Title

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Journal

International Journal of Radiation Biology, 99(9)

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Publication Date

2023

DOI

10.1080/09553002.2023.2142984

Peer reviewed

Published in final edited form as:

Int J Radiat Biol. 2023 ; 99(9): 1332–1342. doi:10.1080/09553002.2023.2142984.

Radiation and CNS effects: summary of evidence from a recent symposium of the Radiation Research Society

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Disclosure statement

No potential conflict of interest was reported by the author(s). Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization (IARC/WHO), the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the IARC/WHO.

Disclosure statement

No potential conflict of interest was reported by the author(s). The content of this article is the sole responsibility of its authors and does not necessarily represent the views of NCRP, VUMC, MSKCC, DOE, NASA or the US Navy.

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Abstract

This article summarizes a Symposium on ‘Radiation risks of the central nervous system’ held virtually at the 67th Annual Meeting of the Radiation Research Society, 3–6 October 2021. Repeated low-dose radiation exposure over a certain period could lead to reduced neuronal proliferation, altered neurogenesis, neuroinflammation and various neurological complications, including psychological consequences, necessitating further research in these areas. Four speakers from radiation biology, genetics and epidemiology presented the latest data from their studies seeking insights into this important topic. This symposium highlighted new and important directions for further research on mental health disorders, neurodegenerative conditions and cognitive impairment. Future studies will examine risks of mental and behavioral disorders and neurodegenerative diseases following protracted radiation exposures to better understand risks of occupational exposures as well as provide insights into risks from exposures to galactic cosmic rays.

Keywords

CNS effects; radiation; neurodegenerative diseases; Parkinson’s disease; dementia; radiation risks

Introduction

A recent report of the National Council on Radiation Protection and Measurements (NCRP) examined radiation exposures in space and its potential for central nervous system effects (NCRP 2019). This report highlighted important concerns about future long-term missions outside the Earth’s orbit for exploration missions such as to Mars due to galactic cosmic ray (GCR) and solar particle exposure. Repeated low-dose radiation exposure over a certain period could lead to reduced neuronal proliferation, altered neurogenesis, neuroinflammation and various neurological complications, including psychological consequences (Narasimhamurthy et al. 2022). Animal studies of moderate-to-high dose exposures have shown that certain measure of cognitive impairment persist for relatively long periods after exposure to space radiation, conceivably by disrupting the integrity of neural circuits in the brain (Britten et al. 2021).

The potential for radiation-induced injury in the brain has initially been described for populations receiving radiation therapy (Turnquist et al. 2020). These studies provided information on the mechanisms of neurotoxicity and neurodegeneration following high-dose ionizing radiation exposure, but questions remain about how precisely radiation causes brain injury, factors which determine whether injury occurs, and potential preventative, treatment and mitigation strategies for patients at high risk or with symptoms of injury. A recent report summarizing the proceedings of the international workshop on non-cancer effects of low doses of IR organized by the Multidisciplinary European Low dose Initiative (MELODI) suggested that in animal models cognitive decline appears as a consequence of

damage to multiple neural cell types arising from decreased blood circulation (Pasqual et al. 2021). Several studies have shown that changes in functioning of glial and neuronal cells and neuronal connectivity, decreased hippocampal neurogenesis, and increased neuroinflammation are also related to cognitive decline (Britten et al. 2021).

In the past decade, epidemiological studies of other radiation-exposed populations (due to occupation, environmental or diagnostic radiation imaging exposures) have evaluated radiation effects on various non-cancer central nervous system (CNS) outcomes. These include a group of neurodegenerative diseases [Alzheimer's disease (AD), Parkinson's disease (PD), dementia (age-related and vascular), amyotrophic lateral sclerosis (ALS), Huntington's and Lewy body diseases, and others], and psychiatric disorders (mental and behavioral diseases). The scant number of epidemiological studies may be due to a large lag time between radiation exposure and the development of symptoms, making follow up difficult and necessitating extrapolation of low-dose effects from the high-dose studies. Further, until recently, neurological and behavioral disorders were not considered possible outcomes following low-level radiation exposures so 'no one was looking for them'. A recent systematic review of radiation risks of non-cancerous CNS diseases (including PD, AD, dementia, schizophrenia, and cerebrovascular diseases) concluded that the deleterious effects of low-to-moderate radiation exposures on CNS diseases could not be excluded but many questions remain (Lopes et al. 2022). The majority of surveyed studies examined cerebrovascular diseases. Due to the small number of studies which examined radiation risks separately for neurodegenerative diseases, researchers conducted a meta-analysis of PD only and reported a significantly increased excess relative risk (based on four studies in two cohorts, The Million Person Study, and Mayak Facility in Russia).

