p<0.001$). While the main effect for dose (0, 50, 150 cGy) was not significant ($F[2,70]=1.23$, $p=0.30$), the age by dose interaction was significant ($F[6,70]=4.18$, $p=0.001$). The main effect for the reinforcement schedule ($F[7,490]=33.33$, $p<0.001$) was also significant. In addition, the age by schedule, dose by schedule, and triple interactions were all significant (all $ps\leq 0.001$). These results indicate that while all

Table 1 Summary of the results of ANOVAs (F)

Run/Fig #	Main effects			Interactions			
	Factor A Age	Factor B Dose	Factor C Schedule	A×B	A×C	B×C	A×B×C
1	9.19**	1.23 ^a	33.33**	4.18**	5.52**	2.58**	3.31**
2	9.46**	0.60 ^a	28.39**	0.84 ^a	4.83**	0.84 ^a	0.87 ^a
3	6.40**	3.69 ^a	38.73**	1.50 ^a	3.14**	0.65 ^a	1.16 ^a
4	— ^b	0.95 ^a	16.82**	— ^b	1.11 ^a	— ^b	— ^b
5	11.11**	9.92**	30.58**	1.09 ^a	5.71**	6.35**	1.33 ^a
6	4.19*	1.36 ^a	38.76**	1.00 ^a	5.26**	0.89 ^a	1.10 ^a

* $p<0.05$; ** $p<0.01$

^an.s

^bOnly a single age was tested

Fig. 1 Effects of age of irradiation/age of testing on cognitive performance. First test of operant responding on an ascending fixed-ratio (FR) schedule. Average total number of bar presses at each reinforcement schedule; mean $\pm$ standard error of the mean (s.e.m.)

doses of ^{56}Fe particles affected operant responding, the pattern of responding varied as a function of both age and dose.

To further analyze the pattern of age-related changes in operant responding following exposure to different doses of ^{56}Fe particles, a series of independent two-way ANOVAs were run for each of the three doses (0, 50, 150 cGy). The first ANOVA evaluated the effects of age of irradiation/testing on performance in the non-irradiated control rats (0 cGy) to determine whether or not there was an age effect which was independent of exposure. Neither the main effect for age nor the age by schedule interaction was significant ($F[3,24]=1.79$, $p>0.10$; $F[7,21]=1.42$, $p>0.10$; respectively). These results indicate that across the ages sampled (2, 7, 12, 16 months), there was no independent effect of age on responding. In contrast, the rats exposed to 50 ($F[21,154]=1.88$, $p<0.05$) or 150 cGy ($F[21, 189]=4.56$, $p<0.001$) of ^{56}Fe particles showed significant interactions between age and reinforcement schedule, indicating a decrement in operant performance at the higher ratio schedules as a function of the age of irradiation and testing.

The second test of operant performance was run 6 to 7 months after irradiation (Fig. 2). At that time, there were only three 16-month-old animals remaining that had been exposed to 150 cGy of ^{56}Fe particles. As such, too few animals remained for a reliable statistical analysis of the results at this dose level. Therefore, two independent three-way ANOVAs were run: (1) four ages (2, 7, 12, 16 months) at two doses (0, 50 cGy); and (2) three ages (2, 7, 12 months) at three doses (0, 50, 150 cGy). For both ANOVAs, the main effects for age of irradiation/testing and reinforcement schedule were significant, as was the schedule by age interaction (all $p<0.001$). As with the first replication (test) the two-way ANOVA showed that there were no significant effects of age of irradiation/testing on operant responding in the non-irradiated control (0 cGy) rats. However, for the rats exposed to 50 cGy, both the main effect for age of irradiation ($F[3,23]=4.96$, $p<0.01$) and reinforcement schedule ($F[7,161]=7.24$, $p<0.001$) were significant, as was the interaction between age of irradiation/testing and reinforcement schedule ($F[21,161]=2.42$, $p<0.001$). These observations showing a significant

Fig. 2 Effects of age of irradiation/age of testing on cognitive performance. Second test of operant responding on an ascending FR schedule. Average total number of bar presses at each reinforcement schedule; mean $\pm$ s.e.m

effect of age on operant responding only when paired with exposure to ^{56}Fe particles suggest that, at the ages and doses tested in the present experiment, age did not affect the ability of rats to respond to changes in environmental contingencies independently of exposure to ^{56}Fe particles.

