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Review article

Behavioral effects of space radiation: A comprehensive review of animal studies

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ABSTRACT

As NASA prepares for the first manned mission to Mars in the next 20 years, close attention has been placed on the cognitive welfare of astronauts, who will likely endure extended durations in confinement and microgravity and be subjected to the radioactive charged particles travelling at relativistic speeds in interplanetary space. The future of long-duration manned spaceflight, thus, depends on understanding the individual hazards associated with the environment beyond Earth's protective magnetosphere. Ground-based single-particle studies of exposed mice and rats have, in the last 30 years, overwhelmingly reported deficits in their cognitive behaviors. However, as particle-accelerator technologies at NASA's Space Radiation Laboratory continue to progress, more realistic representations of space radiation are materializing, including multiple-particle exposures and, eventually, at multiple energy distributions. These advancements help determine how to best mitigate possible hazards due to space radiation. However, risk models will depend on delineating which particles are most responsible for specific behavioral outcomes and whether multiple-particle exposures produce synergistic effects. Here, we review the literature on animal exposures by particle, energy, and behavioral assay to inform future mixed-field radiation studies of possible behavioral outcomes.

1. Introduction

One of the major concerns for astronaut health in prolonged missions is the amount of radiation exposure that crews could accumulate over the duration of their lives. The charged-particle flux that constantly irradiates the solar system originates from supernovas that occurred thousands of years ago within the Milky Way. These galactic cosmic rays (GCR) are composed of approximately 86–91% protons, 8–13% helium nuclei, and 1% heavy ($Z > 2$) energetic (HZE) nuclei (Nelson, 2016; George et al., 2009; Mewaldt, 1994). The solar system is also periodically bombarded by energetic solar ejecta, which are also primarily comprised of protons and helium nuclei, but are carried by solar wind (Nelson, 2016). Astronauts in low-earth orbit are largely protected from exposure to charged particles, with the exception of trapped particles within the Van Allen belts and those funneled into the South Atlantic anomaly, though these particles are of lower energy and far lower fluence (Townsend and Fry, 2002).

To date, the only humans exposed to interplanetary radiation are the Apollo astronauts, whose missions lasted a maximum of 13 days. The eventual manned missions to Mars will likely last 800–1100 days, of which approximately 500 days will be spent on the planet's surface, depending on final mission design (Drake, 2009). Recent data from Curiosity indicate concerning cumulative levels of daily radiation that may likely be encountered by astronauts on these missions. Behind the shielding provided by the Mars Science Laboratory and *en cruise* to Mars, the GCR dose rate was approximately 0.481 ± 0.080 mGy/day, during an untraditionally weak solar maximum (Zeitlin et al., 2013). Data from an unshielded Curiosity on the Martian surface suggest a GCR dose rate of 0.210 ± 0.040 mGy/day (Hassler et al., 2014). Mission dose estimates due to GCR are on the order of 25–50 cGy.

Abbreviations: GCR, galactic cosmic rays; HZE, high Z energetic particles; SPE, solar particle events; LET, linear energy transfer; CNS, central nervous system; MWM, Morris water maze; NOR, novel object recognition; CCR2, C-C chemokine receptor type 2; AD, Alzheimer's disease; Apo E, apolipoprotein E; APP, amyloid precursor protein; PS1, presenilin 1; EPM, elevated-plus maze; OiP, object in place; TO, temporal order; NOX-2, nicotinamide adenine dinucleotide phosphate oxidase-isoform 2; CREB, cyclic-AMP element-response binding protein; NRF2, nuclear factor erythroid 2-related factor; Nr1, n-methyl-D-aspartate receptor 1; GluR1, glutamate receptor 1; Syn1, synapsin 1; SAP97, synapse-associated protein 97; IL-4, interleukin 4; IL-12, interleukin-12; p70, ribosomal protein S6 kinase beta-1; IL-6, interleukin-6; TNF-α, tumor necrotic factor; Nr2a, N-methyl-D-aspartate receptor 2a; Syp, synaptophysin; Dbn1, drebrin 1; Nr2b, N-methyl-D-aspartate receptor 2b

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Additional dosage due to solar particle events (SPE) would depend upon the phase of the 11-year solar cycle during which a mission takes place and the relative intensity of the particular solar cycle, and are estimated to range from 15–50 cGy behind conventional shields (Nelson, 2016; Drake, 2009; Wilson et al., 1997; Kim et al., 2009).

Due to high human exposure risk, multiple shielding strategies are currently being considered. These range from mixtures of Martian soil, conventional spacecraft aluminum alloys, high-density polyethylene, lithium hydride, epoxy, carbon fiber, and combinations of these and other materials (Giraudo et al., 2018). Thick ground-based shields that use the soil on the Martian surface may be a plausible approach for time spent on the planet's surface, but current spacecraft shields are incapable of mitigating all of the dosage due to charged particles in interplanetary cruise. The thickness, and thus payload mass that would be required of many shielding materials, makes their use for full radiation protection infeasible. Until technological advancements allow for complete radiation protection, practical shields will alter the energy distribution and percentage of nuclei and their fragments inside a spacecraft (Zeitlin and La Tessa, 2016; Townsend, 2005). It may, therefore, be imperative that final shielding considerations incorporate strategies to ultimately minimize adverse biological outcomes as a function of particle and energy.

Charged particles are qualitatively different than electromagnetic radiation, due to the different distribution of energy deposition in tissues and materials. Electromagnetic radiation such as X-rays or γ-rays induces sparse ionization events, where energy is exponentially absorbed by tissues, which can induce primary ionization events with low-energy scattered electrons. Conversely, energetic charged nuclei deposit energy in cores of dense ionization events, which are capable of scattering electrons at energies high enough to induce secondary ionization events up to 1 cm away. This energy deposition is considered to occur in a linear fashion, which is dependent upon the kinetic energy of a given particle. Although individual ionization events occur stochastically, the initial linear energy transfer (LET) of a given particle prior to tissue or material interaction can inform the number of ionization events the particle will induce. The LET of a given energetic charged particle will slowly lower as the particle interacts with the target material, comprising the ``plateau region" of the energy-absorption curve. If the target material is thick enough to sufficiently absorb kinetic energy, the particle will reach a characteristic target depth in which the LET will sharply rise, peak, and sharply fall, as the particle's energy is completely absorbed. This phenomenon, the Bragg peak, further complicates shielding strategies, as many ionization events occur at this point, shifting from densely to sparsely ionizing events.

The body of literature examining animal behavioral outcomes in response to high-energy charged-particle radiation suggests differential effects in response to different particles and energies. The earliest behavioral studies of responses to charged-particles showed that whole-body exposure to electrons at approximately 18 MeV/e^- elicited detrimental effects in various paradigms of shock-induced conditioned avoidance, but the doses required to reach these deficits were 25–200 Gy and effects generally resolved within 1 h, indicating far lower sensitivity to electrons than to electromagnetic radiation (Mickley and Teitelbaum, 1978; Mickley, 1980; Hunt, 1983; Bogo, 1984). With the onset of access to high-energy (600 MeV/n) ^{56}Fe, radiobiologists began comparing the effects of densely ionizing, high-LET radiation to those of previous radiation qualities. This work showed that animals had higher sensitivity to ^{56}Fe in measures of conditioned taste aversion, dopamine depletion (in rodents), and emesis (in ferrets) (Rabin et al., 1989, 1992 ; Hunt et al., 1990). These findings led to a surged interest in the effects of charged nuclei of various Z and energies on the central nervous system (CNS) including many endpoints, the majority of which involve behavioral testing (Table 1).

2. Behavioral effects of charged particles in animal models

2.1. ^{56}Fe: the staple particle for in vivo research

^{56}Fe remains, by far, the most widely used particle for in vivo research on radiation effects on the CNS (Fig. 1and Table 2). Early studies employing this particle demonstrated that doses as low as 20 cGy produced deficits in thermoregulation and in acute striatum-dependent conditioned taste aversion (Kandasamy et al., 1994; Rabin et al., 1989, 2000, 2002b). Dosages of 10, 50, and 100 cGy of ^{56}Fe desensitized muscarinic striatal receptors and downstream signaling at 3 days post-exposure (Joseph et al., 1993, 1994; 1999; Villalobos-Molina et al., 1994). However, deficits in conditioned taste aversion were not observed more than 3 days after irradiation, probably due to the observed full restored striatal dopamine that occurred within 8 days (Hunt et al., 1990; Rabin et al., 2003). Furthermore, this effect occurred in 2-month-old rats, but not in 3-, 7-, 12-, or 16-month-old rats (Rabin et al., 2003; Carrihill-Knoll et al., 2007). A variation of this test, the conditioned place preference test, uses spatial cues instead of a taste stimulus, which also is striatum-dependent because conditioning relies upon an intact dopaminergic reward signaling. In the conditioned place preference test, 1 Gy was sufficient to elicit deficits (Rabin et al., 2001). Also dependent upon dopaminergic integrity is the fixed-ratio operant response paradigm, in which an animal must press a bar at increasingly higher frequencies to receive a food reward (Lindner et al., 1997). A dosage of 2 Gy, but not 1 Gy, was sufficient to elicit significant reductions in rewards that required 25 or more presses (Rabin et al., 2002a). These deficits became more pronounced and continued through 5–8, but not 13, months after irradiation (Rabin et al., 2005a). Interestingly, diets rich in antioxidants prevent these deficits, suggesting that dopamine depletion may not be the major driving factor in radiation-induced insults to the dopaminergic system (Rabin et al., 2005a,b). Previous studies had not specified ages of animals at the time of irradiation; however, age during irradiation, as well as follow-up time from irradiation, are important factors in the operant-conditioning task at dosages as low as 25 cGy (Rabin et al., 2012).

Effects of ^{56}Fe radiation on hippocampus-dependent spatial memory tests laid the foundational groundwork for more recent experiments with other particles in hippocampus-dependent assays. One of the first assays of hippocampus-dependent spatial memory was the Morris water maze (MWM), an established test reliant upon animals' innate desire to swim toward a platform (Laeremans et al., 2015). Animals' spatial learning is assessed during probe trials, where the platform is removed; animals with intact memory will spend significantly more time exploring the quadrant that once contained the platform. Reversal learning occurs when a platform is switched from a known, conditioned location to a novel one. Deficits in reversal learning in male rats and mice resulted from 1.5 Gy of whole-body or 3 Gy of cranial radiation, respectively (Shukitt-Hale et al., 2000; Villasana et al., 2013a); lower doses (10–50 cGy) did not impair any stage of the MWM (Haley et al., 2013). The radial arm maze was adopted early on to investigate effects of radiation on spatial and working memory. One month after exposure to 1.5 Gy, male rats suffered sporadic deficits throughout the 16-day paradigm and had increased oxidative stress in only the prefrontal cortex (Denisova et al., 2002). These sporadic deficits remained 9 months after receiving 1 Gy (Shukitt-Hale et al., 2003).