Summaries of the presentations

Several cohorts of occupationally exposed workers have assessed risks of death from mental disorders after exposures to external and internal radiation. A number of these studies reported increased mortality compared with national general population mortality rates, but very few assessed a radiation dose-response. The International Nuclear Workers Study (INWORKS) study is a pooled study of more than 308,000 nuclear workers from France, the United Kingdom, and the United States, who were monitored for low-LET external radiation and followed up for mortality (Hamra et al. 2016). Dr. Leraud presented the results of a recent analysis of INWORKS data with regards to mortality from mental and behavioral disorders and neurodegenerative diseases. Significantly increased risks of mortality from mental disorders, of which 53% were due to dementia, were estimated.

Over the past decade, The Million Person Study (MPS) evaluated the long-term health effects of radiation exposures from intake of radionuclides and after low-LET external radiation in various cohorts of U.S. workers and veterans (Boice, Cohen, Mumma, Ellis, 2022; Boice, Quinn, et al. 2022). This was the first large study to consistently evaluate the risk of cognitive dysfunction and dementia using the same dose estimation protocols and the same definition of outcomes. In particular, following publication of a study of Mayak workers in Russia (Azizova et al. 2020) which suggested a link with PD aflter exposure to low-LET radiation, seven MPS cohorts were examined for radiation risks of

mortality due to Parkinson's disease. In his presentation, Dr. Boice reported generally positive dose-response relationships for PD with radiation dose to the brain in all cohorts. Importantly, the MPS investigators are beginning to evaluate data for 600,000 workers on the incidence of PD obtained from a linkage to the Centers for Medicare & Medicaid Services (CMS) databases. This database has a nation-wide coverage starting in 1999 for information on health outcomes for those aged 65 years and older in the U.S.A. and provides a unique opportunity to examine risks of incident PD as well as a wide range of non-fatal neurocognitive disorders. MPS researchers also will assess cognitive impairment based on standardized test scores in ongoing and future studies.

Radiation-induced cognitive decline after receiving doses in both the low- and high- dose range is a focus of research due to its impact on survival, quality of life and safety of exposed populations. Cell culture and animal-based models are indispensable for gaining insights into cellular mechanisms that mediate cranial radiation-induced cognitive decline and could lead to development of prevention and mitigation strategies in the future (Fike et al. 2009; Feng et al. 2016; Duman et al. 2018). There is a body of evidence suggesting that cranial radiotherapy may reduce hippocampal neurogenesis, induce synaptic loss, activate microglia and trigger neuroinflammation processes, however molecular mechanisms are not fully understood (Feng et al. 2016; Hinkle et al. 2019; Markarian et al. 2021). In the current work led by Dr. O'Banion that was presented at the 2021 RRS conference, the authors showed an association between activated microglial phagocytosis, mediated through CR3 complement component, significant spine loss and cognitive impairment in male mice irradiated with 10 Gy gamma radiation, while female mice were resistant to radiation injury. Cognitive impairment was assessed through evaluation of performance of two tasks: novel object recognition and conditioned fear extinction. Since the link between radiation-induced microglia, synaptic loss and behavioral tasks appeared to be sex-specific, further studies on sex-specific differences are highly warranted.

In addition to concerns about terrestrial and medical radiation exposure, space radiation programs have accelerated research on neurocognitive effects after exposure to low doses of GCR, as astronauts are expected to receive doses of approximately 130 mGy per year during a space mission to Mars (Cucinotta 2014; Britten et al. 2021). The cumulative absorbed radiation dose for a round trip to Mars would be higher (closer to 0.5 Gy) (Cucinotta et al. 2014). Studies of ground-based rodent models showed that radiation exposure in a similar dose range can alter complex cognitive processes, including executive function (Kiffer et al. 2019; Britten et al. 2021). In the new study conducted by Drs. Britten and Stephenson that was presented at the symposium, the authors tested the ability of rats exposed to 100 mGy of GCR Simulation (GCRSim) or ^{4}He ions to perform high cognitive tasks during different cognitive task load (CTL) training stages. Results showed that rats exposed to GCR spectrum had reduced ability to perform in training tasks with a high cognitive task load and took longer to respond in switch trials compared with the sham rats. Since rodent studies are important for identification of cognitive processes that are highly sensitive to space radiation, efforts should be focused on development of specific exercises that help astronauts to train the vulnerable cognitive domains during the mission (Britten et al. 2021).