The third test of operant performance was run 10 months following irradiation using the rats that had been exposed to ^{56}Fe particles at 2 and 7 months of age

(Fig. 3). The group of 2-month-old rats that had been irradiated with 200 cGy was excluded from the three-way ANOVA because there was no corresponding group in the rats radiated at 7 months of age. The ANOVA showed that the main effects for dose ($F[2,43]=6.40$, $p<0.01$) and for reinforcement schedule ($F[7,301]=38.73$, $p<0.001$) were both significant. However, the main effect for age of irradiation/testing (2 and 7/12 and 17 months of age) was not

Fig. 3 Effects of age of irradiation/age of testing on cognitive performance. Third test of operant responding on an ascending FR schedule. Average total number of bar presses at each reinforcement schedule; mean $\pm$ s.e.m

Fig. 4 Effects of age of irradiation/age of testing on cognitive performance. Fourth test of operant responding on an ascending FR schedule. Average total number of bar presses at each reinforcement schedule; mean $\pm$ s.e.m

significant ($F[1,43]=3.69$, $p>0.05$). The only interaction that was significant was the interaction between dose and reinforcement schedule ($F[14,301]=3.14$, $p<0.001$), indicating that the pattern of responding to the different reinforcement schedules varied as a

function of dose, but not of age of irradiation and testing.

Only the rats irradiated at 2 months of age had sufficient numbers remaining 15 months following irradiation (17 months of age) for a test of operant performance (Fig. 4). A two-way mixed ANOVA indicated that only the main effect for the reinforcement schedule ($F[7,189]=16.82$, $p<0.001$) was significant. Neither the main effect for dose ($F[3,27]=0.95$, $p>0.10$) nor the dose by schedule interaction ($F[21,189]=1.11$, $p>0.10$) was significant.

Age of irradiation

A second way of organizing the data is to compare the performance of rats tested at approximately the same age regardless of their age at the time of irradiation. This procedure allows an independent evaluation of the effects of age of irradiation on operant performance without the confounding factor of age of testing. Figure 5 summarizes the performance of the rats tested at 11–14 months of age; Fig. 6 summarizes the performance of rats tested at 17–18 months of age. The data

Fig. 5 Operant responding on an ascending FR schedule in rats 11–14 months of age. These graphs are redrawn from the ones presented in Figs. 1, 2, 3, and 4. Average total number of bar presses at each reinforcement schedule; mean $\pm$ s.e.m

Fig. 6 Operant responding on an ascending FR schedule in rats 17 to 18 months of age. These graphs are redrawn from the ones presented in Figs. 1, 2, 3, and 4. Average total number of bar presses at each reinforcement schedule; mean $\pm$ s.e.m

presented in these figures is the same as those presented in Figs. 1, 2, 3, and 4, but have been organized to present a more direct comparison of the age of testing independently of the age of irradiation/testing.

The three-way ANOVA analyzing the performance of the rats tested at 11–14 months of age indicated that the operant performance of the rats varied as a function of the dose of radiation ($F[2,57]=9.92$, $p<0.001$), age at the time of irradiation ($F[2,57]=11.11$, $p<0.001$), and the reinforcement schedule ($F[7,399]=30.58$, $p<0.001$). While the dose by age of irradiation interaction was not significant ($F[4,57]=1.90$, $p>0.10$), the dose by schedule ($F[14,399]=5.71$, $p<0.001$) and age by schedule interactions ($F[14,399]=6.35$, $p<0.001$) were both significant, indicating that the pattern of responding on the ascending FR reinforcement schedule was dependent upon both dose and age of irradiation in rats tested 11–14 months following exposure.