The novel object recognition (NOR) test is perhaps one of the most widely used cognitive tests in charged-particle radiation research. This hippocampus-dependent behavioral paradigm involves an open-arena habituation, followed by introduction to two identical objects, one of which is later switched for a novel object. Object memory is impaired 2 weeks after exposure to dosages of 10 and 40 cGy and 3 months after exposure to 150 cGy (Impey et al., 2016a; Casadesus et al., 2004). Three months after exposure to 50 cGy (600 MeV/n), motor activity in open field was reduced; however, 2 months after exposure to 10, 50, and 200 cGy (1000 MeV/n), no changes in open field occurred (Allen et al.,

Table 1
Summary of behavioral assays mentioned in this review.

Behavioral assays	Summary of behavioral assays	Dependence
Conditioned taste aversion	After acclimating animals to drinking sucrose water, animals are given increasing doses of LiCl or Amphetamines to increasingly induce taste aversions.	Striatum, parabrachial nuclei
Conditioned place preference	Animals are placed in an apparatus consisting of two large chambers that are separated by a small decision chamber. Each chamber consists of different colors, or patterns. Animals will undergo a habituation period where they will associate one of the chambers with a positive stimulus such as sucrose water. During testing, no stimuli are presented, and time spent in each chamber is measured.	Prefrontal cortex
Morris water maze	Animals are placed in a large circular water-filled pool, and are trained to find a hidden, or missing platform, based on spatial cues. Additional testing can involve reversal training and testing, where animals must learn and be tested on a new platform location. This maze assays spatial memory, and cognitive flexibility.	Hippocampus
Novel object recognition	After a period of acclimation, animals are exposed to two identical objects, and on the following day, one object is switched for a 'novel object'	Hippocampus
Attentional set-shifting	Animals are trained to associate a particular cue such as smell or digging medium texture with a food reward in an arena with buried food. Shifting the cue, and measuring animals digging preference tests for cognitive flexibility.	Prefrontal cortex
Fear conditioning	Fear conditioning occurs when animals associate a stimulus such as the environment (i.e. a distinct cage) and receive a shock. Animals naturally develop an aversion to the environment and show a marked increase in freezing behavior. A variation of this test involves using a cue, such as a distinct sound prior to foot shock, that will result in a similar aversion, such as freezing behavior, or jumps following the cue.	Hippocampus, Amygdala, Prefrontal cortex, Cingulate cortex
Barnes maze	Animals are placed in a large circular arena with many escape holes around the perimeter, but only one contains a 'shelter'. Animals use spatial cues to find the appropriate escape hole.	Hippocampus, prefrontal cortex
Rotorod	This motor test involves placing animals on a small rotating rod that spins increasingly faster. Time spent on the rod and spin frequency, at the time of falling, are measured.	Striatum, cerebellum
Elevated-plus maze	This maze involves placing animals in a maze with open or closed arms. Animals generally prefer to spend time in closed arms, due to height-induced anxiety, but will occasionally explore the open arms.	Amygdala
Object in place	This object-driven test involves placing animals in a square arena with four distinct objects in the corners during familiarization day. On the following day, the location of two of the objects is switched, and animals are generally interested in exploring these novel locations, as opposed to the other objects.	Prefrontal cortex
Temporal order	After habituation to an arena, animals are presented with an identical pair of objects, and on the following day, with a different pair of identical objects. On the testing day, animals are presented with one object from each day, and will generally be interested in exploring the object seen during the first day, unless impaired.	Prefrontal cortex
Y-Maze	This test relies on short-term spatial memory integrity. Mice are placed in a Y-shaped maze for two trials on the same day. The first trial involves exploration of the start and 'familiar' arms. During the second trial, animals can also explore a novel arm, containing a different object than the familiar arm. Animals are generally more interested in a novel object.	Hippocampus
3-Chamber sociability	This 3-stage test involves letting animals acclimate to three empty, adjacent chambers for the first stage. During the second stage, a sex-matched nonagressive unfamiliar animal is placed in small cage in one of the lateral chambers. The third stage involves placing yet another sex-matched nonagressive animal. Animals generally prefer exploring the caged animal during the second stage, and the novel animal during the third stage.	Hippocampus

2015; Pecaut et al., 2004). Interestingly, performance of mice that underwent the NOR familiarization step before 25 cGy cranial radiation was not different from that of nonirradiated mice (Poulose et al., 2017).

Attentional set occurs when an individual learns that a relevant cue, such as a digging medium, but not an irrelevant cue, such as the odor of the digging medium, is associated with a reward. When different media and odors are used, but the same reward is applied for the relevant cue (i.e., digging medium in this case), the cognitive set is reinforced. Cognitive flexibility can be measured by switching the cue from a positive to negative stimulus, such as rewarding animals for a newly introduced stimulus or for the odor cue, in this example. This well-established task is considered to be dependent upon the prefrontal cortex (Heisler et al., 2015). A dosage of 20 cGy (1000 MeV/n) caused severe deficits in the simple discrimination task during attentional set of rats 3 months after irradiation (Lonart et al., 2012). Ten-month-old rats that were prescreened for the ability to develop attentional set displayed marked deficits in compound and simple discrimination (attentional set), but not in the cognitive flexibility task, after low doses of 600 MeV/n ^{56}Fe (1, 3, 5, 10, 15 cGy) (Jewell et al., 2018). Ultimately, radiation-induced shifting of attentional set is dependent on animals' age during treatment (Britten et al., 2014).

Contextual fear conditioning, widely used for cognitive testing, is an example of a behavioral paradigm that is tested with negative, rather than positive, stimulus. The classical test places an animal in a novel environment and applies a negative stimulus, such as a foot shock; as a result, the animal will freeze when placed in the same environment in the future. A conditioning stimulus (i.e., cue; often a distinct sound) may be introduced, sometimes before introducing a negative stimulus, in order for animals to differentiate between the context and the cue. This test elicits heavy involvement from the amygdala, hippocampus, and prefrontal/cingulate cortices (Rudy et al., 2004; Rozeske et al., 2015; Fanselow, 2000). The first fear-conditioning test used in charged-particle radiation research showed that 1, 2, or 3 Gy of cranial radiation enhanced contextual and cued freezing, with males being more sensitive. During conditioning however, females that received a 3-Gy dose displayed deficits in contextual fear conditioning (Villasana et al., 2010). Male mice that received 1 Gy of cranial radiation showed less fear-conditioned freezing than irradiated mice who also received an auditory cue, suggesting deficits in hippocampus-dependent habituation learning (Raber et al., 2011). These effects were not limited to radiation of only the head; mice that received 50 and 100 cGy of whole-body radiation showed deficits in contextual, but not cued conditioning. Interestingly, contextual freezing positively correlates with activation of immediate early gene *Arc* in the hippocampal dentate gyrus (DG); however, when a cued tone is introduced, the correlation is inverse (Raber et al., 2011, 2013b). These effects are seen in doses as

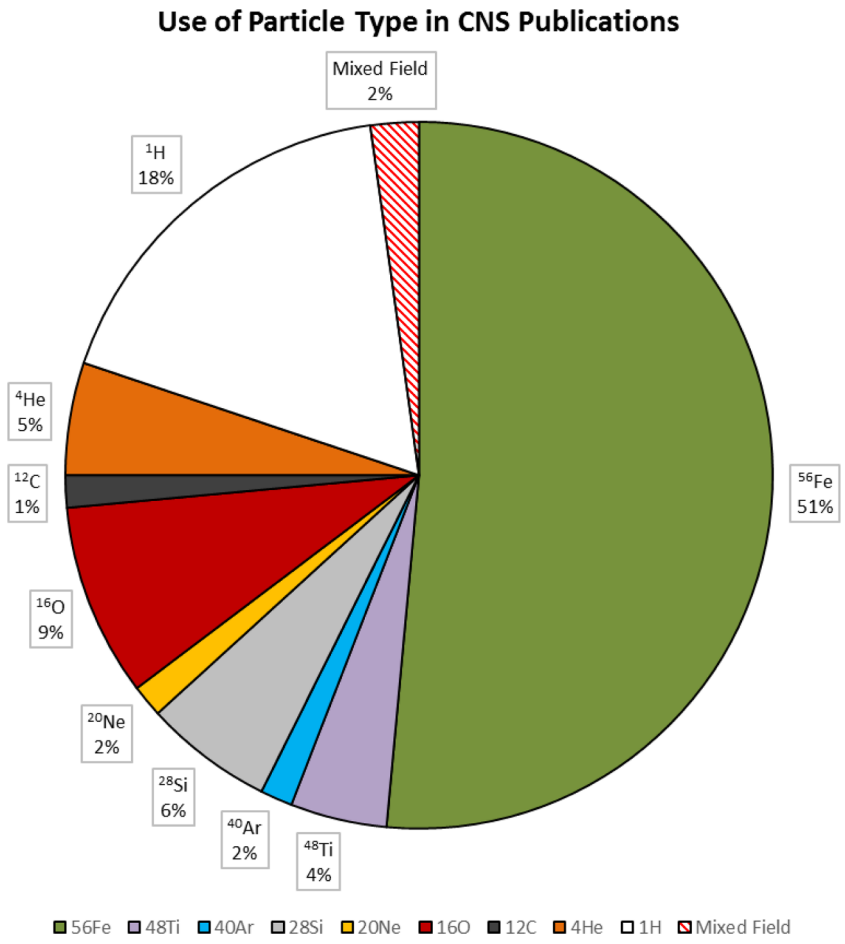

Fig. 1. Charged-particle use by publication. Studies utilizing different particles were counted individually, unless particles were used in combinations (Mixed Fields).

low as 25 cGy but are not seen in C-C chemokine receptor type 2 (CCR2) knockout mice, highlighting the role of inflammation on fear conditioning (Raber et al., 2013a). Furthermore, hippocampal CA1 and DG dendritic spine density increases in result to fear conditioning in sham-irradiated animals compared to non-behaved animals. However, exposure to 50 cGy resulted in deficits in contextual fear conditioning which appears to be the result of radiation-induced inhibition of dendritic spine formation in the hippocampus (Raber et al., 2016b).

Finally, the Barnes maze has drawn a lot of recent interest among space radiation behaviorists. Mice and rats are naturally anxious when exposed to open environments and have an endogenous drive to seek shelter. The Barnes maze takes advantage of this by incorporating visual cues near many possible escape holes around a circular arena. Only one hole contains an escape box where animals can seek shelter, and animals learn the visual cues that lead there; the hippocampus is considered critical to the task (Fox et al., 1998). Initially, dosages as low as 20 cGy were observed to lower performance in the Barnes maze (Lonart et al., 2012; Britten et al., 2012), and further work demonstrated that dosages as low as 5 cGy were detrimental to the task, although a substantial number of animals in each cohort were unaffected (Britten et al., 2016a,b; Wyrobek and Britten, 2016). These deficits correlated with significant changes in the proteome, including markers for memory performance, neurodegeneration, neuronal loss, neuroplasticity, and inflammation (Britten et al., 2017b; Dutta et al., 2018).