Discussion and future directions

This symposium highlighted a new and important direction for further research on mental health disorders, neurodegenerative conditions and cognitive impairment. One of the main limitations of the presented studies of nuclear workers is that most are based on mortality outcomes while morbidity might be more suitable. Many studies suggest substantial underreporting of these disorders on death certificates as well as misclassification (Lopes et al. 2022). In some countries, some neurodegenerative diseases are only listed as a contributing cause and not as the underlying cause of death. Both epidemiological presentations acknowledged these difficulties and suggested interesting ways of improving future studies such as relying more on incidence data. It is equally important to continue laboratory and animal studies to better understand the mechanism of radiation injury to the brain and its effects on cognition. Future studies should examine risks of mental disorders and neurodegenerative diseases from protracted radiation exposures to better understand risks of occupational exposures as well as project risks from exposures to GCR. Finally, as exemplified in our session, epidemiology and experimental work should be interfacing with each other as typified by the old Bench-Bedside-Bed analogies for clinical radiobiology. Such interactions can only be synergistic and the exchange of ideas and understanding will advance this complex and burgeoning field of neurological impairments following ionizing radiation exposure.

Extended abstracts of the presentations

This report includes extended abstracts of the four oral presentations at the symposium on ‘Radiation risks of the central nervous system’ from the 67th Annual Meeting of the Radiation Research Society, held virtually 3–6 October 2021: (1) Mental disorders and neurodegenerative diseases among radiation exposed workers in the INWORKS study; (2) synaptic loss and cognitive impairment after cranial irradiation in mouse models; (3) radiation, cognition, and Parkinson’s disease in the MPS study; and (4) role of low doses of space radiation in increased switch cost and loss of performance in high cognitive task loading situations in animal models.

Mental disorders and neurodegenerative diseases among radiation exposed workers

Klervi Leuraud and Julie Lopes

Introduction—Non-cancerous central nervous system (CNS) disorders form a large and complex group of diseases. The Institute for Health Metrics and Evaluation (Global Health Data Exchange 2022) estimates that in 2019, 970 million people suffered from a mental disorder and 2.7 billion people had neurological disorders. Recent epidemiological studies of nuclear workers have reported dose-risk relationships between occupational exposure to ionizing radiation (IR) and certain types of CNS diseases (Gillies et al. 2017; Azizova et al. 2020). If exposure to such levels of dose really affects the risk of CNS diseases, this could be of concern, considering the dramatic increase in the use of medical imaging procedures over the past decades and the resulting increase in global population exposure to

IR (Ruano-Ravina and Wakeford 2020). Recent findings on mental and behavioral disorders and neurodegenerative diseases in radiation workers are presented.

Mental disorders—Radiation-associated risk of mental disorders has been investigated in INWORKS, a mortality study of more than 308,000 nuclear workers from France, the United Kingdom, and the United States, monitored with individual badge-dosimeters with respect to their occupational exposure to IR (Gillies et al. 2017). Vital status and medical causes of death were obtained by linkage with national registries from 1943 to 2005 and 8.2 million person-years were accrued. The mean individual cumulative dose was 25.2 mSv. A linear excess relative-rate (ERR) model was fitted using Poisson regression methods. Mental disorders mortality showed a significantly elevated ERR per Sv equal to 1.30 (90% confidence internal (CI): 0.23–2.72; $p = .019$). The authors reported that 53% of the deaths were coded as dementia. As risk of dementia is known to increase with age, an extended follow-up of this cohort may provide useful information on any potential effect at low dose.

Of the other recent studies that have looked at the risk of mental diseases in radiation worker populations, none have reported a dose-response relationship. In a Czech cohort of 16,434 uranium miners (Kelly-Reif et al. 2019), an 88% excess mortality was observed for mental health in the cohort compared to national rates, while a 56% decrease in mortality was observed in the Eldorado cohort of 16,236 uranium workers in Canada, compared to national rates (Lane et al. 2010).

Mental health was also investigated in radiation medical workers. The mortality due to mental disorders in about 35,000 male radiologists was non significantly higher to that of 47,500 male psychiatrists [relative risk (RR) = 1.30; 95% IC: 0.60–2.80](Berrington de Gonzalez et al. 2016), while it was significantly lower in male physicians likely to have performed fluoroscopy-guided interventional procedures compared to the group of male psychiatrists (RR =0.55; 95% IC: 0.35–0.84) (Linet et al. 2017). Neuropsychological skills assessed by means of a battery of tests to evaluate language, memory, and logical reasoning dysfunctions were compared between 83 cardiologists, technicians, and nurses working in a cardiac catheterization unit, considered as exposed, and 83 non exposed medical workers (Marazziti et al. 2015). A significant reduction in memory abilities in interventional cardiology staff involving mainly verbal long-term memory and verbal fluency was reported. The authors noticed that these reduced skills suggest alterations of some left hemisphere brain structures that are particularly exposed to IR in interventional cardiology staff.

