Space Radiation-Induced Cognitive Deficits Following Head-Only, Whole Body, or Body-Only Exposures.

Catherine M. Davis[1] and Bernard M. Rabin[2,3]

[1]Dept. Psychiatry and Behavioral Sciences, Johns Hopkins Univ., Baltimore, MD 21224
[2]Dept. Psychology, UMBC, Baltimore, MD 21250
[3]Corresponding Author, e-mail: rabin@umbc.edu

Abstract

During exploratory class missions outside the protection of the earth's magnetic field astronauts will be exposed to particles of high energy and charge (HZE particles). A consequence of exposure to these particles is the potential disruption of cognitive performance which depends upon the integrity of the CNS. Because cells throughout the body will be impacted by HZE particles it may be important to understand the contribution of non-neuronal cells to the development of a performance decrement. The present review examines the effects of partial body exposures (head-only/body-only) in comparison to whole-body exposures on cognitive performance.

Introduction

Future long-duration space missions will involve travel outside of the protection of Earth's magnetosphere, which will greatly increase astronauts' exposure to high energy and charge (HZE) particles and protons. These particles arise from solar particle events (SPE), which originate from the sun, and galactic cosmic rays (GCR) that originate outside the solar system and are likely formed by exploding supernova. During periods of intense solar activity, SPEs can deliver high, and potentially lethal, doses of protons to astronauts and spacecraft outside the protection of the Earth's magnetosphere. GCR on the other hand, occur at much lower flux, but contain protons, helium ions, and HZE particles. While HZE particles are less abundant, they have significantly higher ionizing and penetrating power, and as such, are difficult to shield and display a greater potential for radiation-induced damage (NASA Space Radiation, 2017). Exposure to these particles could permanently damage multiple tissues, including the central nervous system (CNS)

and result in deleterious effects on the brain and behavior that could ultimately jeopardize mission success. Ground-based studies suggest that exposure to protons or HZE particles induce profound neurobehavioral changes in rodents. The exact mechanisms of these HZE-induced changes are currently unknown, but appear to be related to altered neurogenesis, gliogenesis, neuronal signaling, inflammation, and oxidative stress, in addition to structural changes in brain regions important for learning, memory, attention, and other cognitive processes.

In general, HZE and proton exposure has been shown to negatively impact various cognitive domains, including learning and memory, attention, and motivation. For example, exposure to ^{56}Fe particles, the densest HZE ion present in cosmic rays (Curtis & Letaw, 1989), induces deficits in various tests of spatial and recognition memory and attention (Manda et al., 2008; Suresh Kumar et al., 2015; Shukitt-Hale et al., 2000, 2003; Britten et al., 2012, 2016a,b), reduces hippocampal neurogenesis (Rola et al., 2004; Rivera et al., 2013), and alters structural, cellular, and molecular components in brain regions important for learning and memory, such as the entorhinal cortex, thalamus, and hippocampus (Huang et al., 2009; Impey et al., 2016; Cherry et al., 2012; Machida et al., 2010; Parihar et al., 2016). Further, exposure to HZE particles or protons also produces deficits in behaviors which are mediated by several neurotransmitter systems, including dopamine-mediated behaviors such as amphetamine-induced conditioned taste aversion learning (Rabin et al., 1998, 2000, 2002), conditioned place preference (Rabin et al., 2000, 2003), motor performance (Joseph et al., 1992, 1998a), sensitivity to haloperidol-induced catalepsy (Joseph et al., 1998b), changes in oxotremorine-enhanced K($^{+}$)-evoked dopamine release (Joseph et al., 1992; Shukitt-Hale et al., 2004), and alterations in hippocampal glutamate neurotransmission (Machida et al., 2010) in addition to deficits in learning, memory, and attention (Britten et al., 2016; Davis et al., 2014; Lonart et al., 2012; Wyrobek & Britten, 2016; Davis et al., 2015).

A comprehensive review of the effects of exposure to HZE particles on behavioral performance has recently been published by Kiffer and colleagues (2019). The present review is focused on the effects of partial body exposures on cognitive performance in an attempt to determine which effects are dependent on exposure of the CNS and which effects may result from whole or partial body exposure. Although behavior is dependent upon the functioning of the CNS, the role of the body in the disruption of cognitive performance following exposure to HZE particles, either as a component of whole-body (including the head) or body-only (head shielded) irradiation, remains to be clarified.