Perhaps one of the most interesting CNS responses to charged-particle radiation is the induction of Alzheimer's disease (AD)-like symptoms. Mice don't naturally carry the genotype capable of expressing symptoms of AD, but transgenic knock-in models have shown alarming evidence of amyloid accumulation and behavioral deficits in animals receiving doses as low 10 cGy (Cherry et al., 2012). Higher doses, such as 2 Gy, are capable of preventing normal motor behavior on rotorod, a platform that spins at varying frequencies, open-field, where mice with elevated anxiety spend more time in the corners of the square arena, and MWM behaviors (Higuchi et al., 2002). Behavioral differences are associated with the animal's sex, AD apolipoprotein E (apoE) genotype, and with the type of radiation exposure (Villasana et al., 2008). Irradiated female apolipoprotein (apoE)-3 knock-in mice displayed poor spatial memory retention in the MWM. Male apoE-4 mice showed deficits in spatial memory that were rescued after 3 Gy of cranial exposure (Villasana et al., 2011). Female apoE-4 mice displayed NOR deficits with or without 2 Gy of cranial radiation, but female apoE-2 and apoE-3 mice did not (Villasana et al., 2013b). In males, however, 1 or 2 Gy of cranial radiation was sufficient to reduce various parameters of MWM performance in apoE-2, apoE-3, and apoE-4 mice. Notably, apoE-2 males displayed less open-field anxiety than other genotypes (Yeiser et al., 2013). A lower dose (i.e., 50 cGy) of whole-body exposure also affected MWM performance by lowering spatial memory in apoE-2 and apoE-4 males but enhancing spatial memory in apoE-3 males, as assessed by animals' abilities to remember the correct platform quadrant during the first probe trial. However, ApoE-2 mouse spatial memory recovered by probe trial 2, and ApoE-4 mice could only discern the correct quadrant at the third probe trial (Haley et al., 2012). An alternative AD mouse model containing genes for the amyloid precursor protein (APP), and presenilin 1 (PS1) has also been in space radiation research. NOR deficits were seen in male and female APP/PS1 mice that received 1 Gy and in males that received 10 cGy. Decrements in contextual fear conditioning were induced by 1 Gy in males but not in females (Cherry et al., 2012). Nonbehavioral changes due to radiation

Table 2
^{56}Fe.

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
An assessment of the behavioral toxicity of high-energy iron particles compared to other qualities of radiation	Rabin	0.05, 0.10, 0.2, 0.3, 0.4, 0.5, 1, 5	600	Male CD BR VAF/Plus rats	9–12	–	3d	^{56}Fe exposure induced dose-dependent taste aversion, peaking at 0.3 Gy.	–	1989	Rabin et al. (1989)
Emesis in ferrets following exposure to different types of radiation: a dose-response study	Rabin	0.2, 0.3, 0.4, 0.5, 0.6	600	Male Ferret	5–10	–	<1d	The mean effective dose (ED50) for iron was 0.35 Gy, though emesis was induced at dosages of 0.2–0.6 Gy	–	1992	Rabin et al. (1992)
Exposure to heavy charged particles affects thermoregulation in rats	Kandasamy	0.1, 0.3, 0.5, 1, 2, 3, 5	600	Male Sprague-Dawley rats	–	–	10min	Doses between 0.1–3 Gy induced hyperthermia, but 5 Gy induced hypothermia. Temperature changes remained within 1C.	Changes in body temperature were prevented when treating animals with COX-inhibitors meaning changes were likely ROS-mediated.	1994	Kandasamy et al. (1994)
Effects of exposure to heavy particles on a behavior mediated by the dopaminergic system	Rabin	0.5, 0.8, 1, 1.5,2	600, 1000	Male Sprague-Dawley rats	–	–	3d, 4mo	Effects of ^{56}Fe exposure meth-induced taste aversion are seen at 3d, but not 4mo after exposure. Changes were more marked at 1000 than 600 MeV/n.	LiCl Did not induce taste aversion in irradiated animals.	2000	Rabin et al. (2000)
Spatial learning and memory deficits induced by exposure to iron-56-particle radiation	Shukitt-Hale	1.5	1000	Male Sprague-Dawley rats	10–12	3 mo	–	Irradiated animals showed reversal learning deficits in MWM, via nonspatial platform search strategies.	–	2000	Shukitt-Hale et al. (2000)
Effects of exposure to ^{56}Fe particles on the acquisition of a conditioned place preference in rats	Rabin	1	–	Rats	–	–	–	Radiation disrupted reinforcement behavior as assessed by the amphetamine-induced conditioned place preference test.	–	2001	Rabin et al. (2001)
Brain signaling and behavioral responses induced by exposure to (56)Fe-particle radiation	Denisova	1.5	1000	Male Sprague-Dawley rats	12	2 mo	5wks	Irradiated rats underwent sporadic radial arm maze deficits in reference memory.	Radiation elicited noticeable persistent oxidative stress in the PFC, and lower synaptobrevin protein expression in the striatum.	2002	Denisova et al. (2002)
Effects of exposure to ^{56}Fe particles or protons on fixed-ratio operant responding in rats	Rabin	1, 2	1000	Male Albino Sprague-Dawley rats	6–10	–	–	Using the conditioned bar-press task, rats exposed to 2 Gy of ^{56}Fe failed to increase their response ratio for increased work requirement-mediated reward.	–	2002	Rabin et al. (2002a)
Effects of heavy particle irradiation and diet on amphetamine- and lithium chloride-induced taste avoidance learning in rats	Rabin	1.5	1000	Male Sprague-Dawley rats	8	–	3d	Radiation induced meth-induced taste aversion, which was prevented by an antioxidant diet. Lithium chloride did not induce taste aversion. Oxidative stress following radiation may be responsible for disurption of dopamine-mediated meth-induced CTA	–	2002	Rabin et al. (2002b)

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Table 2 (*continued*)

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Apolipoprotein E expression and behavioral toxicity of high charge, high energy (HZE) particle radiation	Higuchi	2	600	Male ApoE KI, WT C57 mice	16		1–4mo	Rotorod performance was altered in both groups at 3 mo and only in ApoE mice at 2 mo. ApoE mice showed open field reduced exploration at all times (2wk- 4mo). MWM performance was adversely affected in KI mice 4mo post irradiation.	–	2002	Higuchi et al. (2002)
Long-term changes in amphetamine-induced reinforcement and aversion in rats following exposure to ^{56}Fe particle	Rabin	1	1000	Male Sprague-Dawley rats	–	–	3, 7, 16 wks	This experiment failed to replicate previous amphetamine-induced controlled taste aversion 3 days following radiation, but prevented acquisition of amphetamine-induced place preference at 3, 7 and 16 weeks from radiation.	–	2003	Rabin et al. (2003)
Cognitive deficits induced by ^{56}Fe radiation exposure	Shukitt-Hale	1	1000	Male Sprague-Dawley rats	6–8	3 mo	9mo	Irradiated rats produced aged-like deficits in the 8-arm radial maze.	–	2003	Shukitt-Hale et al. (2003)
The effects of heavy particle irradiation on exploration and response to environmental change	Casadesus	1.5	1000	Male Sprague-Dawley rats	10	3 mo	3mo	Radiation elicited open field and NOR-like deficits in rats, to the same extent that aged rats have previously performed.	–	2004	Casadesus et al. (2004)
The effects of low-dose, high-LET radiation exposure on three models of behavior in C57BL/6 mice	Pecaut	0.1, 0.5, 2	1000	Female C57 mice	14–17	2 mo	2–8 wk	There were no effects of radiation on acoustic startle, rotorod or open field behaviors.	–	2004	Pecaut et al. (2004)
Effect of diet on the disruption of operant responding at different ages following exposure to ^{56}Fe particles	Rabin	2	1000	Male Sprague-Dawley rats	5–7	3.5–4 mo	5, 8, 13, 18 mo	Radiation induced deficits in operant conditioning at 5 and 8 months, which was prevented by a strawberry diet. No changes were observed at 13–18 months after exposure.	–	2005	Rabin et al. (2005a)
Effects of age and diet on the heavy particle-induced disruption of operant responding produced by a ground-based model for exposure to cosmic rays	Rabin	1.5	1000	Male Sprague-Dawley rats	10	–	6, 12 mo	No changes were seen at 6mo, but irradiated animals showed deficits in operant responding at 12 months, but not on irradiated animals consuming a 2% strawberry diet.	–	2005	Rabin et al. (2005b)
Amphetamine-induced taste aversion learning in young and old F-344 rats following exposure to ^{56}Fe particles	Carrihill-Knoll	0.25, 0.5, 1.5, 2	1000	Male F-344 rats	10	2, 7, 12, 16 mo	3 d	Radiation only disrupted the acquisition of conditioned taste aversion in 2 mo-olds receiving 0.5 Gy	–	2007	Carrihill-Knoll et al. (2007)
Sex-dependent effects of ^{56}Fe irradiation on contextual fear conditioning in C57BL/6 J mice	Villasana	1, 2, 3 head only	–	Male and Female C57 mice	6–8	2 mo	3 mo	Contextual fear conditioning was impaired in irradiated females, but improved in males at all dosages. Females receiving 3 Gy, males receiving 2 Gy failed NOR.	–	2010	Villasana et al. (2010)

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Table 2 (*continued*)

