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The psychological consequences of (perceived) ionizing radiation exposure: a review on its role in radiation-induced cognitive dysfunction

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ABSTRACT

Purpose: Exposure to ionizing radiation following environmental contamination (e.g., the Chernobyl and Fukushima nuclear accidents), radiotherapy and diagnostics, occupational roles and space travel has been identified as a possible risk-factor for cognitive dysfunction. The deleterious effects of high doses (≥ 1.0 Gy) on cognitive functioning are fairly well-understood, while the consequences of low (≤ 0.1 Gy) and moderate doses (0.1–1.0 Gy) have been receiving more research interest over the past decade. In addition to any impact of actual exposure on cognitive functioning, the persistent psychological stress arising from perceived exposure, particularly following nuclear accidents, may itself impact cognitive functioning. In this review we offer a novel interdisciplinary stance on the cognitive impact of radiation exposure, considering psychological and epidemiological observations of different exposure scenarios such as atomic bombings, nuclear accidents, occupational and medical exposures while accounting for differences in dose, rate of exposure and exposure type. The purpose is to address the question that perceived radiation exposure - even where the actual absorbed dose is 0.0 Gy above background dose - can result in psychological stress, which could in turn lead to cognitive dysfunction. In addition, we highlight the interplay between the mechanisms of perceived exposure (i.e., stress) and actual exposure (i.e., radiation-induced cellular damage), in the generation of radiation-induced cognitive dysfunction. In all, we offer a comprehensive and objective review addressing the potential for cognitive defects in the context of low- and moderate-dose IR exposures.

Conclusions: Overall the evidence shows prenatal exposure to low and moderate doses to be detrimental to brain development and subsequent cognitive functioning, however the evidence for adolescent and adult low- and moderate-dose exposure remains uncertain. The persistent psychological stress following accidental exposure to low-doses in adulthood may pose a greater threat to our cognitive functioning. Indeed, the psychological implications for instructed cohorts (e.g., astronauts and radiotherapy patients) is less clear and warrants further investigation. Nonetheless, the psychosocial consequences of low- and moderate-dose exposure must be carefully considered when evaluating radiation effects on cognitive functioning, and to avoid unnecessary harm when planning public health response strategies.

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1. Introduction

Cognitive functioning refers to mental abilities such as learning, reasoning, problem solving, decision making, and attention (Fisher et al. 2019). The maintenance of cognitive function is crucial to maintain function at all ages. For example, cognitive abilities have been identified as predictors of school performance in children (Welsh et al. 2010), work performance in adults (Salthouse 1994; Salthouse 2012), and for maintaining independent living (Willis et al. 2006; Jekel et al. 2015) and positive well-being in older adults (Llewellyn et al. 2008). Factors such as physical activity, education, occupational status, and cognitively stimulating activity can help preserve cognitive functioning (Sofi et al. 2011; Opdebeeck et al. 2016), while factors such as excessive

smoking (Anstey et al. 2007), alcohol consumption (Anstey et al. 2009), and certain genes such as the apolipoprotein E $\epsilon 4$ allele (Beydoun et al. 2012) have been associated with cognitive dysfunction.

Ionizing radiation (IR) has also been identified as a potential risk factor for cognitive dysfunction, in individuals exposed through medical diagnostics/therapy (e.g., cranial irradiation; Greene-Schloesser and Robbins 2012), as a consequence of nuclear disasters such as Chernobyl (Bromet et al. 2011), or during their occupation, for instance nuclear workers or astronauts (Parihar et al. 2015; Limoli 2017). The consequences of high radiation doses (≥ 1.0 Gy) on the brain are fairly well understood, but the effects of moderate (0.1–1.0 Gy) and low doses (≤ 0.1 Gy) on the brain have not been explored as extensively. Any cognitive defects may be

observed via functional (e.g., cognitive scores, school performance) and clinical outcomes (e.g., dementia diagnosis). For example, exposure during prenatal development can lead to morphological anomalies in the brain while exposure in adults can lead to inflammatory disturbances (in cardiovascular and central nervous system; CNS), both of which may be related to cognitive dysfunction. In addition, perceived radiation exposure (i.e., believing or knowing that you have been exposed) is often linked to psychological stress, particularly relating to the anxiety of potential health consequences in both themselves and in their descendants (Fukasawa et al. 2017). Such psychological stress may itself lead to cognitive dysfunction. In this narrative review, we address the question that perceived radiation exposure – even where the actual absorbed dose is 0.0 Gy above background dose – can result in psychological stress, which could in turn lead to cognitive dysfunction. We frame this question in the context of radiation-induced cellular damage and other systemic disturbances, which were previously linked to cognitive defects. In all, we offer a comprehensive and objective review addressing the potential for cognitive defects in the context of low- and moderate-dose IR exposures.