Direct Effects

Initial studies comparing partial and whole body exposures involved exposing subjects to gamma radiation. Gamma radiation is sparsely ionizing radiation in contrast to HZE particle radiation which is densely ionizing, which means that the mechanisms by which biological damage is produced may also be different. One of the first studies to investigate the central or peripheral effects of irradiation on physiological processes was published by Kandasamy and colleagues (1988). Using head-only, whole-body, or body-only (head shielded) exposures, these investigators examined the underlying mechanisms of radiation-induced changes in thermoregulation. Gamma irradiation-induced temperature changes were found to be dose-related, with hyperthermia following doses <15Gy and hypothermia following higher doses (e.g., >20Gy). When the head was shielded from exposure, however, no substantial changes in body temperature were found regardless of the dose used. Importantly, head-only and whole-body exposures (with the head exposed) induced the same temperature changes. Kandasamy and colleagues (1988, 1990) concluded that radiation-induced hyperthermia and hypothermia were both centrally mediated, but that different neurotransmitters or modulators, such as histamine or prostaglandins (e.g., PGE2, PGD2), were responsible for these effects. Similar to these results with gamma irradiation, different HZE particles, including ^{56}Fe, ^{40}Ar, ^{20}Ne, or ^{4}He, were shown to induce dose-dependent biphasic changes in body temperature (Kandasamy et al., 1994). Lower doses of these ions were shown to induce significant hyperthermia, with ^{56}Fe producing the most robust changes in body temperature. Interestingly, the biphasic changes in thermoregulation following ^{56}Fe were dose-dependently attenuated by indomethacin, mepyramine, or cimetidine, which supports a role for prostaglandins and histamine in radiation-induced hyper- or hypothermia, respectively.

In addition to these changes in thermoregulation following radiation exposure, additional work has shown differences in radiation-induced taste aversion learning following head-only or partial-body exposures to gamma radiation in animal models. Conditioned taste aversion learning is a Pavlovian association between a distinctive tastant (e.g., sucrose solution) and a malaise-inducing agent or toxin, such as ionizing radiation. Thus, after pairing the sucrose solution (conditioned stimulus, CS) with exposure to ionizing radiation (unconditioned stimulus, US), subsequent presentations of the sucrose CS result in decreased consumption and avoidance of the CS. One of the earliest studies investigated gamma radiation-induced taste aversion learning using head-only or body-only exposures in rats. In this study, Rabin and colleagues (1994) demonstrated that the

area postrema, a medullary brain region with a role in controlling autonomic functions of the central nervous system and chemoreception, mediated radiation-induced taste aversion learning following body-exposure, but not following head-only exposure. More specifically, lesions of the area postrema completely attenuated radiation-induced decreases in sucrose consumption following body-only exposure. While the same lesions reduced the aversion following head-only exposure, lesioned and irradiated rats still displayed a significant decrease in sucrose consumption; irradiated lesioned rats did, however, consume more sucrose than non-lesioned irradiated rats. These results demonstrated that while aversions from an irradiated body were controlled via the area postrema (most likely due to its chemoreceptive role in toxin detection), exposures to the head-only were mediated by an additional mechanism(s) hypothesized to reside in the central nervous system. Nonetheless, radiation-induced taste aversions, where radiation is the US, are not assessing learning *per se*, but are demonstrating radiation's effects as a toxin on the body.

In general, whole-body and head-only exposures to HZE particles and protons produce similar effects on cognitive performance and markers in the brain. Head-only or whole-body exposures to protons and HZE particles disrupt performance on novel object recognition tasks (Villasana et al., 2013; Haley at al., 2013; Rabin et al. 2015; Parihar et al., 2016), spatial learning and memory using the Morris water maze (Haley et al., 2013; Shukitt-Hale et al., 2007; Villasana et al., 2013; Yeiser et al. 2013), Barnes maze (Britten et al. 2012, 2017), open field activity (Belov et al., 2016; Pecaut et al. 2002; Casadesus et al., 2004; Kiffer et al., 2018), fear conditioning (Parihar et al., 2018; Raber et al., 2011; Villasana et al., 2010), in addition to altering molecular, structural,or functional measurements in the brain (Huang et al., 2010; Obenaus et al., 2008; Parihar et al., 2016, 2018; Poulouse et al., 2017) .

Interestingly, a deficit in one cognitive domain and/or behavioral test does not necessarily predict deficits in another following radiation exposure. Britten and colleagues (2016) have reported that rats exposed to 20 cGy of ^{56}Fe (1 GeV/n) particles showed a deficit in attentional set shift performance but did not also show a deficit in spatial memory (Barnes maze). The different effects of irradiation on behavior between the two measures of cognitive performance may have reflected the fact that the tasks are dependent upon different cortical areas: attentional set shift performance is mediated by the medial prefrontal cortex whereas spatial performance is mediated by the hippocampus. Analyzing the cognitive performance of individual subjects following exposure to protons (150 MeV/n, 25-100 cGy), Davis et al. (2014) reported differences in