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Long-term effects of ^{56}Fe irradiation on spatial memory of mice: role of sex and apolipoprotein E isoform	Villasana	3 head only	600	Male and Female apoE3 or apoE4 C57 mice	10	2 mo	13 mo	ApoE3 females MWM spatial memory was impaired. ApoE4 mice showed disrupted spatial memory, which radiation rescued.	There was no effect of radiation on MAP-2 expression, but synaptophysin was increased in irradiated females.	2011	Villasana et al. (2011)
Effects of ^{56}Fe-particle cranial radiation on hippocampus-dependent cognition depend on the salience of the environmental stimuli	Raber	1 head only	–	Male C57 mice	8	2 mo	3 mo	Radiation induced deficits in hippocampus-dependent spatial habituation learning via contextual freezing.	The behavioral deficits correlated with lowering of Arc expression in the lower blade of the hippocampal DG.	2011	Raber et al. (2011)
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	Rabin	0.25, 0.5, 1.5, 2	1000	Male F-344 rats	10	2, 7, 12, 16 mo	3.5 mo	There was a significant effect of age on the dose needed to produce operant responding deficits. Overall deficits are not only due to age, but also age during irradiation.	–	2012	Rabin et al. (2012)
Apolipoprotein E Genotype-Dependent Paradoxical Short-Term Effects of ^{56}Fe Irradiation on the Brain	Haley	0.5	600	Male apoE2, apoE3 or apoE4 C57 mice	8	–	2 wk	MWM spatial memory was impaired radiation in apoE2 and apoE4 mice, but enhanced by radiation in apoE3.	levels of 3NT and CuZnSOD (ox stress marker) was increased in apoE2 but not in others.	2012	Haley et al. (2012)
Galactic cosmic radiation leads to cognitive impairment and increased aβ plaque accumulation in a mouse model of Alzheimer's disease	Cherry	0.1, 1	1000	Male and Female App/PS1 mice	10	3 mo	9.5 mo males 7 mo females	Radiation at both ages induced contextual fear conditioning and NOR deficits.	Males displayed accelerated Abeta plaque deposition, but not APP. There were no changes in CD68 and Iba-1, but 1 Gy caused endothelial activation in males.	2012	Cherry et al. (2012)
Low (20 cGy) doses of 1 GeV/u (56) Fe–particle radiation lead to a persistent reduction in the spatial learning ability of rats	Britten	0.2, 0.4, 0.6	1000	Male Wistar rats	27–40	1.5 mo	3 mo	All dosages elicited deficits in Barnes maze spatial memory performance.	–	2012	Britten et al. (2012)
Executive function in rats is impaired by low (20 cGy) doses of 1 GeV/u (56)Fe particles	Lonart	0.2	1000	Male Wistar rats	14	–	3 mo	83% of radiated rats showed deficits in barnes maze, with 30% failing all stages.	–	2012	Lonart et al. (2012)
Effects of alpha-lipoic acid on associative and spatial memory of sham-irradiated and (56)Fe-irradiated C57BL/6 J male mice	Villasana	3 head only	600	Male C57 mice	6–7	2 mo	3 mo	Antioxidant ALA prevented radiation-induced impairments inspatial memory retention in MWM probe trials (post reversal). In sham mice, ALA impaired NOR and cued fear conditioning.	Radiation increased MAP-2 immunoreactivity in naïve, and irradiated mice.	2013	Villasana et al. (2013a)
Dose- and ApoE isoform-dependent cognitive injury after cranial ^{56}Fe irradiation in female mice	Villasana	1, 2 head only	600	Female apoE2, apoE3 or apoE4 C57 mice	6–9	2 mo	3 mo	There were no effects of radiation on EPM or open field. 2 Gy of radiation and/or apoE4 isoform resulted in NOR deficits.	–	2013	Villasana et al. (2013b)
ApoE isoform modulates effects of cranial (56)Fe irradiation on spatial learning and memory in the water maze	Yeiser	1, 2 head only	600	Male apoE2, apoE3 or apoE4 C57 mice	6–10	2 mo	3 mo	A dose of 2 Gy induced higher open-field activity. The E2 phenotype also induced higher open-field activity than other phenotypes. Doses of 1 and 2 Gy impaired learning throughout MWM testing.	–	2013	Yeiser et al. (2013)

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Table 2 (*continued*)

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Early effects of whole-body (56)Fe irradiation on hippocampal function in C57BL/6 J mice	Haley	0.1, 0.2, 0.5	600	Male and Female C57 mice	8	2 mo	2 wk	All radiation induced NOR deficits in both sexes. Radiation also induced MWM probe trials. Antioxidant feed with ALA did not prevent radiation-induced behavioral deficits.	No radiation effects of lipid peroxidation (3NT) were observed.	2013	Haley et al. (2013)
Effects of whole body (56)Fe radiation on contextual freezing and Arc-positive cells in the dentate gyrus	Raber	0.5, 1	600	Male C57 mice	8	2 mo	3 mo	Radiation induced contextual but not cued fear deficits. At 0.5 Gy there was a positive correlation with the percentage of Arc-positive cells within the hippocampal DG.	–	2013	Raber et al. (2013b)
Effects of (56)Fe radiation on hippocampal function in mice deficient in chemokine receptor 2 (CCR2)	Raber	0.25	600	Male CCR2 KO and C57 mice	20	2 mo	3 mo	Radiation enhanced contextual fear conditioning habituation only in WT mice.	No changes in microglial activation were observed.	2013	Raber et al. (2013a)
Exposure to mission relevant doses of 1 GeV/Nucleon (56)Fe particles leads to impairment of attentional set-shifting performance in socially mature rats	Britten	0.1, 0.15, 0.2	1000	Male Wistar rats	16–27	Juveniles: 2 mo Mature: 6–11 mo	3 mo	Doses of 0.15 and 0.2, but not 0.1 Gy induced ATSET deficits in juvenile and mature rats.	Radiation lowered the readily releasable pool of cholinergic, but not GABAergic nerve terminals in the basal forebrain of mature rats.	2014	Britten et al. (2014)
Executive Function in Rats is Impaired by Low (20 cGy) Doses of 1 GeV/u ^{56}Fe Particles	Lonart	0.1, 0.15, 0.2	1000	Male Wistar rats	12–46	Juveniles: 1–1.5 mo Mature: 6–11 mo	3 mo	20 cGy of ^{56}Fe impaired ATSET shifting. Deficits were generally age dependent and varied between intra-dimmensional shifting, reversal, compound discrimination and reversal.	–	2014	Lonart et al. (2012)
Acute effects of exposure to (56)Fe and (16)O particles on learning and memory	Rabin	0.25	600	Male Sprague-Dawley rats	12	2 mo	1 d	^{56}Fe induced NOR deficits in mice who did not undergo training prior to radiation, but did not affect mice who trained immediately prior to irradiation.	Radiation generally increased NOX-2 expression in the hippocampus and most other brain regions. COX2 increased due to radiation in the hippocampus and had differing changes in other regions. Notably, non-trained mice showed more profound changes in NOX-2 and COX-2 than did trained mice.	2015	Rabin et al. (2015b)
(56)Fe irradiation alters spine density and dendritic complexity in the mouse hippocampus	Allen	0.5	600	Male C57 mice	12	2 mo	3 mo	Radiation lowered average locomotor activity in open-field day1.	Radiation lowered total and thin spine density, as well as dendritic length, but increased mushroom spine density in the hippocampal DG. Radiation decreased spine density and mushroom spines in the basal CA1, and significantly altered dendritic length in the apical and basal CA1. Similar, but less pronounced changes were observed in the CA3.	2015	Allen et al. (2015)

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Table 2 (*continued*)

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Short- and long-term effects of ^{56}Fe irradiation on cognition and hippocampal DNA methylation and gene expression	Impey	0.1, 0.2, 0.4	600	Male C57 mice	42	6 mo	2 wk, 20 wk	0.1, 0.4 Gy impaired NOR at the 2wk timepoint.	Consistent with NOR deficits, percentages of neurons expressing arc were only normal in 0.2 Gy-treated mice. Epigenetic changes in 5hmc and 5mc were more profound at 2wks following radiation than at 20 wks. Pathways where changes were significant are involved neuronal and synaptic maintenance.	2016	Impey et al. (2016a)
Effect of behavioral testing on spine density of basal dendrites in the CA1 region of the hippocampus modulated by (56)Fe irradiation	Raber	0.5	600	Male C57 mice	6	2 mo	3 mo	Behavioral testing (cued fear conditioning) alone increased sham CA1 and DG spine density, though this effect was not seen in irradiated animals.	–	2016	Raber et al. (2016b)
Impaired spatial memory performance in adult wistar rats exposed to low (5–20 cGy) doses of 1 GeV/n (56)Fe particles	Britten	0.05, 0.1, 0.15, 0.2	1000	Male Wistar rats	20–90	6–11 mo	3 mo	All dosages elicited deficis in Barnes maze spatial memory performance, though within each cohort, a substantial fraction of animals were unaffected.	–	2016	Britten et al. (2016)
Individual variations in dose response for spatial memory learning among outbred wistar rats exposed from 5 to 20 cGy of (56) Fe particles	Wyrobek	0.05, 0.1, 0.15, 0.2	1000	Male Wistar rats	20–90	6–11 mo	3 mo	Radiation elicited a dose-dependent decline in spatial memory as assessed by the Barnes maze.	–	2016	Wyrobek and Britten (2016)
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	Britten	0.2	1000	Male Wistar rats	24	6–11 mo	3mo	Radiation compromised spatial learning via the Barnes maze, and attention set shifting, but a given animal did not suffer behavioral deficits in both.	–	2016	Britten et al. (2016b)
Neurochemical differences in learning and memory paradigms among rats supplemented with anthocyanin-rich blueberry diets and exposed to acute doses of ^{56}Fe particles	Poulouse	0.25 head only	600	Male Sprague-Dawley rats	5	2 mo	1–2d	Rats were split into learning or memory groups, the former irradiated prior to conditioning, the latter after. There was no effect of radiation on NOR.	Blueberry supplementation attenuated protein carbonylation, increased by radiation, in the PFC. BB also reduced NOX2 and COX2, upregulated Nrf2 in hippocampus, PFC.	2017	Poulose et al. (2017)

also have been observed in apoE knock-in mice. Synaptophysin, a presynaptic-density marker, was increased in female, but not male, apoE-3 mice after 3 Gy of cranial radiation, and 0.5 Gy caused an increase in oxidative stress in male apoE-2 mice, but not those with other apo genotypes (Villasana et al., 2011; Haley et al., 2012). Finally, radiation accelerated age-related decrements in fast excitatory post-synaptic potentials in CA1 Schaffer collateral neurons, and reduced synaptic efficacy (Vlkolinsky et al., 2010).

The staggering amount of research on in-vivo effects of ^{56}Fe on the CNS is not limited to behavioral studies. Given the densely ionizing nature of high-energy ^{56}Fe interactions with tissues, exposure is expected to result in much oxidative stress. Indeed, several studies report oxidative stress markers in the prefrontal cortex and hippocampus after exposure to ^{56}Fe (Denisova et al., 2002; Suman et al., 2013; Poulose et al., 2014). Endothelium, one of the most radiosensitive tissues, undergoes massive reductions in cell numbers in the brains of exposed animals—0.5 Gy results in 34% cellular loss (Mao et al., 2010). There is a well-observed but complex relationship between oxidative stress and neuroinflammation. ^{56}Fe exposure results in different inflammatory responses at different dosages and times (Poulose et al., 2017; Raber et al., 2013a; Rola et al., 2008; Obenaus et al., 2008; Huang et al., 2010; Rabin et al., 2015b). Following suit, one of the most alarming observations of ^{56}Fe effects in recent years has been the marked decrease of hippocampal neurogenesis and proliferating neurons within the DG (Casadesus et al., 2005; Rola et al., 2004, 2005, 2017, 2008; Rivera et al., 2013; Decarolis et al., 2014; Sweet et al., 2016). Although no neurogenesis occurs in the other hippocampal areas, the CA3 and CA1 do not escape radiation-induced modifications—0.5 Gy was sufficient to lower dendritic spine density in the DG, CA3, and CA1 and to alter the dendritic Sholl length in the DG and CA1 (Allen et al., 2015). Furthermore, astrogliosis has been reported in animals receiving 4 Gy (Cummings et al., 2007). Genomic and proteomic analyses have found radiation-dependent changes in specific pathways involved in inflammation, oxidative stress, neuronal maintenance, and synaptic plasticity (Impey et al., 2016a; Britten et al., 2017b; Dutta et al., 2018; Decarolis et al., 2014; Shukitt-Hale et al., 2013). As would be expected, electrophysiological studies have confirmed hippocampal circuitry is significantly altered after exposures to radiation (Vlkolinský et al., 2007, 2005, 2008, Marty et al., 2014). The excitatory network within the hippocampus is glutamatergic, yet radiation lowers the readily releasable pool of glutamate within synaptosomes (Britten et al., 2010). Despite the popularity of ^{56}Fe as a model HZE particle in the CNS and the overwhelming biological risks suggested by the literature, ^{56}Fe is scarce; its maximum relative abundance in GCR is approximately 0.003% of the spectrum (Mewaldt, 1994).