To address the question, a literature search was conducted using PubMed, PsycInfo and PsycArticles databases. Examples of search terms covered ‘radiation anxiety’, ‘radiation psychological stress’, ‘radiation and cognitive functioning’, ‘radiation and cognitive impairment’, ‘neuroinflammation’, ‘radiation and vascular effects’, and ‘psychological stress and cognitive functioning’. Only peer-reviewed articles available in English were chosen.

2. Psychological impact of perceived exposure

Perceived radiation exposure is often described in the context of excessive psychological stress (Figure 1, ‘perceived exposure’). For example, the impact on mental health is argued to be the largest public health consequence following the Chernobyl disaster (Bennett et al. 2006; International Atomic Energy Agency 2006; Havenaar et al. 2016) with reports of increased levels of anxiety and depression irrespective of the dose received (Ginzburg 1993; Pastel 2002; Danzer and Danzer 2016). Other groups such as American nuclear test-veterans have reported anxieties about adverse health effects in themselves and their descendants (Murphy et al. 1990), and may experience changes in identity, worldview, and lifestyle (Vyner 1983). The term *radiophobia* has been used to denote the fear of radiation exposure following Chernobyl (Pastel 2002). Phobias are an excessive or unreasonable persistent fear regarding an object or situation (American Psychiatric Association 2013). However, in the absence of dosimetry it is difficult to assess whether or not an individual’s fear of radiation is unreasonable or excessive (Pastel 2002). Following the Fukushima disaster, where the psycho-social impact was also reported to be significant (Kamiya et al. 2015) despite no deaths being directly caused by acute radiation exposure (Steinhauser et al. 2014), a new term was introduced. *Radiation-anxiety* is defined as the negative cognition regarding the potential adverse health effects following radiation exposure (Fukasawa et al. 2017). It is also associated with problems such as perceived stigma and discrimination (Becker 1997; Ben-Ezra et al. 2015; Fukasawa et al. 2017).