performance between the rodent psychomotor vigilance task (rPVT) and a line orientation discrimination task. These two behavioral tests are mediated by different brain regions: the rPVT is a sustained attention test controlled by the frontal-parietal attention network and motor regions (Drummond et al., 2005), whereas the line discrimination test is a reversal test primarily controlled by the orbitofrontal cortex (Izquierdo et al., 2017). Disruption of performance on the rPVT was related to changes in the dopamine transporter and D_2 receptor, in addition to tyrosine hydroxylase levels in the frontal, but not parietal cortex, suggesting brain region specific changes that could account for these behavioral differences (Davis et al., 2014, 2015). Thus, it appears that radiation exposure can alter some cognitive domains while leaving others intact, which is most likely a function of more severe damage to one brain region over another. However, these differences could also be evident due to the complexity or sensitivity of the behavioral tasks employed, with more complicated or sensitive tasks being disrupted across multiple cognitive domains. Similarly, a cognitive deficit observed during one series of experiments may not be observed in a subsequent series of experiments (Rabin et al., 2015). In addition to HZE particle-induced changes in the performance of specific cognitive tasks, there are also changes in cognitive performance as a function of age such that deficits that are not observed in young subjects may be observed in older subjects (Rabin et al., 2005, 2014).

While these studies suggest that that there are no qualitative differences as a function of the method of exposure, it is possible that there may be differences in the severity of the deficits reported. Most studies examining the CNS effects of HZE and proton irradiation have employed whole-body exposures to best mimic what is expected for astronauts on a long duration mission. These studies show that whole-body exposures routinely elicit changes in the CNS, including deficits in behavioral tests and decreases in cell division and neurogenesis in the brain (Rola et al., 2004; Rivera et al., 2013; Raber et al., 2004, Casadesus et al., 2005).

Because cognitive performance depends upon neuronal function, the observation of equivalent changes in neuronal function and cognitive performance following head-only and whole-body exposures to HZE particles and protons, raises a question about the contribution of exposure to the body on space radiation-induced changes in neuronal function and cognitive performance. There have only been a few studies that have directly compared the effects of partial or whole-body exposures to protons and HZE particles on cognitive performance and neuronal function. Overall, the effects of head-only or whole-body exposure to protons are similar (Rabin et al., 2015).

Differences are observed in the threshold needed to effect a change in cognitive performance. Which exposure condition (head-only/whole body) is most effective in disrupting performance varies as a function of the specific cognitive task (novel object recognition/operant responding) and the particle energy. Similar results are obtained with partial/whole body exposures to ^{16}O particles (Rabin et al., 2014). Whether whole-body, head-only or body-only exposures disrupt cognitive performance at the lowest dose varies as a function of the task. There are no differences between the three treatment conditions in the performance of a novel location task. Body-only exposures did not affect performance of a novel object recognition task, but were the most effective treatment condition in disrupting operant responding compared to head-only or whole-body exposures. While the use of shielding (tungsten bricks) does permit some radiation exposure to the shielded area (≈ 7% of the dose), the dose to which the shielded area is exposed is significantly below the threshold dose of 1 cGy for the disruption of cognitive performance by exposure to ^{16}O particles (Rabin et al., 2011).

Overall, these results suggest that whole-body exposures to the types of radiation encountered in space are not more likely to disrupt cognitive performance than are head-only or body-only exposures. Further, these results suggest that irradiation of the head is not a necessary condition for the disruption of cognitive performance. As such, the indirect effects of exposure to HZE particles may play a critical role in the disruption of cognitive performance.

Indirect Effects

HZE particle irradiation is densely ionizing, which means that it produces biological damage that is distinct from that produced by sparsely ionizing radiation (e.g., X- and gamma-rays). For example, DNA lesions resulting from direct HZE particle strikes are complex and subsequently difficult to repair (Durante, 2009). While the exact implications of these differences are not fully understood, it is now recognized that direct particle strikes to the nucleus are only one of several ways that HZE exposure can damage cells, including cells in the CNS. For example, damage can occur from activation of oxidative stress, inflammation, and changes in various cellular proteins. These indirect effects can also result in genetic damage or radiation-induced changes in other important biological processes that more readily induce oxidative stress that damages cellular components, including proteins, nucleic acids, and lipids (Li et al., 2014) in the same cell or in neighboring cells that have not been directly hit by an ion. This fact is especially important for the

CNS, since oxidative damage is linked to aging and numerous disease states, including neurodegenerative disorders. While direct particle strike and oxidative stress can damage cells in the CNS, these activated or altered biochemical processes could damage additional areas of the brain, which in turn could negatively affect behavior.