A series of articles observed higher prevalence of cognitive or psychiatric disorders in Ukrainian Chernobyl cleanup workers with highest radiation doses, after a series of neuropsychological tests have been performed. The authors found that the level of cognitive impairment increased as level of dose increased (Bazyka et al. 2015; Loganovsky et al. 2020). A limit of these studies is the small size of the group of workers. A study of Estonian clean-up workers compared the morbidity in a cohort of 3,700 workers to an unexposed population. Information on diseases was obtained through linkage with the mandatory universal health insurance system in Estonia. The authors did not observe any increase in morbidity for mental disorders in the worker population (Rahu et al. 2014).

Neurodegenerative diseases—Azizova et al. investigated the impact of chronic protracted occupational exposure on the risk of Parkinson's disease in 22,377 workers at the Mayak Facility in Russia (Azizova et al. 2020). Workers were followed-up from 1948 to 2013 with mandatory annual clinical checkups for every worker. The diagnosis of Parkinson's disease was based on a set of criteria defined by the UK Parkinson's disease Society brain bank. For each worker, annual doses due to external gamma rays and doses due to neutrons were available, as well as information on smoking and alcohol consumption and on a panel of medical conditions: BMI, hypertension, gout, gastric ulcer, head injuries, diabetes mellitus, that are known or suspected to have an impact on Parkinson's disease risk. The workers accrued more than 570,000 person-years and cumulated 460 mGy from gamma-rays to the brain in male, 360 mGy in female; 300 cases of Parkinson's disease were diagnosed, at ages more than 60 years in 92% of cases. A linear ERR model was fitted using Poisson regression methods. A significant dose-risk association was observed, with an ERR per Gy of 1.02 (95% CI: 0.59–1.63). Based on diagnosis of Parkinson's disease, detailed information on other medical conditions and individual dosimetry, this study provides interesting arguments in favor of a dose-response association between risk of Parkinson's disease and protracted exposure to IR during adulthood, at least for doses above 100 mGy.

Few other studies have specifically considered neurodegenerative diseases in radiation workers. Pinkerton et al. compared the mortality from neurodegenerative diseases in a cohort of flight attendants to that of the US general population. Cosmic radiation doses were not available (Pinkerton et al. 2016). The authors observed a statistically significant excess of mortality by amyotrophic lateral sclerosis but no difference for the mortality by Parkinson's disease. More than cosmic radiation, the authors suspect that this excess could be attributable to exposure to engine combustion products (Pinkerton et al. 2016).

Discussion—Studying CNS diseases is challenging. These diseases are under- and heterogeneously reported, which hampers a comprehensive analysis of the risks. Making a diagnosis of a mental impairment is not easy: there are multiple tests or scales for the assessment of mental disorders and cognitive impairment, which can explain that these disorders are heterogeneously reported. Some neurodegenerative diseases (as Alzheimer's disease and Parkinson's disease) are listed on many death certificates as a contributing cause and not as the underlying cause of death (Redelings et al. 2006). The study of morbidity is certainly to be preferred over mortality. From what can be observed in epidemiological studies, only very few studies report on dose-risk associations and inconsistent results are observed among studies. Regarding neurodegenerative diseases, it is not an easily distinguishable outcome as epidemiological studies often consider a larger group of diseases of the nervous system that includes peripheral nerve system, sometimes also eye and ear impairments. Another limitation is that men are predominantly present in the nuclear worker studies. But women seem to be more affected by certain diseases, as it is the case for Alzheimer's disease (Ferretti et al. 2018). The role of low dose IR received in adulthood in the impairment of CNS health is possible but still unclear. Given the heavy constraints when studying mental disorders and neurodegenerative diseases, the results should be considered cautiously. Our understanding of these diseases and the role IR may play in their onset

will not be possible without a better understanding of the mechanisms underlying their development.

Microglial activation and complement deposition contribute to synaptic loss and cognitive impairment after cranial irradiation

Joshua Hinkle, Tyler Pugeda, Thomas Delgado, John Olschowka, Jacqueline Williams, and M. Kerry O'Banion

ABSTRACT—Neuroinflammation and synaptic loss have been implicated in cognitive dysfunction seen after brain radiation exposure. Based on evidence that elements of the complement cascade are critical for synaptic pruning by microglia during development and are upregulated in neurodegenerative diseases and aging where synapse density is reduced, we previously demonstrated that deletion of complement receptor 3 (CR3), which is expressed on microglia, protected male mice from dendritic spine loss in the molecular layer of the hippocampus after radiation exposure. Using Thy1-eYFP mice with or without the CR3 receptor, we also found a clear correlation between microglial activation, spine loss and cognitive dysfunction 30 d after 10 Gy cranial irradiation, only in male mice, that is dependent on CR3 expression. Moreover, treatment with leukadherin-1 (LA1), which engages the CR3 receptor, prevents spine loss and cognitive dysfunction due to radiation exposure. To guide application of potential therapeutic interventions, we carried out time course analyses of synaptic density, microglial activation and complement deposition and found that these processes are initiated in the first few days following radiation exposure, suggesting a relatively acute response with long-lasting consequences.