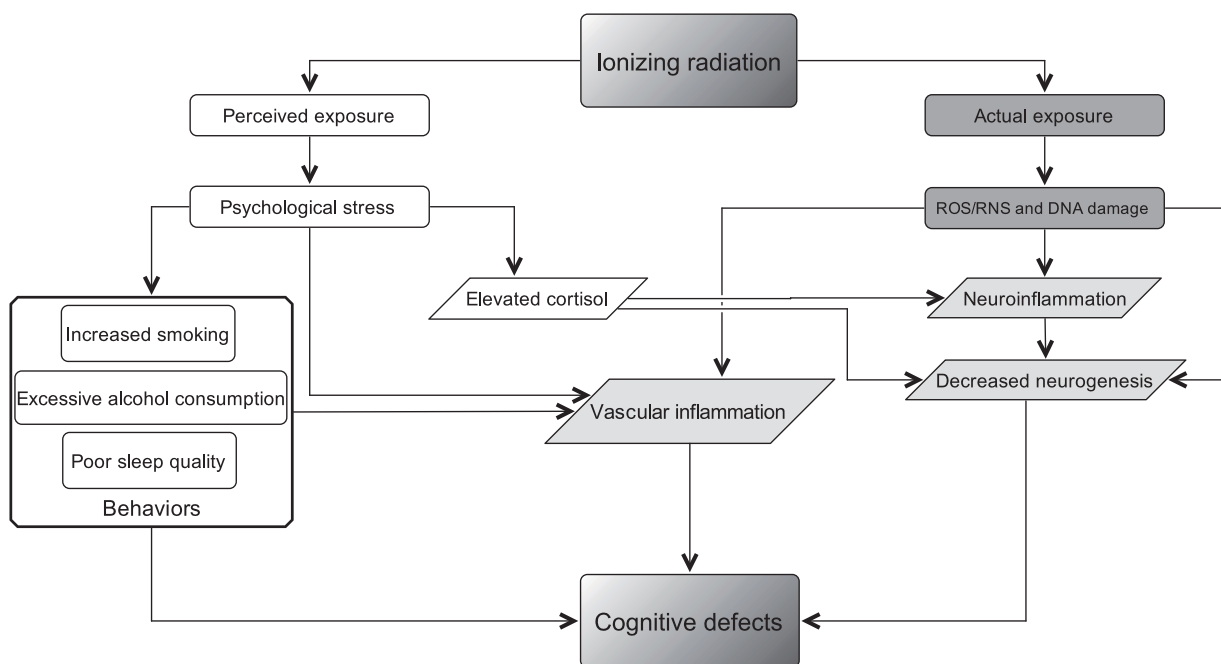


Figure 1. Ionizing radiation (IR) may cause cognitive defects via two broad mechanisms, stemming from perceived and actual exposure. First concerning actual exposure effects (dark gray boxes) observed at high doses (>1.0 Gy) and potentially moderate (0.1–1.0 Gy) and low doses (<0.1 Gy), and second concerning psychological stress effects (white boxes) following perceived exposure at any dose level (≥ 0.0 Gy). Both actual IR effects and psychological stress effects on cognitive function share common mediators such as vascular inflammation, neuroinflammation, and decreased neurogenesis (shown in light gray boxes). Also shown are the mediators of cognitive defects specific to psychological stress, such as elevated cortisol and health-risk behaviors (shown in white boxes). These stress-specific mediators may further exacerbate any possible cognitive defects caused by actual IR exposure.

Most non-single item measures of radiation-anxiety are based on Slovic's model of risk perception (Takebayashi et al. 2017), which posits two psychological dimensions: *dread risk* and *unknown risk*. In the context of radiation exposure, dread risk typically refers to the negative health effects on the individual and on future generations. Unknown risk refers to the possibility that the true health consequences of exposure are not understood (Slovic 1987). For technological risks (i.e., man-made), negative risk perception has been associated with stress and anxiety (Lima 2004), and may cause greater distress than that observed for natural risks due to scientific uncertainty and the perception of 'interfering with nature' (Sjöberg 2000; Lima 2004). This uncertainty is a key component of the psychological impact (Danzer and Danzer 2016). The dose received and whether health consequences will occur is difficult for the individual to ascertain, and those exposed to subclinical doses e.g., due to an accident, could interpret the introduction of radioprotective measures as a signal for serious harm. One notable example is the increased detection of thyroid cancer in children following the Fukushima nuclear disaster, which was erroneously attributed to radiation exposure, despite effective thyroid doses in children being well below 0.1 Sv (Tokonami et al. 2012; Yamashita et al. 2018). Even though the introduction of radioprotective actions intended to minimize harm in low-dose scenarios, it could bring unwarranted psychological consequences and pose greater harm than any direct effects brought by low-dose exposure (Thomas and Symonds 2016; Midorikawa et al. 2017). Furthermore, the psychological consequences regarding adverse effects may last a lifetime. For example, in an aged cohort that had lived in the vicinity of the A-bomb explosion in uncontaminated suburbs in Nagasaki, poorer mental health correlated with anxiety about the radiological hazard was observed (Kim et al. 2011), indicating that the psychological effects can persist over a lifetime. One possible explanation for this is that 'worry' (the core cognitive feature of anxiety) could be a mental problem-solving mechanism that enables the individual to prepare for a future outcome involving possible negative consequences (Tallis and Eysenck 1994; Brosschot et al. 2006). One factor that might impact on this process is increased age. For example, if one is nearing end of life then the future may not appear as uncertain, but their descendants' future remains uncertain meaning the worry may be redirected to the descendent. Supporting this, evidence shows that older adults tend to report worrying more about the health and welfare of loved ones (Gonçalves and Byrne 2013). Furthermore, older adults were more concerned about the effects of radiation exposure on future generations following Fukushima, while those of reproductive age (15–49) were more concerned about the delayed health effects in themselves (Suzuki et al. 2015).