Several lines of evidence suggest that body tissues not directly targeted by irradiation will subsequently show signs of radiation-induced tissue changes (Pecaut et al., 2003; de Toledo et al., 2011; Jain et al., 2011; Kennedy et al., 2012; Marquette et al., 2003; Nagasawa & Little, 1992; Zou et al., 2012). For example, rats exposed to head-only titanium ions (50 cGy, 1100 MeV/n) displayed a down-regulation of proteins in the liver that are important for fatty acid metabolism (Jain et al., 2011). Importantly, these changes occurred in non-targeted tissue, i.e. the liver was not irradiated, but radiation-induced changes in proteins were found in this organ at 20-months post-exposure. Further, body-only (head-shielded) irradiation activates pro-inflammatory cytokines in the brain six hours after exposure (Marquette et al., 2003). These results support the existence of space radiation-induced non-targeted effects (Jain et al., 2011; Cucinotta & Chappell, 2010; Turker et al., 2009) and demonstrate that these effects persist long after the actual exposure. Given the fact that these non-targeted effects persist for months following exposure, they are most likely a consequence of prolonged oxidative stress and peripheral immune system activation (Jain et al., 2011; Marquette et al., 2003). Indeed, there is a great deal of communication between the peripheral immune system and the brain, and activation of the peripheral immune system influences cognition, mood, and ultimately behavior (reviewed in Dantzer et al., 2008; Maier & Watkins,1998). For example, peripheral administration of interleukin-1 (IL-1), lipopolysaccharide (LPS), and other infectious agents induce activation of IL-1 in the brain, which suggests that the brain is activated by and responds to increases in peripheral pro-inflammatory cytokines (Dantzer et al., 2008; Maier & Watkins, 1998; van Dam et al., 1992). In experimental animals, activation of pro-inflammatory cytokines in the brain in response to peripheral immune system activation impairs contextual fear conditioning (Pugh et al., 1998). Further, in humans, major depressive disorders are more common in patients diagnosed with rheumatoid arthritis, cardiovascular disease, or type-2 diabetes, various conditions that lead to chronic inflammation (reviewed in Dantzer et al., 2008). In addition to these cognitive impairments in animals and humans, IL-1β and TNF-α administration also alter circadian activity patterns by flattening the diurnal activity rhythm (Cavadini et al., 2007; Ohdo et al., 2001).

Since irradiation is a potent pro-inflammatory agent, exposure of the whole body would be expected to lead to an increase in peripheral pro-inflammatory cytokines that would cause activation of these cytokines in the brain, which could lead to long-term changes in physiological and neurobehavioral function. Although body-only (head-shielded) exposures cause minimal immediate changes in body temperature (Kandasamy & Hunt, 1990), the fact that non-targeted effects of space-radiation are apparent 20-months post-exposure (Jain et al., 2011) suggests that alterations in behavior and other physiological processes could be evident beyond the 120-minute time-point previously reported (Kandasamy & Hunt, 1990). Further, effects in the periphery are potent enough to cause changes in the brain that lead to neurobehavioral deficits (Rabin et al. 2014). Interestingly, activating the peripheral immune system (LPS injection) following head-only ^{56}Fe exposure restored the radiation-induced inhibition of hippocampal plasticity (Vlkolinsky et al., 2007). Although the neurobehavioral implications of these results were not tested, this study suggests that the peripheral immune system can interact with and alter radiation-induced brain changes.

In conclusion, radiation-induced neurobehavioral deficits have been reported following head-only, body-only, and whole-body exposures, which demonstrates that exposure of the head is not required for these behavioral deficits. Deficits following body-only exposure are hypothesized to be a function of the indirect effects of HZE exposure, including activation of the peripheral immune system.

Acknowledgments

Preparation of this review was supported by NASA grants NNX15AC71G and 80NSSC18K1080 to CMD and NNX16AE06G to BMR.

References

Belov, O.V., Belokopytova, K.V., Bazyan, A.S., Kudrin, V.S., Narkevich, V.B. et al. Exposure to ^{12}C particles alters the normal dynamics of brain monoamine metabolism and behavior in rats. Physica Med., 2016, 32: 1088-1094.

Britten, R.A., Davis, L.K., Johnson, A.M., Keeney, S., Siegel, A., Sanford, L.D., Singletary, S. J., & Lonart, G. Low (20 cGy) doses of 1 GeV/u (56)Fe--particle radiation lead to a persistent reduction in the spatial learning ability of rats. Radiat. Res., 2012, 177: 146-151.

Britten, R.A., Jewell, J.S., Miller, V.D., Davis, L.K., Hadley, M.M., & Wyrobek, A. Impaired spatial memory performance in adult Wistar rats exposed to low (5-20 cGy) doses of 1 GeV/n (56)Fe particles. Radiat. Res., 2016, 185: 332-7.

Britten, R.A., Miller, V.D., Hadley, M.M., & Jewell, J.S.Performance in hippocampus- and PFC-dependent cognitive domains are not concomitantly impaired in rats exposed to 20cGy of 1GeV/n (56)Fe particles. Life Sci. Space Res., 2016, 10: 17-22.