In contrast, the ANOVA for the rats tested 17 to 18 months following exposure indicated that the main effect for dose was not significant ($F[2,62]=1.36$, $p>0.10$). However, the main effects for age of irradiation ($F[2,62]=4.19$, $p<0.05$) and for reinforce-

ment schedule ($F[7,427]=38.76$, $p<0.001$) were both significant. Only the age by reinforcement schedule interaction was significant ($F[14,427]=5.26$, $p<0.001$), indicating that the age at which the rats were exposed to ^{56}Fe particles affected responding 15 to 16 months later, but that dose of radiation was not a factor affecting operant performance at this age.

Because the animals tested at 11–14 and 17 to 18 months following exposure to ^{56}Fe particles differed in terms of the number of times that they had been run on the operant task, it was possible that this factor may have accounted for the significant age effects. To evaluate this possibility, two sets of additional ANOVAs were run. The first set, using a mixed two-way ANOVA, analyzed the performance of the control (0 cGy) rats at both 11–14 and 17 to 18 months of age. The main effect for age was not significant for either group ($F[2,22]=3.04$, $p>0.05$; $F[2,24]=1.88$, $p>0.10$, respectively). The second set, using mixed three-way ANOVAs, evaluated the performance of the radiated rats (50 and 150 cGy) at the two different ages with the control rats (0 cGy) excluded from the analysis. At both ages of testing

(11–14 and 17 to 18 months), the main effect for age of irradiation (2, 7, and 12 months) was significant ($F[2,37]=11.24$, $p<0.01$; $F[2,42]=7.36$, $p<0.01$, respectively). As noted above, only for the rats tested at 11–14 months of age was there a significant main effect of dose (50, 150 cGy) ($F[1,37]=4.51$, $p<0.05$).

Discussion

Overall, these results show that there is an interaction between age of irradiation and the age of testing in the disruption of operant responding following exposure to ^{56}Fe particles. With regard to the first series of analyses, the present results are consistent with previous research in showing that there is a progressive deterioration in operant performance as a function of age. Specifically, research using S–D rats has shown a progressive deterioration in the performance of an operant responding task using an ascending FR reinforcement schedule following exposure to ^{56}Fe particles (Rabin et al. 2005b, c). Similarly, previous research using Fischer-344 rats has shown that middle-aged rats (7 or 12 months of age) show a performance decrement in the acquisition of an amphetamine-induced conditioned taste aversion following exposure to a lower dose of ^{56}Fe particles than young rats (2 months of age) (Carrihill-Knoll et al. 2005). Compared to young animals, middle-aged rats also show an increase in baseline anxiety at lower doses following exposure to ^{56}Fe particles (Rabin et al. 2007). And, as observed with the current task, exposing old rats (=16 months of age) to HZE particles does not produce a deficit in performance greater than that which occurs as a function of the aging process (Rabin et al. 2007; Carrihill-Knoll et al. 2005).

One concern with the present results is possible differences in task learning and carryover effects between the radiated and non-irradiated rats. Analysis of our data on the acquisition and reacquisition of the operant response (data not shown) indicates that both radiated and non-irradiated rats required the same number of trials, on the average, to learn the response. Similarly, as shown in the Figs. 1, 2, 3, and 4, there are no differences in responding between the irradiated and non-irradiated rats on the FR-1 and FR-5 schedules, which indicates that the carryover effects, if present, are the same for both sets of animals.

This analysis is consistent with the results of previous experiments and extends those results to a different endpoint, operant responding on an ascending FR schedule. The present results are also consistent with the observation that as the subjects age, the effects of age on cognitive performance exert a greater influence than do the effects of exposure to ^{56}Fe particles. This is seen in two ways: first, exposing old animals (16 months) to ^{56}Fe particles does not produce a decrement in cognitive performance; and second, dose is not a significant factor affecting performance in rats tested at 16 to 17 months of age, regardless of the age of irradiation.