2.2. ^{48}Ti and ^{28}Si: the intermediate HZE particles

Recently, significant attention has been placed on the effects of ^{48}Ti and ^{28}Si on behavior. Behavioral deficits in response to ^{48}Ti have been observed in the attentional set shifting, Barnes maze, elevated-plus maze (EPM), NOR, object in place (OiP), temporal order (TO), and contextual fear memory assays. At surprisingly low dosages and energies (500–1000 MeV/n 10–20 cGy), ^{48}Ti sufficiently lowered compound discrimination and reversal, but not simple discrimination, in rats undergoing attentional set shifting 3 months later (Hadley et al., 2016). Three months after exposure to doses as low as 5 cGy, spatial memory (assessed by Barnes maze, NOR, OiP) also were compromised (Britten et al., 2017a; Parihar et al., 2015c, 2016). Deficits in NOR and its variation, the OiP test, where novel objects are also placed in a different location, were also seen at 1.5 and 6 months after radiation, suggesting early, persistent changes in object novelty and spatial object memory (Parihar et al., 2015c, 2016). The TO test, another object recognition variation, assays recency memory by introducing different pairs of objects on the first 2 days and then, on the testing day, a combination of one object seen on the first day and one seen on the second. Animals generally are more interested in exploring the less recent object, unless the prefrontal or perirhinal cortices are adversely affected (Barker et al., 2007). The EPM tests for height-induced anxiety by letting animals freely explore an elevated arena with open and closed arms, and amygdala-dependent anxiety drives the amount of time animals explore the open arms (Walf and Frye, 2007). TO exploration and EPM anxiety were adversely affected 3 and 6 months after a low dose (5 cGy) of ^{48}Ti (Parihar et al., 2016); however, EPM-assessed anxiety was not seen in rats of various ages 2 or 6 months after exposure to 1 or 10 cGy (Rabin et al., 2018). Significant dendritic remodeling has been observed in mice exposed to ^{48}Ti (Parihar et al., 2015c, 2016).

There appear to be particle-dependent differences in murine behavioral effects of radiation with ^{48}Ti and ^{28}Si. Contextual fear memory was impaired in animals that received 1.6 Gy of ^{28}Si, but not in those that received ^{48}Ti (Raber et al., 2015b). Further, contextual fear memory improved in response to 25 cGy (600 MeV/n) of ^{28}Si, but it was compromised by 20 cGy (300 MeV/n) 3 months following exposure. Energy-dependent changes also were consistently seen at higher dosages. One Gy induced cued fear decrements in animals exposed to 300 MeV/n, but not to 600 MeV/n, ^{28}Si, and 1.6 Gy (1000 MeV/n) was detrimental to contextual fear memory (Raber et al., 2015b, 2014; Rudobeck et al., 2014; Whoolery et al., 2017; Iancu et al., 2018). Additionally, 5–20 cGy compromised attentional set shifting 3 months after exposure (Britten et al., 2018). The improvements in contextual fear memory at 0.25 Gy correlated with an improvement in the magnitude of long-term potentiation in the hippocampal CA1 (Raber et al., 2014; Rudobeck et al., 2014). Both sexes suffered immediate (within 24hr) losses in neurogenesis, proliferating neurons, and immature neurons, which were more pronounced at 1 Gy in the hippocampal DG. All these changes are reversed at 3 months, with the exception of proliferating cells of males that received 1 Gy (Whoolery et al., 2017).

2.3. ^{16}O and ^{12}C: the representative HZE particles

Charged-particle radiation studies in the US have been largely dependent on the accelerator technologies available at NASA's Space Radiation Laboratory (La Tessa et al., 2016; Schimmerling, 2016). The access to ^{16}O and ^{12}C allowed for more accurate representation of the HZE spectrum. ^{16}O and ^{12}C are the most abundant HZE particles in the GCR spectrum, with maximum recorded relative abundances of 0.369% and 0.384%, respectively (Mewaldt, 1994). Particles of $Z > 9$ will contribute an estimated 5–10% of the total radiation dosage on a mission to Mars. In Addition, NASA's permissible exposure limits for particles of $Z > 9$ for 1 year is 10 cGy and for a career is 25 cGy (Nelson et al., 2016).

All studies of the behavioral effects of ^{16}O generally have involved doses below 1 Gy and have demonstrated behavioral deficits in the NOR, OiP, operant responding, cued fear conditioning, EPM, Y-maze, and 3-chamber sociability tests (Table 3). NOR deficits occur immediately in response to 5 or 25 cGy (Rabin et al., 2015b), and these deficits also are seen 1.5 (1, 30 cGy) and 9 (5, 10, 25 cGy) months after exposure (Parihar et al., 2015c; Rabin et al., 2014; Kiffer et al., 2019; Howe et al., 2019). Animals also performed poorly in the OiP task 1.5 months after receiving 5, 25, or 30 cGy of ^{16}O. The Y-maze is a test of object recognition that incorporates spatial memory and involves short-term recall. Y-maze results showed that short-term memory was impaired in males 2 (10, 25 cGy) weeks, and 9 (5 cGy) months after exposure, but not in females 9 (10, 25 cGy) months after exposure (Kiffer et al., 2019; Howe et al., 2019; Carr et al., 2018). Oddly, 0.4 and 0.8 Gy increased indices of cued fear memory, and had no effect on contextual fear memory 1month post-exposure (Raber et al., 2015a).

Studies involving ^{16}O were the first to expose deficits in social memory as a result of HZE particle radiation. The 3-chamber sociability paradigm involves 3 trials in which a mouse is able to explore an arena

Table 3
^{16}O.

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Comparison of the effects of partial- or whole-body exposures to ^{16}O particles on cognitive performance in rats	Rabin	0.01, 0.05, 0.1, 0.25 head only, body only, or whole body	1000	Male Sprague-Dawley rats	10	2 mo	3 wk-2 mo	NOR: 0.01 Gy head only, whole body induced deficits, NSL: 0.01 Gy head only, body only; 0.05 Gy head only, whole body; 0.25 Gy whole body induced deficits, Operant Conditioning: All whole body radiation doses induced deficits, 0.01 Gy head only induced deficits, no body only radiations were detrimental. EPM: no changes.	–	2014	Rabin et al. (2014)
Acute effects of exposure to (56)Fe and (16)O particles on learning and memory	Rabin	0.05	600	Male Sprague-Dawley rats	12	2 mo	1 d	^{16}O induced NOR deficits in mice who did not undergo training prior to radiation, but did not affect mice who trained immediately prior to irradiation.	Radiation generally increased NOX-2 expression in the hippocampus and most other brain regions. COX-2 increased due to radiation in the hippocampus, and had differing changes in other regions. Notably, non-trained mice showed more profound changes in NOX-2 and COX-2 than did trained mice	2015	Rabin et al. (2015b)
(16) Oxygen irradiation enhances cued fear memory in B6D2F1 mice	Raber	0.4, 0.8, 1.6	250	Male and Female B6D2F1 mice	9–15	6 mo	1 mo	0.4 and 0.8 Gy increased cued fear memory, but no effects were observed on contextual fear memory	–	2015	Raber et al. (2015a)
What happens to your brain on the way to Mars	Parihar	0.05, 0.3	600	Male Thy1-EGFP mice	5	6 mo	1.5mo	0.3 Gy ^{16}O induced deficits in NOR and OiP behaviors	All radiation reduced dendritic length, branching, spine density, fillopodia, long, and mushroom spine density. PSD-95 increased in all radiation groups	2015	Parihar et al. (2015c)
Whole-body oxygen (16O) ion-exposure-induced impairments in social odor recognition memory in rats are dose and time dependent	Mange	0.05, 0.25	1000	Male Long-Evans rats	40	6 mo	1, 6 mo	Social Odor Recognition deficit in both dosages at 1 mo, and in 0.25 Gy at 6mo	There's no loss in Ki67 + cells in the SVZ-suggesting intact olfaction	2017	Mange et al. (2018)
Peripheral T cells as a biomarker for oxygen-ion-radiation-induced social impairments	Krukowski	0.25, 0.4	600	Male C57 mice	18–24	5.5 mo	4 mo	Animals receiving 0.25 Gy show social memory deficits	0.25 Gy mice also showed a significant reduction in CD8 + T cells	2018	Krukowski et al. (2018c)
Age as a factor in the responsiveness of the organism to the disruption of cognitive performance by exposure to HZE particles differing in linear energy transfer	Rabin	0.001, 0.005	1000	Male F-344 rats	10	2, 11, 15/ 16 mo	2, 6 mo	anxiety (EPM) increased in 11 and 15 mo old mice receiving ^{16}O. Operant conditioning was only affected in 2 mo, but not 11 and 15 mo-old rats receiving radiation.	–	2018	Rabin et al. (2018)
Early effects of ^{16}O radiation on neuronal morphology an cognition in a murine model	Carr	0.1, 0.25, 1	600	Male C57 mice	5	6 mo	2 wk	0.1 and 0.25 Gy resulted in Y-maze short-term memory deficits	0.1 and 0.25 Gy elicited downregulation of Nr1, GluR1, Syn1 and upregulation of Nr2b mRNA, and increased spine density in the DG and CA1. All dosages resutled in decreased dendrite complexity and sholl length in the DG, and minor morphological changes to the CA1	2018	Carr et al. (2018)

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Table 3 (*continued*)

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Long-term changes in cognition and physiology after low-dose 16O irradiation	Allen	0.05	600	Male C57 mice	10	6mo	9mo	A low-dose of 0.05 Gy resulted in short-term spatial memory, and object memory, measured by the Y-maze and NOR tasks, respectively.	Radiation lowered mushroom spines throughout the hippocampus. Dendritic length was reduced in the hippocampal DG, but increased at further distances from the soma in the apical CA1. Radiation also appeared to upregulate NMDA receptor subunits, along with pre- and post-synaptic density marker mRNA in the whole hippocampus.	2019	Howe et al. (2019)
Late effects of ^{16}O irradiation on female social and cognitive behavior and hippocampal physiology	Kiffer	0.1, 0.25	600	Female C57 mice	12	6 mo	9 mo	There was no effect of radiation on Y-Maze, though both dosages induced similar deficits in NOR, and only 0.25 Gy induced social novelty deficits	Radiation induced massive reductions in dendritic morphology in the DG, CA3 and CA1 similarly due to both dosages, but the basal CA2 underwent far more dendritic remodeling at 0.25 Gy, possibly inducing the social memory deficit. Changes in spine morphology were similar to dendrite morphology.	In Press	Kiffer et al. (in press)

with three chambers (1) with no other mice in the arena (i.e., habituation trial), (2) with one stranger, conspecific mouse (i.e., sociability trial), and (3) with yet another stranger conspecific mouse (i.e., social novelty memory trial) (Moy et al., 2004). A variation of this paradigm involves introducing wooden beads impregnated with social odors in trials identical to the in vivo model (Millan and Bales, 2013). Sociability is compromised in males receiving 50 cGy, but not in females (Krukowski et al., 2018b). In addition, social novelty deficits occurred within 1 month of radiation with as little as 5 cGy of ^{16}O, and within 4–9 months with as little as 1 cGy (Kiffer et al., 2019; Mange et al., 2018; Krukowski et al., 2018c; Jones et al., 2019).