Britten, R.A., Jewell, J.S., Duncan, V.D., Davis, L.K., Hadley, M.M., & Wyrobek, A.J. Spatial memory performance of socially mature Wistar rats is impaired after exposure to low (5 cGy) doses of 1 GeV/u ^{48}Ti particles. Radiat. Res., 2017, 187: 60-65.

Casadesus, G., Shukitt-Hale, B., Cantuti-Castelvetri, I., Rabin, B.M., & Joseph, J.A. The effects of heavy particle irradiation on exploration and response to environmental change. Adv. Space Res., 2004, 33: 1340-1346.

Casadesus, G., Shukitt-Hale, B., Stellwagen, H.M., Smith, M.A., Rabin, B.M., & Joseph, J.A. Hippocampal neurogenesis and PSA-NCAM expression following exposure to ^{56}Fe particles mimics that seen during aging in rats. Exp. Gerontol., 2005, 40: 249-254.

Cavadini, G.I., Petrzilka, S., Kohler, P., Jud, C., Tobler, I., Birchler, T., & Fontana. A. TNF-alpha suppresses the expression of clock genes by interfering with E-box-mediated transcription. Proc. Nat. Acad. Sci. USA, 2007, 104: 12843-12848.

Cherry, J.D., Liu, B., Frost, J.L., Lemere, C.A., Williams. J.P., Olschowka, J.A., & O'Banion, M.K. Galactic cosmic radiation leads to cognitive impairment and increased abeta plaque accumulation in a mouse model of Alzheimer's disease. PLoS One, 2012, 7: e53275

Curtis, S.B., & Letaw, J.R. Galactic cosmic rays and cell-hit frequencies outside the magnetosphere. Adv. Space Res., 1989, 9: 293-298.

Cucinotta, F.A., & L.J. Chappell. Non-targeted effects and the dose response for heavy ion tumor induction. Mutat Res., 2010, 687: 49-53.

Dantzer, R., O'Connor, J.C., Freund, G.G., Johnson, R.W., & Kelley, K.W. From inflammation to sickness and depression: when the immune system subjugates the brain. Nat. Rev. Neurosci., 2008, 9: 46-56.

Davis, C.M., DeCicco-Skinner, K.L., Roma, P.G., & Hienz, R.D. Individual differences in attentional deficits and dopaminergic protein levels following exposure to proton radiation. Radiat. Res., 2014, 181: 258-71.

Davis, C.M., DeCicco-Skinner K.L., & Hienz, R.D. Deficits in sustained attention and changes in dopaminergic protein levels following exposure to proton radiation are related to basal dopaminergic function. PLoS One, 2015, 10: e0144556.

de Toledo, S.M., et al. Vitro and vivo exposures to high charge and high energy (HZE) particles induce persistent non-targeted stressful effects. International Astronautics Association. 2011. Houston, TX.

Drummond, S.P.A., Bischoff-Grethe, A., Dinges, D.F., Ayalon, L., Mednick, S.C., & Meloy, M.J. The neural basis of the psychomotor vigilance task. Sleep, 2005, 28: 1059-1068.

Haley, G.E., Yeiser, L., Olsen, R.H.J., Davis, M.J., Johnson, L.A., & Raber, J. Early effects of whole-body 56Fe irradiation on hippocampal function in C57BL/6 mice. Radiat. Res., 2013, 179: 590-596.

Huang, L., Smith, A., Badaut, J., & Obenaus, A. Dynamic characteristics of 56Fe-particle radiation-induced alterations in the rat brain: magnetic resonance imaging and histological assessments. Radiat. Rs., 2010, 173: 729-737.

Huang, L., Smith, A., Cummings, P., Kendall, E.J., & Obenaus, A. Neuroimaging assessment of memory-related brain structures in a rat model of acute space-like radiation. J. Magn. Reson. Imaging, 2009, 29: 785-792.

Impey, S., Jopson, T., Pelz, C., Tafessu, A., Fareh, F., Zuloaga, D., Marzulla, T., Riparip, L.K., Stewart, B., Rosi, S., Turker, M.S., & Raber, J. Short- and long-term effects of 56Fe irradiation on cognition and hippocampal DNA methylation and gene expression. BMC Genomics, 2016, 17: 825.

Izquierdo, A., Brigman, J.L., Radke, A.K., Rudebeck, P.H., & Holmes, A. The neural basis of reversal learning: an updated perspective. Neurosci., 2017, 345: 12-26.

Jain, M.R., Li, M., Chen, W., Liu, T., de Toledo, S.M., Pandey B.N., Li, H., Rabin, B.M., & Azzam, E.I. In vivo space radiation-induced non-targeted responses: late effects on molecular signaling in mitochondria. Curr. Mol. Pharmacol., 2011, 4: 106-111.