However, while this analysis confirms the results of previous experiments, both in terms of the long-term consequences of exposure to ^{56}Fe particles and in terms of the effects of exposure across the life span, it has the same limitation as noted above for previous experiments: because the initial testing of operant responding occurred 2–4 months following exposure, there is the confounding of age of irradiation with the age of testing. In contrast to the previously tested endpoints, operant responding can be evaluated multiple times in a single subject. As such, it is possible to separate age of testing from age of irradiation. While this involved multiple statistical analyses of the same data set, it provides novel information about the role of age in the effects of exposure to HZE particles on cognitive performance and can also provide a basis for future experiments with analyses based upon independent groups.

The secondary analysis, which evaluated the effects of age of irradiation independently of age of testing, showed that age of irradiation affects performance for as long as 15 to 16 months following exposure to ^{56}Fe particles. In contrast, the effects of exposure to different doses of ^{56}Fe particles on cognitive performance were a significant factor only with the rats tested at 9–12 months of age following exposure. At 15 to 16 months post-irradiation, there were no significant differences between the non-irradiated controls and the rats exposed to ^{56}Fe particles; the performance of the control and irradiated rats is similar. These observations are consistent with the results of the analyses combining age of irradiation with age of testing and suggest that with 17 to 18-month-old rats, the effects of age outweigh the effects of irradiation.

With regard to the long-term effects of age of irradiation on performance, it may be noted that if the changes in operant responding were due primarily to the effects of aging, then there should have been age-related changes in the performance of the non-irradiated control animals. However, because a significant main effect for age of irradiation was seen only in the groups exposed to ^{56}Fe particles, it would suggest that the long-term effects of exposure to HZE particles may depend upon the age of the subject at the time of irradiation. The factors that may mediate the long-term effects of age of exposure across a time interval of 9–16 months are not known. In this regard, however, it may be noted that Mendez-Lopez et al. (2009) have reported age and sex differences in brain function related to cognitive performance.

Exposure to ^{56}Fe particles produces changes in neuronal function, especially in signal transduction in the striatum and hippocampus (Casadesus et al. 2005; Denisova et al. 2002; Joseph et al. 1994) and changes in hippocampal neurogenesis (Casadesus et al. 2005; Raber et al. 2004; Rola et al. 2004, 2005), as well as changes in dendritic spines in the prefrontal cortex (Quasem et al. 2007). For the most part, performance on an ascending operant task seems to be dependent upon the integrity of the striatum and the dopaminergic system. Partial lesions of the striatal dopaminergic system using the neurotoxin 6-hydroxydopamine disrupt the performance of middle-aged rats on this task (Lindner et al. 1997, 1999). This observation has implications for the cognitive performance of astronauts on long-duration exploratory class missions, such as a mission to Mars. Because astronauts will most likely be middle-aged individuals, the present results indicating that the effects of exposure to ^{56}Fe particles on neuronal function can vary as a function of the age of irradiation suggest that these individuals may be more likely to be affected by exposure to low doses of HZE particles, resulting in both immediate and long-term changes in cognitive performance.

Overall, these results show that there is an interaction between age of irradiation and the age of testing in the disruption of operant responding following exposure to ^{56}Fe particles. The specific task utilized in the present experiments, operant responding on an ascending FR reinforcement schedule, is a measure of the ability of the organism to respond to changes in environmental contingencies, including changes in reinforcement contingencies. Because the striatal dopaminergic system

may be involved in the activational aspects of motivation and affect the effort put into obtaining reinforcement (Salamone 1994; Salamone and Correa 2002), it is possible that exposing middle-aged astronauts to lower doses of HZE particles may interfere with the successful completion of mission requirements. The nature of this age-dependent change in cognitive performance and its relationship to the age of radiation cannot be defined at the present time, and additional research will be needed to understand how exposing organisms to HZE radiation at different ages affects long-term neuronal and cognitive functioning.

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