Before examining how psychological stress following perceived radiation exposure may impact cognitive functioning, it is important to summarize what is currently known about the effects of low and moderate doses of IR on cognitive functioning (Figure 1, 'actual exposure'). For the purpose of this review, we focus on observations from human studies and organize literature into prenatal, childhood, and adult exposure.

3. Cognitive functioning and IR

3.1. Observations from human studies

It is generally accepted that the developing prenatal brain is more susceptible to radiation exposure as compared to the adult brain (Hladik and Tapio 2016), with detrimental effects being observed not just with high but after moderate and low doses as well (Yang et al. 2017). The first studies examining moderate doses in this field focused on Japanese survivors of the atomic bombings in Hiroshima and Nagasaki (Plummer 1952; Yamazaki et al. 1954; Otake and Schull 1998). Gamma and neutron exposure during the first and second trimester significantly increased the risk for morphological birth defects such as microcephaly (a reduced brain size) and functional cognitive defects when the mother was within 1200 m from the epicenter (fetal brain dose approximately 0.356–0.851 Gy; Chen 2012).

More studies exploring the health consequences of low-dose prenatal exposure to fallout from the Chernobyl nuclear accident showed reduced school test results (average Cs-137 deposition in most contaminated area = 44.1 kBq/m²; Almond et al. 2009) and lower verbal intelligence quotient (IQ) scores (mean external dose for exposed areas = 0.935 mSv; Heiervang et al. 2010) in children born in contaminated areas of Sweden and Norway, respectively. Such studies however may be at risk of misclassification due to comparisons being made between areas of low exposure levels, which is especially true for Heiervang et al. (2010) considering the small sample size (Pasqual et al. 2020). Other research has shown reduced mean intelligence quotient (IQ) scores between prenatally exposed and control groups but no significant correlation between IQ and individual thyroid doses (estimated mean dose = 0.4 Gy; Kolominsky et al. 1999). The impact on IQ detriments observed by Kolominsky et al. (1999) could possibly be explained partly by unfavorable psychological and sociocultural factors associated with relocation. Regarding individuals exposed during childhood due to nuclear accidents, no differences in attention, memory, and school performance were observed in children aged between 10 and 12 years, who were in utero to age 15 months at the time of the accident (effective dose approximately 0.033 Sv), as compared to unexposed non-evacuees (Litcher et al. 2000). A follow up study also did not identify any detriment at 19 years of age in individuals exposed in utero to age 15 months (Taormina et al. 2008). Similarly, other studies observed no effect of early childhood low-dose exposure (proxy estimation by residence location at time of accident; in utero and up to 4 years of age) on adolescent cognitive functioning (Joseph et al. 2004).

There is some evidence examining low and moderate doses from medical procedures during childhood. For example, a negative relationship between dose and learning ability and logical reasoning was observed in men when tested at 18 years of age, who received radiotherapy (included beta, gamma, and x-ray irradiation) for cutaneous hemangioma before the age of 18 months (median estimated dose to brain = 0.02 Gy, range = 0–2.8 Gy; Hall et al. 2004). For those exposed later in childhood, recent observations in

those exposed to low-dose computed tomography scans (total dose between 0.023 and 0.146 Gy based on 56% of participants) between the age of 6 to 16 suggest no difference in later cognitive functions (Salonen et al. 2018). However, this remains to be verified in larger, more statistically powerful studies (Pasqual et al. 2020). Overall, the strength of the epidemiological evidence for cognitive outcomes when exposed to low or moderate doses during childhood and prenatal development is limited, and indeed there are methodological concerns with some studies (for in-depth review and evaluation see Pasqual et al. 2020).