Joseph, J.A., Kandasamy, S.B., Hunt, W.A., Dalton, T.K., & Stevens, S. Radiation-induced increases in sensitivity of cataleptic behavior to haloperidol: possible involvement of prostaglandins. Pharmacol. Biochem. Behav., 1988, 29: 335-341.

Joseph, J.A., Erat, S., & Rabin, B.M. CNS effects of heavy particle irradiation in space: behavioral implications. Adv. Space Res., 1998, 22: 209-216.

Joseph, J.A., Hunt, W.A., Rabin, B.M., & Dalton, T.K. Possible "accelerated striatal aging" induced by 56Fe heavy-particle irradiation: implications for manned space flights. Radiat. Res., 1992, 130: 88-93.

Kandasamy, S.B., Hunt, W.A., & Mickley, G.A. Implication of prostaglandins and histamine H1 and H2 receptors in radiation-induced temperature responses of rats. Radiat. Res., 1988, 114: 42-53.

Kandasamy, S.B., & Hunt, W.A. Involvement of prostaglandins and histamine in radiation-induced temperature responses in rats. Radiat. Res., 1990, 121:, 84-90.

Kandasamy, S.B., Rabin, B.M., Hunt, W.A., Dalton, T.K., Joseph, J.A., & Harris, A.H. Exposure to heavy charged particles affects thermoregulation in rats. Radiat. Res., 1994, 139: 352-356.

Kennedy, A.R. Acute radiation effects resulting from exposure to solar particle event-like radiation. In NASA Human Research Performance Investigators' Workshop, 2012. Houston, TX.

Kiffer, F., Howe, A.K., Carr, H., Jing, W., Alexander, T., Anderson, J.E., Groves, T., Seawright, J.W., Sridharan, V., Carter, G., Boerma, M., & Allen, A.R. Late effects of 3H irradiation on hippocampal physiology. Life Sci. Space Res., 2018, 17: 51-62.

Kiffer, F., Boerma, M., & Allen, A. Behavioral effects of space radiation: A comprehensive review of animal studies. Life Sci. Space Res., 2019, 21: 1-21.

Lonart, G., Parris, B., Johnson, A. M., Miles, S., Sanford, L. D., Singletary, S. J., & Britten, R.A. Executive function in rats is impaired by low (20 cGy) doses of 1 GeV/u (56)Fe particles. Radiat. Res., 2012, 178: 289-294.

Machida, M., Lonart, G., & Britten, R.A. Low (60 cGy) doses of (56)Fe HZE-particle radiation lead to a persistent reduction in the glutamatergic readily releasable pool in rat hippocampal synaptosomes. Radiat. Res., 2010, 174: 618-623.

Maier, S.F., & Watkins, L.R. Cytokines for psychologists: implications of bidirectional immune-to-brain communication for understanding behavior, mood, and cognition. Psychol. Rev., 1998. 105: 83-107.

Manda, K., Ueno, M., & Anzai, K. Space radiation-induced inhibition of neurogenesis in the hippocampal dentate gyrus and memory impairment in mice: ameliorative potential of the melatonin metabolite. AFMK. J. Pineal Res., 2008, 45: 430-438.

Marquette, C., Linard, C., Galonnier, M., Uye, A.V., Mathieu, J., Gourmelon, P., & Clarencon, D. IL-1beta, TNFalpha and IL-6 induction in the rat brain after partial-body irradiation: role of vagal afferents. Int. J. Radiat. Biol., 2003, 79: 777-785.

Nagasawa, H., & Little, J.B. Induction of sister chromatid exchanges by extremely low doses of alpha-particles. Cancer Res., 1992, 52: 6394-6396.

NASA Space Radiation. Space radiation (eBook). 2017. NASA Human Research Program. https://www.nasa.gov/sites/default/files/atoms/files/nasa_space_radiation_ebook_0.pdf

Obenhaus, A., Huang, L., Smith, A., Favre, C.J., Nelson, G., & Kendall, E. Mangetic resonance imaging and spectroscopy of the rat hippocampus 1 month after exposure to 56Fe-particle radiation. Radiat. Res., 2008, 169: 149-161.

Ohdo, S., Koyanagi, S., Suyama, H., Higuchi, S., & Aramaki, H. Changing the dosing schedule minimizes the disruptive effects of interferon on clock function. Nat. Med., 2001, 7: 356-360.

Parihar, V.K., Allen, B.D., Caressi, C., Kwok,S., Chu, E., Tran, K.K., Chmielewski, N.N., Gidzinski, E., Achatya, M.M., Britten, R.A., Baulch, J. E., & Limoli, C.L. Cosmic radiation exposure and persistent cognitive dysfunction. Sci. Rep., 2016, 6: 34774.

Parihar, V.K., Maroso, M., Syage, A., Allen, B.D., Angulo, M.C., Soltesz, I., & Limoli, C.L. Peristent nature of alterations in cognition and neuronal circuit exctiability after exposure to simulated cosmic radiation in mice. Exp. Neurol., 2018, 305: 44-55.