Introduction—Animal models of CNS radiation injury have revealed reductions in synaptic connectivity and neural process complexity that are associated with cognitive impairment (Chakraborti et al. 2012; Parihar and Limoli 2013). Several studies using microglial depletion strategies have linked microglia to synaptic loss and behavioral changes after radiation exposure (Acharya et al. 2016; Feng et al. 2016; Krukowski et al. 2018). Over the past decade, microglia have been recognized as playing critical roles in synaptic pruning during development, as well as in aging and neurodegenerative disease (Stevens et al. 2007; Tremblay et al. 2010; Schafer et al. 2012; Shi et al. 2015; Hong et al. 2016). Mechanistically, interactions between microglia and synapses depend on components of the complement system, including complement components C1q and C3, as well as CR3 which is solely expressed on microglia in the CNS (Gomez-Arboledas et al. 2021). Based on these findings, we hypothesized that CNS irradiation induces enhanced microglial CR3-mediated phagocytosis that results in significant spine loss and is associated with cognitive impairment. We previously published evidence that CR3 was required for dendritic spine loss in the dentate gyrus molecular layer after 10 Gy cranial irradiation in male C57BL/6 mice (Hinkle et al. 2019). In the current study, we focused on hippocampal dependent behavior, microglial activation, and dendritic spine changes in irradiated mice using genetic and pharmacologic strategies to block CR3.

Methods—Three experiments were performed. In the first, male and female Thy1-YFP and Thy1-YFP::CR3 null mice, 8–10 weeks of age, were cranially irradiated with 10 Gy

gamma using a ^{137}Cs source as previously described (Hinkle et al. 2019). An equal number of sham irradiated mice were used (n = 10 for each group). Thirty days post-irradiation, mice were subject to a series of behavioral tests, followed by tissue collection to assess markers of microglial activation (iba-1, CD11b, CD68) and YFP-labeled synaptic density in the dentate gyrus molecular layer. A second set of male Thy1-YFP mice was treated with leukadherin-1 (LA1), a partial agonist of CR3, for 30 days, starting 3 days prior to 10 Gy cranial irradiation. Additional groups (n = 10) included irradiated mice treated with vehicle as well as LA1- and vehicle-treated sham irradiated mice. Behavioral testing and tissue analysis was identical to the first experiment. In the third study, groups of male C57BL/6 wild-type mice were cranially irradiated with 10 Gy and brain tissues were secured for histo-logical analysis 6 h, 24 h, 3 days, 7 days, 14 days and 30 days post-irradiation.

Results—We found a clear association between microglial activation, molecular layer synaptic spine loss, and deficits in two behavioral tasks (novel object recognition and conditioned fear extinction) in irradiated male mice, but not in female mice. Although evidence of microglial activation occurred in the CR3 knockout mice, there was no accompanying change in spine density or novel object recognition performance. Interestingly, mice with CR3 deletion did not show extinction to conditioned fear, regardless of radiation status, suggesting disruption of normal mechanisms associated with learning. In the second experiment, which was only performed in male mice, LA1 treatment abrogated radiation-induced spine loss and deficits in novel object recognition performance. Finally, the time course experiment revealed a peak of microglial activation at 7 days post-irradiation based on expression of CD68.

Discussion—Together these findings support our hypothesis that CR3 provides a mechanistic link between microglial activation, synaptic spine loss, and behavioral deficits following cranial irradiation. This is consistent with a report of induced complement expression and dependence of C1q for radiation-induced cognitive deficits (Markarian et al. 2021). Furthermore, it raises the possibility that strategies targeting complement-dependent phagocytosis or other aspects of microglial synapse pruning (e.g. microglial activation or synapse targeting) may provide approaches for preventing or mitigating CNS radiation late effects. In addition, our findings that female mice are resistant to CNS radiation injury in this model are consistent with observations by others (Krukowski et al. 2018; Parihar et al. 2020), and raise sex-differences as an important area for further investigation.

Radiation, cognition, and Parkinson’s disease

John D. Boice, Jr., Sarah S. Cohen, Michael T. Mumma, and Lawrence T. Dauer

ABSTRACT—The Million Person Study of Low-Dose Health Effects (MPS) is evaluating the risk of cognitive dysfunction and dementia following intakes of radionuclides and after low-LET external radiation in the workplace. A recent study of Mayak workers in Russia suggested a link with Parkinson’s disease following low-LET radiation. High-LET radiation from galactic cosmic ray simulations have reported the potential to accelerate the development of Alzheimer’s disease, dementia and anxiety disorders in experimental studies. To date, seven MPS cohorts have evaluated Parkinson’s disease at the level of