Although the adult brain is considered more resilient in comparison to the developing brain, recent evidence from cranial radiotherapy patients highlights the impact of high-dose exposure on brain morphology and network functionality/connectivity (Ma et al. 2017; Jacob et al. 2018; Qiu et al. 2018; Cramer et al. 2019; Huang et al. 2019). Further, there is growing evidence that exposure of the adult brain to moderate doses may be detrimental to cognitive functioning. Following the Chernobyl nuclear accident, Gamache et al. (2005) observed poorer cognitive functioning in clean-up workers, as compared to foresters and agricultural workers over a 4 year period, with each group receiving mean doses of 0.63, 0.13 and 0.09 Gy, respectively. Furthermore, in a cohort working on the Chernobyl 'Shelter Object' project (0–0.0567 Sv total dose from external and internal sources), an increase in verbal memory deficits were observed compared to before the project (Loganovsky et al. 2015). Other studies observed no significant difference in verbal memory between clean-up workers exposed to greater than 0.5 Sv and clean-up workers exposed to less than 0.02 Sv, but observed reduced brief global cognitive scores in the former group (Bazyka et al. 2015). Such studies (Loganovsky et al. 2015; Bazyka et al. 2015) should be treated cautiously if interpreting any effect to radiation dose, due to limited control for other variables. Indeed, Bazyka et al. (2015) observed higher rates of stress-related disorders in the most exposed clean-up workers, therefore any observed association between dose and cognitive function could be attributed to psychological stress rather than to radiation itself.

Another source of chronic low- and moderate-dose exposure is in space (Limoli 2017; Cucinotta and Cacao 2019), where heavy ions are the major contributors to the effective radiation dose. The recent NASA twins study observed reductions in cognitive efficiency persisting for up to 6 months post-flight in the flight subject (physical dosimeter = 0.07618 Gy, effective dose = 0.146 Sv) compared to the ground subject (Garrett-Bakelman et al. 2019) and there is emerging evidence from animal studies that support this (see later section, Britten et al. 2012; Lonart et al. 2012; Parihar et al. 2016; Parihar et al. 2018). Indeed, Garrett-Bakelman et al. (2019) acknowledge that, aside from direct radiation effects, the stress of returning back to earth may also account for these cognitive decrements. Cosmic radiation is comprised of various radiation types, including alpha, beta, gamma radiation, and heavy charged particles termed high-charge and high-energy (HZE) ions. The latter cause considerably more damage to cells and tissue as

compared to particles of lower mass (Limoli 2017). Such differences in radiation quality and biological effectiveness are important to consider when comparing cognitive outcome findings from different exposure scenarios, limiting the value of any direct comparison between, for example, space and terrestrial studies discussing similar absorbed doses, as the effective doses will likely differ greatly. Indeed, radiation quality and dose-rate may also be important when evaluating the contrasting findings seen in the A-bomb survivor studies in this regard.

Such A-bomb survivor studies provide insight into the long-term effects of IR exposure on cognitive functioning. For example, no association between radiation dose and vascular dementia or Alzheimer's disease in Hiroshima survivors born before September 1932 has been observed (Yamada et al. 2003). Additionally, a longitudinal study on Hiroshima survivors exposed to ≤ 4.0 Gy of radiation at or after adolescence, indicated that neither cognitive functioning or cognitive decline was associated with radiation dose (Yamada et al. 2016). Similarly, no difference in general cognitive functioning in Nagasaki A-bomb survivors was reported (Kinoshita et al. 2019), but indeed the sample size is small and a more extensive battery of cognitive tests is required. Overall, studies with humans suggest the adult brain is susceptible to moderate absorbed dose cosmic radiation, but research is conflicted whether moderate and low absorbed doses of photon radiation impacts cognitive functioning (e.g., radiotherapy). Exposure to alpha and beta radiation may occur following nuclear incidents. Given the relatively densely ionizing nature of alpha and beta radiation, these may have different effects on cognitive function compared to photon irradiation. Accordingly, a significant challenge in evaluating the impact of widespread exposures (e.g., A-bomb, Chernobyl) relates to determining the types of radiation and dose rates. Further study is required to examine effects relating to dose, various dose-rates and type of radiation and whether these potential effects persist over a lifetime.