Pecaut, M.J., Haerich, P., Zuccarelli, C.N., Smith, A.L., Zendjas, E.D., & Nelson, G.A. Behavioral consequences of radiation exposure to simulated space radiation in the C57BL/6 mouse: open field, rotorod, and acoustic startle. Cog. Affect. Behav. Neurosci., 2002, 2: 329-340.

Pecaut, M. J., Nelson, G. A., Moyers, M. F., Rabin, B.M., & Gridley, D.S. "Out-of-field" effects of head-localized proton irradiation on peripheral immune parameters. In Vivo, 2003, 17: 513-522.

Poulose, S.M., Rabin, B.M., Bielinski, D.F., Kelly, M.E., Miller, M.G., Thanthaeng, N., & Shukitt-Hale, B. Neurochemical differences in learning and memory paradigms among rats supplemented with anthocyanin-rich blueberry diets and exposed to acute doses of 56Fe particles. Life Sci. Space Res., 2017, 12: 16-23.

Pugh, C.R., Kumagawa, K., Fleshner, M., Watkins, L.R., Maier, S.F., & Rudy, J.W. Selective effects of peripheral lipopolysaccharide administration on contextual and auditory-cue fear conditioning. Brain Behav. Immun., 1998, 12: 212-229.

Raber, J., Rola, R., LeFevour, A., Morhardt, D., Curley, J., Mizumatsu, S., VandenBerg, S.R., & Fike, J.R. Radiation-induced cognitive impairments are associated with changes in indicators of hippocampal neurogenesis. Radiat. Res., 2004, 162: 39-47.

Raber, J., Rosi, S., Chakraborti, A., Fishman, K., Dayger, C., Davis, M.J., Villasana, L., & Fike, J.R. Effects of 56Fe-particle cranial radiation on hippocampus-dependent cognition depend on the salience of the environmental stimuli. Radiat. Res., 2011, 176: 521-526.

Rabin, B.M., Hunt, W.A., & Lee, J. Effects of dose and of partial body ionizing radiation on taste aversion learning in rats with lesions of the area postrema. Physiol. Behav., 1984, 32: 119-122.

Rabin, B.M., Joseph, J.A., & Erat, S. Effects of exposure to different types of radiationon behaviors mediated by peripheral or central systems. Adv. Space Res., 1998, 22: 217-225.

Rabin, B.M., Joseph, J.A., Shukitt-Hale, B., & McEwen, J. Effects of exposure to heavy particles on a behavior mediated by the dopaminergic system. Adv. Space Res., 2000, 25: 2065-2074.

Rabin, B.M., et al., Effects of heavy particle irradiation and diet on amphetamine- and lithium chloride-induced taste avoidance learning in rats. Brain Res., 2002, 953: 31-66.

Rabin, B.M., Joseph, J.A., & Shukitt-Hale, B. Long-term changes in amphetamine-induced reinforcement and aversion in rats following exposure to ^{56}Fe particles. Adv. Space Res., 2003, 31: 127-133.

Rabin, B.M., Shukitt-Hale, B., Joseph, J.A., & Denisova, N. Effects of exposure to ^{56}Fe particles on the acquisition of a conditioned place preference in rats. Phys. Med., 2001, 17 Suppl 1: 196-197.

Rabin, B.M., Joseph, J.A., & Shukitt-Hale, B. A longitudinal study of operant responding in rats irradiated when 2 months old. Radiat. Res., 2005, 164: 552-555.

Rabin, B. M., Carrihill-Knoll, K. L., & Shukitt-Hale, B. Operant responding following exposure to HZE particles and its relationship to particle energy and linear energy transfer. Adv. Space Res., 2011. 48: 370-377.

Rabin, B.M., Shukitt-Hale, B., & Carrihill-Knoll, K.L. Effects of age on the disruption of cognitive performance by exposure to space radiation. J. Behav. Brain Sci., 2014, 4: 297-307.

Rabin, B.M., Carrihill-Knoll, K.L, & Shukitt-Hale, B. Comparison of the effectiveness of exposure to low LET helium particles (^{4}He) and gamma rays (^{137}Cs) on the disruption of cognitive performance. Radiat. Res., 2015, 184: 266-272.

Rabin, B.M., Shukitt-Hale, B., Gomes, S., & Carrihill-Knoll, K.L. Comparison of the effects of partial and whole body exposures to ^{16}O particles on cognitive performance in rats. Radiat. Res., 2014, 181: 251-257.

Rabin, B.M., Heroux, N.A., Shukitt-Hale, B., Carrihill-Knoll, K.L., Beck, Z., & Baxter, C. Lack of reliability in the disruption of cognitive performance following exposure to protons. Radiat. Environ. Biophys., 2015, 54: 285-295.