The dopaminergic system is not spared from ^{16}O radiation. Doses of 1–25 cGy lowered operant conditioning (Rabin et al., 2014), and, alarmingly, doses as low as 1 or 5 mGy induced anxiety in 15-month-old mice (Rabin et al., 2018). ^{16}O induced various detrimental effects on the CNS that included altered immune activation and other oxidative-stress responses (Rabin et al., 2015b; Krukowski et al., 2018c). Furthermore, ^{16}O induces differential expression of glutamatergic synaptic markers in the hippocampus and, most pressing, dendritic remodeling changes that include generally lowered Sholl length and dendritic complexity throughout the entire hippocampus and prefrontal cortex (Parihar et al., 2015c; Kiffer et al., 2019; Howe et al., 2019; Carr et al., 2018; Dickstein et al., 2018).

To date, only two in vivo studies have investigated the effects of ^{12}C on the CNS. These studies found that ^{12}C induces immediate loss in neurogenesis, proliferating neurons, neural precursors, and immature neurons. The losses are recovered by 3 months, but they revert at 9 months after exposure to 1–3 Gy in a dose-dependent manner (Rola et al., 2005; Zanni et al., 2018).

2.4. ^{4}He: the neglected particle

Because helium nuclei are the second most abundant particles in the spectra of both GCRs and SPEs, ^{4}He remains one of the most important particles for research on behavioral effects of space radiation. Despite this, relatively few studies have incorporated ^{4}He (Table 4) (Nelson, 2016; George et al., 2009; Mewaldt, 1994). The known behavioral changes that result from ^{4}He radiation include those measured via the acquired taste aversion, operant conditioning, hyperthermia, EPM, OiP, NOR, TO, MWM, and fear extinction paradigms. Dopaminergic behaviors were adversely affected in a dose-dependent manner in acquired taste aversion (20–500 cGy) and operant conditioning (0.01–10 cGy) (Rabin et al., 1991, 2015c). ^{4}He radiation also induces acute hyperthermia in a dose-dependent manner, though these effects revert with cyclooxygenase inhibition (Kandasamy et al., 1994). OiP deficits resulted from 0.1–30 cGy of ^{4}He and lasted up to 1 month after exposure (Parihar et al., 2018; Rabin et al., 2015c, 2019). The only NOR deficits were seen in response to 0.025–100 cGy, but not lower dosages, and were rescued by microglial depletion (Rabin et al., 2015c, 2019; Krukowski et al., 2018a). Abnormal TO behavior occurred 1.5–13 months after 5–30 cGy of ^{4}He, and deficits in MWM and fear extinction occurred 1 year after radiation (Parihar et al., 2018). Anxiogenic behaviors were observed via the EPM for up to 1 year after receiving 0.1–5 cGy cranial, or 5–30 cGy whole-body radiation (Rabin et al., 2015c; Parihar et al., 2018). Interestingly, a different study demonstrated no changes in EPM-mediated behavior 18 days to 3 months after dosages of 15–100 cGy (Krukowski et al., 2018a). The same study revealed significant changes to the inflammatory genome after radiation and a different genetic profile when radiation was introduced in combination with microglial inactivation. Electrophysiological experiments concluded that 5 cGy caused a decrease in the resting membrane potential and an increase in the mean input resistance of principle cells of the perirhinal cortex. Further, radiation lowered the frequency and amplitude of spontaneous excitatory postsynaptic currents in principle cells, lowered the functional connectivity between the CA1 and perirhinal cortex, and increased activated microglia 1 year after exposure

Table 4
^{4}He.

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Relationship between linear energy transfer and behavioral toxicity in rats following exposure to protons and heavy particles	Rabin	0.2, 0.3, 0.5, 1, 2, 5	165	Male CD BR VAF/ Plus rats	7–10	–	–	All exposures produced dose-dependent increases in the intensity of the acquired taste aversion in non-LET-dependent manner	–	1991	Rabin et al. (1991)
Exposure to heavy charged particles affects thermoregulation in rats	Kandasamy	0.1, 0.3, 0.5, 1, 2, 3, 5	165	Male Sprague-Dawley rats	–	–	–	All doses, but especially lower ones, induced hyperthermia.	Changes in body temperature were prevented when treating animals with COX-inhibitors	1994	Kandasamy et al. (1994)
Comparison of the effectiveness of exposure to low-LET helium particles ((4)He) and gamma rays ((137)Cs) on the disruption of cognitive performance	Rabin	0.001, 0.005, 0.01, 0.05 head only	1000	Male Sprague-Dawley rats	10	–	–	Following radiation, rats receiving all dosages displayed more anxiety in EPM, more deficits in OiP recognition in all but rats receiving 0.01 Gy. No deficits in NOR were seen, but rats receiving 0.005, 0.01, 0.05, 0.1 Gy made fewer responses as reinforcement schedule was increased in operant responding.	–	2015	Rabin et al. (2015c)
Age as a factor in the responsiveness of the organism to the disruption of cognitive performance by exposure to HZE particles differing in linear energy transfer	Rabin	0.0001, 0.0005, 0.001	1000	Male F-344 rats	10	2, 11, 15/ 16 mo	2, 6 mo	Age and dose at the time of exposure induced differential effects in operant conditioning and only age during irradiation induced anxiety as measured by the EPM.	–	2018	Rabin et al. (2018)
Persistent nature of alterations in cognition and neuronal circuit excitability after exposure to simulated cosmic radiation in mice	Parihar	0.05, 0.3	400	Male C57 mice	12	6 mo	1.5, 4, 13 mo	Deficits: OiP, TO: all dosages and time points; EPM: all dosages at 1 yr; MWM: Radiation increased latency at final sessions, and induced no quadrant preference during probe trials at 1 yr. Fear Condit: no changes; Fear Extinct: deficits at 1 yr.	Radiation caused a decrease in the resting membrane potential, and an increase in the mean input resistance of principle cells of the perirhinal cortex. Radiation also lowered the frequency and amplitude of the spontaneous excitatory postsynaptic currents in principle cells of the perirhinal cortex, but also lowered functional connectivity between the CA1 and perirhinal cortex. Radiation also increased activated microglia (ED-1) 1 year after exposure	2018	Parihar et al. (2018)
Temporary microglia-depletion after cosmic radiation modifies phagocytic activity and prevents cognitive deficits	Krukowski	0.15, 0.5, 1	250	Male C57 mice	5	5 mo	18 d, 3 mo	0.15 Gy and 0.5 Gy induced NOR deficits, which were rescued by PLX, but resulted in no changes in anxiety as assessed by the EPM.	This study compared radiation alone and in combination with microglial depletion (DPX). 0.5 Gy DPX upregulated Syn1 and downregulated PSD-95. Gene arrays show differential results between radiation and radiation plus microglial depletion on the 'inflammosome'.	2018	Krukowski et al. (2018a)

Table 5
^{1}H.

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Relationship between linear energy transfer and behavioral toxicity in rats following exposure to protons and heavy particles	Rabin	0.2, 0.3, 0.5, 1, 2, 5	155	Male CD BR VAF/ Plus rats	7–10	–	–	Proton exposure produced dose-dependent increases in the intensity of the acquired taste aversion	–	1991	Rabin et al. (1991)
5-HT3 receptor antagonists ameliorate emesis in the ferret evoked by neutron or proton radiation	Rabin	2.5	200	Male Ferret	4–7	–	<1d	Dosages of 0.5 or higher of 5-HT prevented proton-induced emesis in ferrets	–	1992	King et al. (1999)
Behavioral consequences of radiation exposure to simulated space radiation in the C57BL/6 mouse: openfield, rotorod, and acoustic startle	Pecaut	3, 4 behind 15 g/cm2 Al	250	Male C57 mice	6–12	2.5 mo	1, 2, 4, 8, 12 wk	Rotorod performance at 18 rpm was lowered in all groups and only at 4 Gy at 26 rpm before 2 wk. Open-field anxiety was seen at time points after 2 weeks	–	2002	Pecaut et al. (2002)
Effects of exposure to ^{56}Fe particles or protons on fixed-ratio operant responding in rats	Rabin	4	250	Male Albino Sprague-Dawley rats	6–10	–	–	There was no effect of proton radiation on conditioned bar press performance	–	2002	Rabin et al. (2002a)
The effects of proton exposure on neurochemistry and behavior	Shukitt-Hale	1.5, 3, 4	250	Male Sprague-Dawley rats	12	2 mo	1.5mo	There was no effect of radiation on methamphetamine-induced CTA, nor MWM-assessed spatial memory.	–	2004	Shukitt-Hale et al. (2004)
Individual differences in attentional deficits and dopaminergic protein levels following exposure to proton radiation	Davis	0.25, 0.5, 1, 2 Head only	150	Male Long-Evans rats	3–7	3 mo	5d-8mo	Radiation disrupted psychomotor vigilance, occurring in only a subset of animals regardless of dosage.	Only rats who showed behavioral deficits displayed changes in dopamine transporter and dopamine (D2) receptor expression.	2014	Davis et al. (2014)
Central nervous system effects of whole-body proton irradiation	Sweet	0.1, 0.2, 0.5, 0.1, 0.2	1000	Male and Female C57 mice	20–25	3 mo	2 d, 1 mo, 3 mo, 6 mo, 1 yr	Exposure to protons did not elicit contextual nor queued fear conditioning deficits.	0.1 Gy and up reduced cell division in the DG at 2 d, with females being more radiosensitive. 2 Gy showed more microglia (GFAP) at 3 mo. Endothelial immune activation (ICAM-1) was lowered at every dosage. 2 Gy lowered neurogenesis at 3 mo.	2014	Sweet et al. (2014)
A single low dose of proton radiation induces long-term behavioral and electrophysiological changes in mice	Bellone	0.5	150	Male B6C3F1/J (WT) mice	16	2.5 mo	3 6 mo	Proton exposure impaired MWM reversal learning 6 mo later.	Radiation increased field excitatory postsynaptic potentials, reduced spontaneous oscillations 9mo post-exposure	2015	Bellone et al. (2015)
Lack of reliability in the disruption of cognitive performance following exposure to protons	Rabin	0.25, 0.35, 0.5, 0.8, 1, 1.25, 1.5, 2 head only or whole-body	150, 1000	Male Sprague-Dawley rats	10	–	1–3 mo	Deficits: NOR: 0.5, 1 Gy 1000 MeV of head only radiation, 0.25 Gy 150 MeV; Operant conditioning: 0.5, 1, 1.25 Gy of 1000 MeV	Interestingly, one of the head-only experiments using 1 Gy of 1000 MeV protons induced increased recognition in NOR, which can also be considered a deficit.	2015	Rabin et al. (2015b)
28Silicon irradiation impairs contextual fear memory in B6D2F1 mice	Raber	0.5	1000	Male and Female B6D2F1 mice	12–27	7 mo	3 mo	There was no effect of proton radiation on contextual nor cued fear conditioning	–	2015	Rabin et al. (2015a)