3.2. Observations from animal studies

It is acknowledged that the epidemiological studies noted above are generally opportunistic, therefore some cohort designs are not always ideal. To further examine the impact of low- and moderate-dose exposure on cognitive functioning, a series of animal studies have highlighted a link between radiation exposure and cognitive defects, supporting the previously discussed findings in exposed human populations (summarized in Table 1). Prenatal exposure in rodents is primarily characterized by gross morphological defects of the brain, more subtle hippocampal anomalies and cognitive defects in later life (Gao et al. 2002; Verreet et al. 2015; Kokošová et al. 2015; Ganapathi and Manda 2017; Craenen et al. 2018). Similar observations on behavior in adulthood were made following neonatal exposure (Eriksson et al. 2016). A plausible explanation for the major structural defects is the highly dynamic character of the brain during prenatal and neonatal life, as it undergoes major

Table 1. Summary of animal data in order of age at exposure (prenatal to adult) and organized into radiation type and dose level.

Irradiated animal	Lowest dose at which effect was seen	Dose rate	Age at exposure	Key study outcomes in adult animals	Reference
Female mice (C57BL/6 J)	0.071 Gy internal beta particles	See paper for details	Prenatal (E12.5)	Hippocampal cellular anomalies and behavioral deficits	Gao et al. (2002)
Female mice (C57BL/6 J)	0.2 Gy gamma-rays	1.465 Gy/min	Prenatal (E5.5)	Abnormal hippocampal neurogenesis and behavior	Ganapathi and Manda (2017)
Female mice (C57BL/6 J)	0.5 Gy X-rays	0.375 Gy/min	Prenatal (E7.5)	Structural brain defects	Craenen et al. (2018)
Female mice (C57BL/6 J)	1.0 Gy X-rays	0.35 Gy/min	Prenatal (E11)	Cognitive dysfunction and structural brain defects	Verreet et al. (2015)
Female rats (Wistar)	1.0 Gy gamma-rays	Not stated	Prenatal (E16)	Behavioral and cognitive defects, no observed cellular anomalies	Tomášová et al. (2012)
Female rats (Wistar)	1.0 Gy gamma-rays	Not stated	Prenatal (E17)	Hippocampal cellular anomalies and cognitive deficits	Kokošová et al. (2015)
Male and female mice (C57BL/6 J and NMRI)	0.5 Gy gamma-rays	0.02 Gy/min	Neonatal (PND 3 or 10)	Behavioral changes	Eriksson et al. (2016)
Male and female mice (BALB/c)	2.0 Gy X-rays (acute or fractionated)	1.2 Gy/min or 1.0 Gy/min	Adolescent	Cellular anomalies but no cognitive deficit	Peng et al. (2019)
Male mice (C57BL/6 J)	0.05 Gy of ^4He (400 MeV/n)	0.05 Gy/min	Adult	Hippocampal and cortical circuit-level functional and morphological anomalies, and behavioral defects	Parihar et al. (2018)
Male rats (Wistar)	0.2 Gy of ^{56}Fe (1 GeV/u)	0.5 Gy/min	Adult	Cognitive dysfunction	Lonart et al. (2012)
Male rats (Wistar)	0.2 Gy of ^{56}Fe (1 GeV/u)	0.5 Gy/min	Adult	Cognitive dysfunction	Britten et al. (2012)
Male mice (C57BL/6 J), male and female mice (Nestin-GFP)	0.2 Gy of ^{28}Si (300 MeV/n)	1.0 Gy/min	Adult	Short-term cellular anomalies and cognitive defects	Whoolery et al. (2017)
Male mice (C57BL/6 J)	0.3 Gy ^{56}Fe (1 GeV/n)	See paper for details	Adult	Cellular anomalies	Sweet et al. (2016)
Transgenic mice (Tg(Thy1-EGFP) MJrsJ) and rats (Wistar)	0.3 Gy of ^{16}O or ^{48}Ti (600 MeV/n)	0.05–0.25 Gy/min	Adult	Various neuro-morphological defects, neuroinflammation and behavioral defects	Parihar et al. (2016)
Male mice (C57BL/6)	Combined 0.5 Gy ^1H and 0.1 Gy ^{16}O	0.18–0.19 Gy/min (^1H) and 0.18–0.33 Gy/min (^{16}O)	Adult	Molecular, cellular, and behavioral anomalies	Kiffer et al. (2018)
Male and female mice (APP/PS1)	1.0 Gy ^{56}Fe (1 GeV/u)	0.1–1 Gy/min	Adult	Cognitive defects and accumulation of beta-amyloid isoforms	Cherry et al. (2012)
Mice	0.1 Gy gamma-rays	0.64 Gy/min	Adult	Transcriptional changes similar to the ageing human brain / Alzheimer's disease	Lowe et al. (2009)
Female ApoE-deficient mice (C57BL/6)	0.3 Gy gamma-rays	0.001 Gy/day	Adult	Cellular and molecular signaling alterations	Kempf et al. (2016)
Male rats (Sprague Dawley)	0.3 Gy (photon; type not stated)	Not stated	PND 21, or 50, or 70	Age-associated dose-dependent cellular and behavioral anomalies	Achanta et al. (2009)
Mice (Kunming)	0.3 Gy X-rays	Not stated	Adult	Increased neurogenesis and behavioral performance	Wei et al. (2012)
Male and female mice (C57/BL6)	0.5 Gy X-rays	0.05 Gy/day	Adult	Molecular and cellular changes, decreased cell proliferation	Silasi et al. (2004)
Male and female mice (Nestin-CFP)	Combined 0.34 Gy neutron and 0.36 Gy gamma-rays	See paper for details	Adult	Cellular anomalies, no cognitive defect	Mineyeva et al. (2019)