Rabin, B.M., Polouse, S., Bielinski, D.F., & Shukitt-Hale, B. Effects of head-only or whole-body exposure to very low doses of ^{4}He (1000 MeV/n) particles on neuronal function and cognitive performance. Life Sci. Space Res., 2019, 20: 85-92.

Rivera, P.D, Shih,H.-Y., LeBlanc, J.A., Cole, M.G., Amaral, W.Z., Mukherjee, S., Zhang, S., Lucero, M.J., et al. Acute and fractionated exposure to high-LET (56)Fe HZE-particle radiation both result in similar long-term deficits in adult hippocampal neurogenesis. Radiat. Res., 2013, 180: 658-667.

Rola, R., Raber, J., Rizk, A., Otsuka, S., VandenBerg, S.R., Morhardt, D.R., & Fike, J.R. Radiation-induced impairment of hippocampal neurogenesis is associated with cognitive deficits in young mice. Exp. Neurol., 2004, 188: 316-30.

Sanchez, M.C., Nelson, G.A., & Green, L.M. Effects of protons and HZE particles on glutamate transport in astrocytes, neurons and mixed cultures. Radiat. Res., 2010, 174: 669-678.

Shukitt-Hale, B., Casadesus, G., McEwen, J.J., Rabin, B.M., & Joseph, J.A. Spatial learning and memory deficits induced by exposure to iron-56-particle radiation. Radiat. Res., 2000, 154: 28-33.

Shukitt-Hale, B., Casadesus, G., Cantuti-Castelvetri, I., Rabin, B.M., & Joseph, J.A. Cognitive deficits induced by ^{56}Fe radiation exposure. Adv. Space Res., 2003, 31: 119-126.

Shukitt-Hale, B. Szprengiel, A., Pluhar, J., Rabin, B.M., & Joseph, J.A. The effects of proton exposure on neurochemistry and behavior. Adv. Space Res., 2004, 33: 1334-1339.

Shukitt-Hale, B., Casadesus, G., Carey, A., Rabin, B.M., & Joseph, J.A. Exposure to ^{56}Fe irradiation accelerates normal brain aging and produces deficits in learning and memory. Adv. Space Res., 2007, 39: 1087-1092.

Suresh Kumar, M.A., Peluso, M., Chaudhary, P., Dhawan, J., Beheshti, A., Manickam, K., et al. Fractionated radiation exposure of rat spinal cords leads to latent neuro-inflammation in brain, cognitive deficits, and alterations in apurinic endonuclease 1. PLoS One, 2015, 10: e0133016.

Turker, M.S., Connolly, L., Dan, C., Lasarev, M., Gauny, S., Kwoh, E., & Kronenberg A. Comparison of autosomal mutations in mouse kidney epithelial cells exposed to iron ions in situ or in culture. Radiat. Res., 2009, 172: 558-566.

van Dam, A.M., Brouns, M., Louisse, S., & Berkenbosch, F. Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: a pathway for the induction of non-specific symptoms of sickness? Brain Res., 1992, 588: 291-296.

Villasana, L., Dayger, C., & Raber, J. Dose and ApoE isoform–dependent cognitive injury after cranial ^{56}Fe irradiation in female mice. Radiat. Res., 2013, 179: 493-500.

Villasana, L., Rosenberg, J., & Raber, J. Sex-dependent effects of 56Fe irradiation on contextual fear conditioning in C57BL/6J mice. Hippocampus, 2010, 20: 19-23.

Villasana, L.E., Rosenthal, R.A., Doctrow, S.R., Pfankuch, T., Zuloaga, D.G., Garfinkel, A.M., Raber, J. Effects of alpha-lipoic acid on associative and spatial memory of sham-irradiated and 56Fe-irradiated C57BL/6J male mice. Pharmacol. Biochem. Behav., 2013, 103: 487-493.

Vlokolinsky, R., Krucker, T., Smith, A.L., Lamp, T.C., Nelson, G.A., & Obenaus, A. Effects of lipopolysaccharide on 56Fe-particle radiation-induced impairment of synaptic plasticity in the mouse hippocampus. Radiat. Res., 2007, 168: 462-470.

Wyrobek, A.J., & Britten, R.A. Individual variations in dose response for spatial memory learning among outbred Wistar rats exposed from 5 to 20 cGy of (56) Fe particles. Environ. Mol. Mutagen., 2016, 57: 331-340.

Yeiser, L.A., Villasana, L.E., & Raber, J. ApoE isoform modulates effects of cranial ^{56}Fe irradiation on spatial learning and memory in the water maze. Behav. Brain Res., 2013, 237: 207-214.

Zhou, Y., et al. Identification of a mechanism for immune dysfunction induced by solar particle event radiation and hindlimb suspension. In NASA Human Research Performance Investigators' Workshop, 2012. Houston, TX.