(*continued on next page*)

Table 5 (*continued*)

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Targeted overexpression of mitochondrial catalase prevents radiation-induced cognitive dysfunction	Parihar	0.5, 2	150	Male MCAT (C57) mice	3–6	2 mo	1–1.5 mo	WT mice suffered dose-dependent deficits in NOR and OiP, whereas no changes were observed in MCAT mice.	WT mice receiving 2 Gy underwent a significant decrease in dendritic length, complexity, and branch points in the hippocampal CA1 compared to MCATs. Sholl lengths were markedly different between MCAT and WT mice. No significant changes in spine density were observed. WT radiation resulted in marked alterations in LTP, whereas no changes were observed in MCATs. 0.5 Gy produced marked phosphorilation of GluR1, which was prevented by MCATs. Alternatively, MCATs showed increased phosphorilation of GluR2 at 0.5 Gy.	2015	Parihar et al. (2015b)
Deficits in sustained attention and changes in dopaminergic protein levels following exposure to proton radiation are related to basal dopaminergic function	Davis	0.25, 1 head only	150	Male F-344 rats, Male Lewis rats	10–12	3 mo	5–34 wk	F-344 rats exposed to 0.25 Gy suffered more Psychomotor Vigilance deficits than those exposed to 1 Gy. Lewis rats suffered no behavioral deficits.	F-344 rats showed higher protein concentrations of tyrosine hydroxylase and dopamine transporter, which were unaffected by radiation, whereas Lewis rats showed lower levels of these proteins, which were increased in the PFC with radiation. Radiation affected Akt phosphorilation in both strains only at 0.25 Gy. Both strains underwent different strain specific inflammatory cytokine changes.	2015	Davis et al. (2015)
Effects of proton and combined proton and ^{56}Fe radiation on the hippocampus	Raber	0.1, 0.5, 1	150	Male C57 mice	8–11	2 mo	1, 3 mo	0.1 Gy of radiation enhanced contextual fear memory, but lowered object recognition memory at 1mo after exposure.	Radiation caused complex changes in chemokine and cytokine expression.	2016	Raber et al. (2016a)
Low-dose proton radiation effects in a transgenic mouse model of Alzheimer's disease - Implications for space travel	Rudobeck	0.1, 0.5, 1	150	Male C57-WT, APP/PSEN1 mice	C57 = 8, APP/PSEN1 = 12	3 mo	3, 6 mo	Transgenic mice performed worse than WT in the MWM prior to irradiation. However, only WT mice showed deficits in reversal learning in the MWM and BM at 6 mo following irradiation.	WT: radiation increased excitability and synaptic efficacy. TG: radiation reduced amplitudes of population spikes, and inhibited paired-pulse facilitation in the hippocampal CA1.	2017	Rudobeck et al. (2017)
Bi-directional and shared epigenomic signatures following proton and ^{56}Fe irradiation	Impey	1	150	Male C57 mice	21	6 mo	2, 20 wk	Behavioral deficits: NOR:lowered object recognition at 2 wk. MWM: deficits at first, but not second probe trial at 2 wk.	Hippocampal DNA methylation and hydroxymethylation due to radiation at 2 wk was very similar at 20 wk. Genetic markers for postsynaptic processes were more epigenetically altered than presynaptic markers. Arc expression in novel environments was altered in the hippocampal CA1 and CA3 of irradiated mice.	2017	Impey et al. (2017)

(*continued on next page*)

Table 5 (*continued*)

Title	First author	Dose (Gy)	Energy (MeV/n)	Animal	n/ cohort	Age at IR	Follow up time	Behavioral findings	Other important findings	Year	Refs.
Late effects of 1H on hippocampal physiology	Kiffer	0.5, 1	150	Male C57 mice	10	6 mo	9 mo	Both dosages elicited open field anxiety in mice.	1 Gy of radiation caused a reduction in mushroom spines throughout the hippocampal CA1, apical CA3, and DG. Dose-dependent alterations to sholl dendritic length throughout the hippocampus were observed. There were differential dose-dependent alterations in mRNA expression of genes related to hippocampal cognition and inflammation.	2018	Kiffer et al. (2018b)

(Parihar et al., 2018). Low doses of 4He radiation (0.05, 0.1 cGy) increases protein expression of NOX-2, a major source of free-radical production in cells, and unexpectedly also increases pCREB, an important transcription factor associated with long-term memory formation. A dose of 0.1 Gy also unexpectedly increases NRF2, an important transcription factor involved in expression of endogenous antioxidants (Rabin et al., 2019).

2.5. ^{1}H: the most important particle

The most abundant particle in GCR and SPE is by far ^{1}H—on an interplanetary mission, protons will contribute approximately 50–60% of the GCR dose (Nelson et al., 2016). This has led to much attention on the effects of ^{1}H on the CNS (Table 5). The first behavioral experiments with protons examined changes in striatum-dependent behaviors. The intensity of acquired taste aversions the conditioned taste aversion paradigm increased in a dose-dependent manner after exposure to20–500 cGy (150 MeV/n) ^{122}, and operant conditioning decreased with 50–150 cGy (1000 MeV/n) ^{127}; however, higher doses (1.5–4 Gy, 250 MeV/n) caused no changes in either (Rabin et al., 2002a; Shukitt-Hale et al., 2004). A variant of operant conditioning tests, the psychomotor vigilance test also uses a bar-press task, but, instead of relying on repetition for a conditioned response, animals must watch a visual cue and respond within a very brief timeframe to receive a food reward (Baunez et al., 2001). Psychomotor vigilance was disrupted by 25–200 cGy head-only radiation, with the most disruption resulting from the lower dosage (Davis et al., 2014, 2015). Differential effects on MWM-dependent spatial memory have been observed; 2 weeks after exposure to 1 Gy ^{1}H, mice spent less time in the target quadrant during the first probe trial (Impey et al., 2017). Reversal learning was impaired 6 months after animals received 10, 50, or 100 cGy (Rudobeck et al., 2017; Bellone et al., 2015). Spatial memory (assessed by the Barnes maze) also was compromised 3–6 months after 10–100 cGy exposure (Rudobeck et al., 2017). Hippocampus-dependent memory errors were not limited to spatial memory. NOR was diminished in animals 3 months after receiving 10, 25, 50, or 200 cGy (Rabin et al., 2015a, 2016a; Parihar et al., 2015b), or 2 weeks after 1 Gy exposure (Impey et al., 2017). Open-field activity appears to have been altered 1–3 months after 3 or 4 Gy irradiation behind 15 g/cm^2 Al, or 9 months after 50 or 100 cGy (without shielding) (Pecaut et al., 2002; Kiffer et al., 2018b). Interestingly, contextual or cued fear memory was not affected in animals that received 10–200 cGy (Raber et al., 2015b, 2016a; Sweet et al., 2014). Other behavioral effects of ^{1}H radiation include lowered motor performance on the rotarod 2 weeks after a 4-Gy dose, and emesis in ferrets after 2.5 Gy (Pecaut et al., 2002; King et al., 1999).

The destructive effects of ^{1}H radiation on brain cells have been observed since the very early days of particle accelerators. The first known experiments of charged-particle radiation on the CNS were successful attempts at using proton beams to surgically dissect the hypothalamus (Tobias, 1955). It is, therefore, not surprising that ^{1}H radiation, even at low dosages of 50–200 cGy, alters dendritic length, complexity, and spine composition in the hippocampal DG, CA3, and CA1 (Kiffer et al., 2018b; Parihar et al., 2015a;b). Following suit, electrophysiological insults due to protons have been observed in the excitatory and inhibitory networks of the hippocampus. After 3 months, 1 Gy resulted in hyperpolarization of the resting membrane potential, decreased input resistance, increased persistent sodium current, and increased rate of miniature excitatory postsynaptic currents within the CA1, as well as increased synaptic excitability in the perforant connections from the subiculum to the DG (Marty et al., 2014; Parihar et al., 2015b; Sokolova et al., 2015). Exposure to 50 cGy significantly increased field excitatory postsynaptic potentials, reduced spontaneous oscillations, and decreased CB_1-dependent tonic inhibition of GABA release in the CA1 (Bellone et al., 2015; Parihar et al., 2015b; Lee et al., 2017). Molecular changes due to ^{1}H radiation indicate altered expression of glutamatergic receptor (Nr1, GluR1, Syn1, SAP97 and

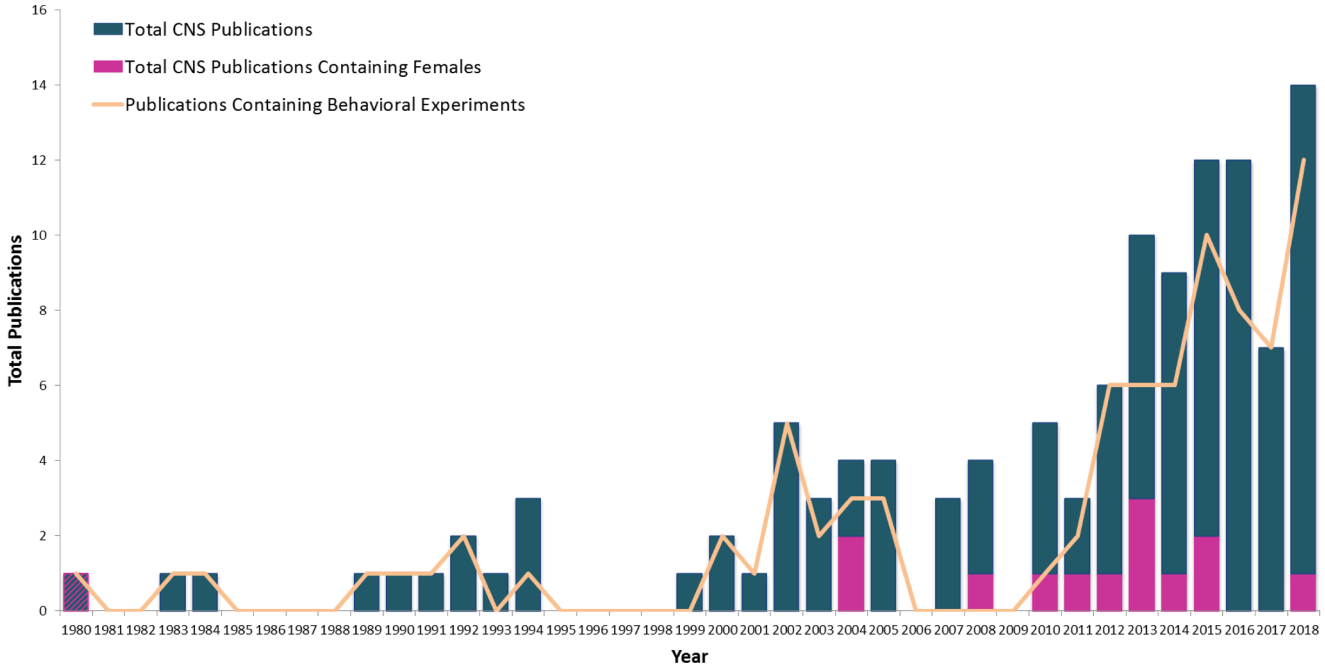

Fig. 2. Historical in-vivo studies, utilizing high-energy charged-particle radiation. Bars depict publications containing CNS endpoints. Within these publications, a large subset contains behavioral experiments, represented by the line. Blue bars depict studies that only used male animals, whereas pink bars represent published studies that incorporated females.