developmental processes. Of note, most recent studies have focused on the teratogenic impact of low-LET exposure, leaving the health effects of prenatal exposure to high-LET exposures largely unexplored. There is relatively little

research examining low-dose photon radiation on adult cognitive functioning, but cellular anomalies such as decreased neurogenesis (Figure 1, 'decreased neurogenesis') and cell proliferation have been observed in relation to moderate-

dose photon irradiation (Silasi et al. 2004), although other data exists suggesting no detrimental effect of moderate doses of photons on neurogenesis (Achanta et al. 2009; Wei et al. 2012; Kempf et al. 2016; Sweet et al. 2016). Indeed a number of studies also report no association between cognitive deficits and impaired neurogenesis following moderate and high-dose exposures (Tomášová et al. 2012; Peng et al. 2019; Mineyeva et al. 2019). By contrast, there are a wealth of studies examining cognitive effects following high-LET exposure in adulthood. Such moderate-dose cosmic irradiation of the adult brain does appear to elicit behavioral changes (Britten et al. 2012; Lonart et al. 2012; Whoolery et al. 2017; Kiffer et al. 2018) and more subtle (cellular) anomalies at the hippocampal and cortical level (Lowe et al. 2009; Cherry et al. 2012; Parihar et al. 2016; Sweet et al. 2016; Parihar et al. 2018).

Most of these experimental studies however rely on data from external exposures. For internal exposures, radionuclides have the potential to accumulate in certain brain areas by crossing the blood-brain barrier (Fitsanakis et al. 2006) or via the olfactory nerve following intranasal exposure (Ibanez et al. 2014). Alpha-emitting radioisotopes are more effective in inducing damage than X- or gamma-rays (Brugge and Buchner 2011), and have been observed to lead to poorer spatial working memory in rats (Houpert et al. 2005; Houpert et al. 2007). Separately, repeated exposure to depleted Uranium (which is relatively non-radiotoxic) has been associated with poorer spatial working memory (Monleau et al. 2005). This latter study also raises important considerations especially in the context of low-dose exposure whereby the combined effect of radiation and non-radiological chemicals may be relevant for adverse effect. For example, although low-moderate-dose gamma irradiation (0.05–0.2 Gy) of postnatal mice (day 10) does not elicit behavioral defects, the combined exposure with ketamine (7.5 mg kg⁻¹) severely impaired learning and memory (Buratovic et al. 2018). As such, it is important to further understand to what extent neurocognitive effects are attributable to low-dose/rate irradiation or if a synergistic effect exists with non-radiation exposures. This mixed exposure phenomena may also extend to psychological stress, which has already been considered in other areas of biology (Feng et al. 2012; Katsube et al. 2017), and will become increasingly important to consider in the evaluation of mixed low-dose exposure cognitive effects. The psychological impact has also been recently considered in the evaluation of low-dose IR epidemiological studies (Wang et al. 2016; Vaiserman et al. 2018). Drawing on this, it could be hypothesized that the potential relationship between low-/moderate-dose IR and cognitive functioning observed in epidemiological data could be impacted by the psychological stress of perceived exposure.