mortality among 515,857 workers and veterans. The excess relative risks (ERR) per 100 mGy dose to brain was estimated for nuclear power plant workers (NPP), industrial radiographers (IR), medical radiation workers (MRW), nuclear weapons test participants and former DOE workers at Mallinckrodt Chemical Works, Mound facility in Ohio, and Los Alamos National Laboratory. There was a general tendency for the risk of Parkinson's disease to increase with increasing estimates of radiation dose to brain. The pooled ERR per 100 mGy for the combined NPP + IR + MRW cohorts was 0.30 (95% CI 0.08, 0.56). Confirmation of these associations are being sought from ongoing studies of an additional 300,000 workers and from linkages within the Centers for Medicare & Medicaid Services (CMS) databases for incidence data on Parkinson's disease for 600,000 workers. Further, a wide range of nonfatal conditions related to dementia and depression are being identified, as are cognitive impairment scores among 600,000 cohort workers alive in 1999 when the CMS data systems became available.

Introduction—Parkinson's disease is a neurodegenerative disease second only to Alzheimer's in worldwide incidence (Bloem et al. 2021). Parkinson's occurs more frequently in men than in women and risk increases with age. The causes are uncertain but are likely to be multifactorial; genetics and environmental exposures have been associated with increased risks. Remarkably, cigarette smoking protects against Parkinson's disease (Mappin-Kasirer et al. 2020). Equally remarkable is the possibility that ionizing radiation might increase the risk of Parkinson's. This possibility originates from a Russian study of Mayak workers exposed to gamma radiation and reported to be at significant risk of Parkinson's disease (Azizova et al. 2020). High-LET radiation from galactic cosmic ray simulations has been associated with the potential to accelerate the development of Alzheimer's, dementia, and cognitive impairment in experimental studies (NCRP 2019; Britten et al. 2021; Boice 2022). Occupational workers within the Million Person Study of Low-Dose Health Effects (MPS) exposed to chronic low-dose radiation are being evaluated for Parkinson's disease and other forms of dementia (Boice, Quinn, et al. 2022).

Methods—The MPS has been ongoing for over 20 years and recently has focused on mortality from dementia, Alzheimer's, Parkinson's, motor neuron disease (e.g. ALS), depression and anxiety disorders (Boice, Cohen, Mumma, Ellis, 2022; Boice, Quinn, et al. 2022). Soon incidence data and measures of cognitive impairment will be available with linkage to Centers for Medicare & Medicaid Services (CMS) databases (Boice, Quinn, et al. 2022). To date, seven MPS cohorts have evaluated Parkinson's disease at the level of mortality among 515,857 workers and veterans. The excess relative risks (ERR) per 100 mGy dose to brain were computed using Cox regression models for 135,000 nuclear power plant (NPP) workers (Boice, Cohen, Mumma, Hagemeyer, et al. 2022), 124,000 industrial radiographers (IR) (Boice, Quinn, et al. 2022), 109,000 medical radiation workers (MRW) (Boice, Cohen, Mumma, Howard, et al. 2022), 114,000 atomic veterans (Boice, Cohen, Mumma, Chen, et al. 2022), and 2500 former DOE workers at Mallinckrodt Chemical Works (MCW) in Missouri (Golden et al. 2022), 5000 workers at Mound facility in Ohio (Boice et al. 2014), and 26,000 workers at Los Alamos National Laboratory (LANL) in New Mexico (Boice, Cohen, Mumma, Golden, et al. 2022; Table 1). A pooled analysis was conducted to estimate risk from the combined NPP, IR and MRW studies of 367,722

workers. The cohorts with intakes of high-LET radionuclides also received exposures to low-LET radiations.

Results—Among the 515,857 workers and veterans available for analysis, nearly 1,500 deaths from Parkinson's disease were evaluated. The ERR estimates at 100 mGy (95% CI) based on a linear model were 0.24 (−0.02, 0.50) for NPP workers, 0.24 (−0.02, 0.50) for IR, 0.17 (−0.20, 0.54) for MRW, 0.23 (−0.01, 0.54) for Mound workers (including other dementias), −0.22 (−0.90, 0.46) for atomic veterans, −0.06 (−0.018, 0.06) for Mallinckrodt workers (including other dementias), and 0.16 (−0.07, 0.40) for LANL workers. The pooled ERR per 100 mGy for the NPP+IR+MRW cohorts was 0.30 (95% CI 0.08, 0.56). A meta-analysis of NPP+IR+MRW+LANL+AVETS cohorts yielded an estimate of 0.19 (95% CI 0.05, 0.32). These estimates are comparable to the ERR per 100 mGy reported in the Mayak study of 0.10 (0.06, 0.16).