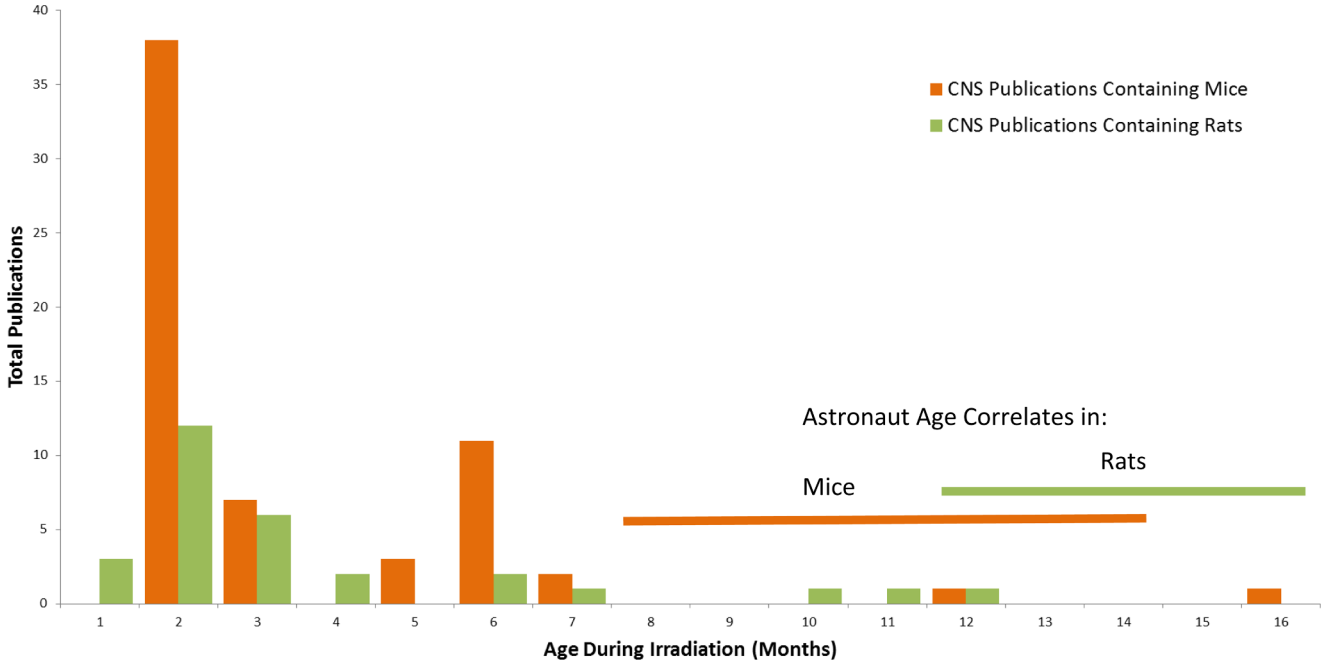

Fig. 3. Animal ages during irradiation in the literature. Orange bars depict the ages of mice at the time of exposure, and green bars describe ages of rats. Astronaut age correlates were determined as the period between mean astronaut candidate age during selection, and mean astronaut retirement age (Slaba et al., 2015b). This figure omits 8 publications that used 'retired breeder' rats of ages ranging from approximately 8–11mo.

synaptic density markers in the hippocampus (Kiffer et al., 2018b; Parihar et al., 2015a; Chmielewski et al., 2016). The dopaminergic system also was marked by molecular alterations (Davis et al., 2014; Davis et al., 2015). Furthermore, vast differential activation of inflammatory processes was dose and time-dependent (Raber et al., 2016a; Kiffer et al., 2018b; Sweet et al., 2014; Pecaut et al., 2003). Epigenetic analyses generally corroborate the radiation-induced molecular and structural changes. Exposure to 1 Gy elicited a methylation profile at 2 weeks that largely persisted for 5 months (Impey et al., 2017, 2016b). It should be noted that adverse effects to ^{1}H radiation are generally reduced or not seen in animal models that are resistant to oxidative stress (Parihar et al., 2015b; Chmielewski et al., 2016; Liao et al., 2013).

2.6. Mixed fields

The complex radiation field encountered in space presents numerous difficulties for designing relevant ground-based models.

Approaches to solving limitations involving the available energies, fluence, and time between delivery of charged-particle species is dependent upon available accelerator technologies. NASA's Space Radiation Laboratory (NSRL) has recently made breakthroughs in mixed-field simulations, and it aims to continue developing simulations that are more representative of GCRs (Norbury et al., 2016). Moving forward, GCR simulations may involve exposures to the same particles at various energies (Slaba et al., 2015a,b).

The first attempt at investigating CNS effects of a mixed radiation field involved a 10 cGy priming dose of protons (150 MeV/n) followed the next day by a 50 cGy dose of ^{56}Fe (600 MeV/n). This exposure led to NOR deficits 3 months later; however, the results were identical to ^{56}Fe-only exposure, and proton-only exposures resulted in no NOR deficits. Cytokine analyses revealed particle-dependent changes. IL-4 concentrations were lower in animals that received only ^{56}Fe, but not ^{56}Fe in combination with ^{1}H. Conversely, IL-12, p70, IL-6, and TNF-α levels were elevated only in animals that received both, but not individual, particles (Raber et al., 2016a).

Upgrades to the NSRL have been progressively allowing for a faster transition of ion sources, reaching one step closer to true mixed field exposures. Our recent study utilized exposures of first, 50 cGy ^{1}H (150 MeV/n) followed by 10 cGy ^{16}O, delivered within the same hour (Kiffer et al., 2018a). Three months later, irradiated animals had deficits in short-term spatial memory, as assessed by the Y-maze. Additionally, radiation led to upregulation of Nr2a, GluR1, Syn1, Syp, Dbn1, and SAP97 and downregulation of Nr2b. Finally, in irradiated animals, the dendritic Sholl length was increased in the DG but reduced in the CA1. We conducted a separate study with the same exposures on a different set of animals, and those results suggested that, 9 months after exposure, the radiation-dependent changes to Sholl length were nearly identical to those observed after 3 months in the previous study (Kiffer et al., 2018c). Previous studies with ^{16}O or ^{1}H had reported only reductions in dendritic Sholl length in the DG, suggesting potential synergy in the combination of ^{1}H and ^{16}O, but more work is warranted to confirm exact timelines (Kiffer et al., 2018b; 2019; Carr et al., 2018; Parihar et al., 2015a; Howe et al., 2019).

The first CNS study to incorporate the first phase of NSRL's GCR simulation involved GCRs exposures of 15 cGy (approximately 9 cGy ^{1}H [250 MeV/n], 3 cGy ^{4}He [250 MeV/n], and 3 cGy ^{16}O [600 MeV/n]) and 50 cGy (approximately 30 cGy ^{1}H [250 MeV/n], 10 cGy ^{4}He [250 MeV/n], and 10 cGy ^{16}O [600 MeV/n]) [116]. There were no effects on EPM-mediated anxiety in irradiated mice, consistent with previous findings with animals of similar age (Rabin et al., 2014; Krukowski et al., 2018a). The first evidence of radiation-induced sociability deficits in males resulted from 50 cGy of GCR (Krukowski et al., 2018a). This also induced social memory deficits in males, consistent with previous findings (Mange et al., 2018), and suggesting that the change is likely due to ^{16}O; this change has been observed in females at a later time point (Kiffer et al., 2019). Open-field-mediated anxiety was observed 2.5 months after 50 cGy of GCR, which previously had been observed only in ^{1}H exposures (Pecaut et al., 2002; Kiffer et al., 2018b). Finally, 15 and 50 cGy of GCR resulted in NOR deficits only in males. In previous studies, protons, ^{4}He, and ^{16}O induced NOR deficits in dosages similar to or lower than the GCR exposures, but they have occurred at a later time point in females than in males (Kiffer et al., 2019; Krukowski et al., 2018a; Rabin et al., 2019). Overall, the paucity of single particle studies including females, presents difficulties in delineating which particles may be responsible for specific sex differences in behavioral deficits. Future mixed-field studies should further incorporate a battery of behavioral experiments that have been widely cited in the literature.

3. Conclusions and future directions

Hazards associated with spaceflight must be well understood prior to human exposures. Single-particle studies have been essential for the foundational understanding of biological hazards of charged-particle radiation. The behavioral outcomes due to exposure to various charged particles draw vast concern for future manned interplanetary spaceflight. Findings of behavioral experiments over the last 30 years suggest that much attention should be placed on shielding and countermeasures considerations. Improvements in particle-accelerator technologies continuously allow for more representative experimentation, which may be crucial for accurate risk assessment as there may be confounding factors in CNS outcomes due to particle and energy.

Despite improvements in accelerator technologies, major obstacles and gaps in knowledge remain for behavioral studies. Due to practical limitations, it's currently infeasible to expose animals to mission-relevant dose rates of charged-particle radiation, and to model realistic exposures that involve particles incoming from various angles.

Moving forward, there are several obstacles in the field which require immediate attention. Currently, fewer than 10% of all CNS charged-particle radiation studies have involved females (Fig. 2). It's imperative that future research involves females and males due to the reported sex-differences in behavior following charged-particle radiation exposures (Krukowski et al., 2018b). The overwhelming majority of animals in CNS studies are irradiated at 7 or fewer months of age (Fig. 3). This proves problematic in translating animal research findings to the astronaut population, as mean astronaut ages during selection and retirement range from 34- to 48-years-old, respectively (Kovacs and Shadden, 2017). This age range roughly translates to animal ages of 8–14 months in mice and 13–19 months in rats (Dutta and Sengupta, 2016; Sengupta, 2013). Importantly, animal age has a direct impact on wide measures of behavioral outcomes (Shoji et al., 2016). In addition, it's currently unknown whether the order of particles animals are exposed to results in different biological outcomes. Finally, little is known about the biological effects of high-energy nuclear fragment components such as neutrons, pions, and muons, which are an important component of the complex interplanetary radiation field, and is estimated to contribute approximately 10% of the total Mars mission dosage (Nelson et al., 2016).

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