Discussion—There was consistent evidence that chronic occupational exposures increased the risk of Parkinson's disease in MPS cohorts. These unexpected findings, however, need to be confirmed in ongoing follow-up of these and other MPS cohorts (such as Rocky Flats, Hanford, Savanah River, Fernald, and Oak Ridge Laboratories: X-10, Y-12, K-25) (Boice, Cohen, Mumma, Ellis, 2022). Additional confirmation will come from linkages within the Centers for Medicare & Medicaid Services databases for incidence data on Parkinson's and other neurological diseases (Boice, Quinn, et al. 2022). Further, cognitive impairment scores among the 600,000 cohort workers alive in 1999, when the CMS data systems became available, will be evaluated for any associations with estimated dose to brain from low-LET and high-LET radiations.

In conclusion, Parkinson's disease is a complex neurodegenerative disease associated with dopamine deficiency and many environmental and genetic factors influence risk (Simon et al. 2020). Occupational studies have recently correlated ionizing radiation with increased incidence and mortality rates of Parkinson's disease. Mechanisms have yet to be elucidated but may include neuroinflammation, oxidative stress, mitochondrial dysfunction, altered autophagy, and impaired protein aggregation. Understanding the determinants of Parkinson's disease will remain an important area of future research.

Exposure to low doses of space radiation (SR) leads to increased switch cost and loss of performance in high cognitive task loading (CTL) situations

R. A. Britten and S. Stephenson

Introduction—The inability of pilots to perform tasking switching, termed 'cognitive lock-up', is a major cause of human errors involved with aviation accidents (Board 1973). Switching attention from one set of cognitive rules to another is a complex process that requires multiple brain regions to act in harmony (Yin et al. 2015). The behavioral outcome of task switching is a 'switch cost', manifested as a slower and/or more error prone response than when repeating or continuing the same task (Schneider and Logan 2009). Exposure to <25 cGy Space Radiation (SR) significantly impairs several executive functions (Britten

et al. 2021); given the disastrous consequences of cognitive lock-up the impact that SR exposure has on task switch performance was established in male Wistar rats.

Methods—Male Wistar rats that were regularly exercised were pre-screened for Attentional Set shifting performance as previously described (Britten et al. 2020). Rats that had high Attentional Set-shifting (ATSET) performance were irradiated with 10 cGy of 250 MeV/n He ions or the 6-ion GCRSim beam at Brookhaven National Laboratory at ~7 months of age. Three months later the rats were screened for performance in a newly developed rodent switch task, that is analogous to a warning light response test used to evaluate pilots' response times (Wilson et al. 2007).

Prior to performing in the switch task itself, the rats undergo several training steps. The initial habituation steps (H1–H4) train the rat to respond quickly to a single lit hole on the touchscreen to gain a food reward. The H4 has a much higher cognitive task load (CTL) than the previous H3 stage due to three modifications (number of 'reward' holes, response time and a punishment for an incorrect choice). Thereafter the rats are trained to hit an 'activating' light to start a trial, to select an appropriate green reward light when a target light appears on the left or right hand side of the touchscreen, and to repeat that process up to 8 times before gaining a food reward.

Results—The majority of the rats exposed to 10 cGy of He ions (56%) or the 6-ion GCRSim beam (64%) were unable to complete the H4 training stage. In contrast, <20% of shams were unable to complete this stage. To establish which of the modifications introduced in the H4 stage the SR-exposed rats were unable to resolve, rats that failed the H4 stage were presented with a compartmentalized H4 stage, where first the number of rewarded holes (3A), and then the response time (3B) was reduced, before being represented with the full H4 stage (aversive stimuli for an incorrect choice) again. Over 90% of the SR-exposed rats that previously failed the H4 stage were able to complete this incremental progression training.

Rats that passed the H4 training stage then underwent switch task testing. Approximately 15% of the SR-exposed rats failed to successfully complete this advanced training, in contrast none of the sham rats failed to complete switch task training.

Relative to the performance of sham rats in the switch task, the rats exposed to 10 cGy GCRsim had significantly slower response times in switch but not repeat trials. The GCR-exposed rats also had significantly ($p < .01$) higher switch response ratios (switch/repeat trial response time) and absolute switch costs (switch minus repeat trial response time) than either the sham or He-exposed rats. Rats exposed to GCRSim had an absolute switch cost of 700 ms.

Discussion—On the deep space mission to Mars, astronauts may need to make extremely complicated decisions, often rapidly, in order to ensure both their survival and the success of the mission. In situations where initial risk assessments identify multiple high-risk issues, the optimal strategy may be to resolve these issues 'simultaneously' by alternating attention between the tasks, i.e. task switching. This study has established that exposure to 10 cGy of

either GCRSim or 4He ions (which account for ~35% of the dose within ‘Local-Field’ GCR spectrum) significantly reduces the ability of rats to perform in the high CTL H4 training stage. Furthermore, GCR-exposed rats took 700 ms longer to respond in switch trials than did the shams. A 1000 ms increase in switch cost (from 1.5 to 2.5 s) in sleep-deprived pilots led to a doubling of error rates in cockpit simulations (Wilson et al. 2007). Should similar effects occur in humans exposed to SR, astronauts may underperform in high-pressure (emergency) situations or when resolving complex problems. Task switching performance may be inherently sensitive to radiation exposure, since performance in the Trail Making Task B (a task switching test), unlike many other cognitive tasks, is not spared by the use of intensely modulated proton therapy over that seen following whole brain irradiation (Kahalley et al. 2020).

Summary—This experiment is the first to establish that SR exposure impacts performance in a warning light selection type switch task. Our data suggest that SR exposure leads to a decreased ability to switch attention (higher switch cost) and a marked inability to perform in high CTL tasks. Should SR have the same impact in humans, the operational performance on astronauts traveling to Mars may thus be sub-optimal.

Acknowledgements

Boice et al. are grateful to the over 100 colleagues who have collaborated on the Million Person Study of Low-Level Health Effects, and to the funding partners who make their recent studies of cognition possible: NASA (80NSSC19M0161), DOE (DE-AU0000046) and US Navy (N00024-17-C-4322).

Funding

Britten and Stephenson would like to acknowledge NASA funding [NNX14AE73G]. Hinkle et al. acknowledge research support from NASA [NNX16AE07G and 80NSSC2K0542] and the Del Monte Institute for Neuroscience Pilot Grant Program.

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Ljubica Zupunski, PhD, MPH, is a postdoctoral scientist in the Environment and Lifestyle Epidemiology Branch, at the International Agency for Research on Cancer, Lyon, France. Dr. Zupunski is a molecular biologist and physiologist with experience in radiation protection, cancer risk assessment and radiation epidemiology. Her research activities are focused on the cancer risks in population highly exposed to radionuclides released after Chernobyl nuclear power plant accident. Dr. Zupunski is also working on the environmental exposures to uranium in the populations living in the proximity to mine tailings.

Klervi Leuraud, PhD, is an epidemiologist. She directs the Research Department on the Biological and Health Effects of Ionizing Radiation at the French Institute for Radiological Protection and Nuclear Safety (IRSN). Her research activities focus on the effects of occupational exposure to radiation in nuclear workers. She is participating in the international INWORKS study. Klervi Leuraud serves as an expert on the United Nations Scientific Committee on the Effects of Atomic Radiation.

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Richard A. Britten, PhD, is a Professor of Radiation Oncology at Eastern Virginia Medical School (EVMS), where he finally settled after working in the UK, the USA and Canada. His 30-year career in radiation biology, has been quite varied but the one consistent factor has been an emphasis on particle radiation [fast neutrons, protons, Galactic Cosmic Radiation (GCR)]. Professor. Britten is currently funded by NASA to determine the incidence and mechanistic basis of GCR-induced neurocognitive impairment, the interaction of sleep perturbation and GCR on neurocognitive performance, and is also part of the UC-Irvine NSCOR. His program has now started to investigate the breakdown of neural network functioning after exposure to radiation and chemotherapeutic agents, with a particular focus on pediatric cancer patients.

Samuel Stephenson, B.S.Ed., is a fourth-year medical student at Eastern Virginia Medical School (EVMS). He completed his undergrad at the University of Virginia and majored in kinesiology before beginning medical school. Mr. Stephenson has a passion for aerospace medicine and has worked with Professor Britten throughout his time at EVMS with an emphasis on switch task development and testing in response to Galactic Cosmic Radiation (GCR) and He radiation. Mr. Stephenson is pursuing his residency training in internal medicine with the goal of following that up with aerospace medicine training to become a flight surgeon.

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Table 1.

Radiation risk of death from Parkinson's disease among seven cohorts within the Million Person Study (Boice, Quinn, et al. 2022).

MPS cohort	No. workers	No. deaths Parkinson's	ERR per 100 mGy (95% CI)
Low-LET			
Nuclear Power Plant	135,193	140	0.24 (−0.02, 0.50)
Industrial radiographers	123,556	127	0.24 (−0.02, 0.50)
Medical radiation workers	109,019	87	0.17 (−0.20, 0.54)
Sum [NPP + IR + MRW]	[367,722]	[354]	[0.30 (0.08, 0.56)]
Atomic veterans	114,270	874	−0.22 (−0.90, 0.46)
High-LET			
Mallinckrodt (U)	2514	93[a]	−0.06 (−0.18, 0.06)[a]
Mound (Po)	4977	22[a]	0.23 (−0.01, 0.54)[a]
Los Alamos Natl Lab (Pu)	26,328	293	0.16 (−0.07, 0.40)
Total	515,857	1614	

[a]Combined dementia, Alzheimer's, Parkinson's, motor neuron disease (e.g. ALS).