4. Role of psychological stress in radiation-induced cognitive dysfunction

It is known that psychological stress (e.g., anxiety) can cause short-term cognitive dysfunction (Scott et al. 2015) perhaps

due to cognitive interference depleting attention resources (Stawski et al. 2006; Eysenck et al. 2007). Further, observational studies show that chronic psychological stress over time may also affect cognitive functioning. Although findings have not always been consistent (de Bruijn et al. 2014), it is generally accepted that poorer cognitive functioning and accelerated cognitive decline in older adults is associated with greater levels of anxiety or stress (Sinoff and Werner 2003; Aggarwal et al. 2014; Munoz et al. 2015; Gulpers et al. 2019), and self-reported worry symptoms (Pietrzak et al. 2012; de Vito et al. 2019). Anxiety may also be a risk factor for dementia incidence (Petkus et al. 2016) and progression in those with mild cognitive impairment (Li and Li 2018). Accordingly, psychological stress is an important risk factor for poorer cognitive functioning in old age. Although there is currently no research examining the relationship between cognitive functioning and psychological stress specifically relating to radiation exposure, there is evidence suggesting that temporary displacement (Ishiki et al. 2016) and loss of housing (Hikichi et al. 2017) is associated with risk of cognitive impairment in older adults affected by Great East Japan Earthquake and Tsunami. Additionally, although more research is required with larger cohorts, recent evidence demonstrates the impact of stress due to other natural disasters on cognitive functioning. For example, natural disaster exposure has been associated with cognitive functioning in adults (Bell et al. 2019; Walling et al. 2020), but such decrements can recover with time (Cherry et al. 2011). Interestingly, prenatal maternal stress following natural disasters has been associated with toddler cognitive functioning (Laplante et al. 2018).

The possible relationship between the psychological impact arising from perceived exposure and cognition could be explained, at least in part, by cortisol (Figure 1, 'elevated cortisol'). Cortisol is a glucocorticoid hormone and functions to regulate numerous bodily processes with levels known to increase during periods of stress (Staufenbiel et al. 2013). Following Chernobyl, elevated cortisol levels were reported in some (Souchkevitch and Lyasko 1997) but not all (Goncharov et al. 1998) studies on clean-up workers, while elevated cortisol levels and self-reported stress symptoms were reported in Three Mile Island residents (Schaeffer and Baum 1984). The biological basis for the possible association with cognition is that elevated corticosterone decreases the expression of brain-derived neurotrophic factor (Smith et al. 1995; Li et al. 2008; Makhathini et al. 2017) which is important for neurogenesis (Figure 1, 'decreased neurogenesis') and which has been associated with a decrease in hippocampal volume (Erickson et al. 2010), cognitive functioning (Shimada et al. 2014; Siuda et al. 2017), and cognitive decline (Buchman et al. 2016). Indeed, elevated cortisol levels accompanied with decreased cognitive functioning have also been observed in older adults born in contaminated areas around the Mayak site (Burtovaya et al. 2016), which could be partly attributed to (maternal) psychological stress. Experimental work showing that persistent stress in adult mice is associated with impaired spatial

memory 6 to 7 months after cessation of stress (Wheelan et al. 2018) and likely due to glucocorticoid activity supports this.

Furthermore, it is generally accepted that cardiovascular risk-factors (induced by vascular inflammation; Wirtz and von Känel 2017) can be resultant of psychological stress (Figure 1, 'vascular inflammation'). For example, anxiety has been associated with high blood pressure (see Tully et al. 2013 for review), which could be attributed to the stress-induced increased secretion of pro-inflammatory cytokines such interleukins (e.g., IL-6), interferons, and tumor necrosis factors (Hänsel et al. 2010). In the context of radiological incidents, increased psychological stress and systolic blood pressure has been observed in both exposed and nearby 'potentially-exposed' individuals three and a half years following the Goiânia accident (Collins and de Carvalho 1993). Two years following the Fukushima nuclear accident, increases in systolic blood pressure was also observed in both evacuated male residents and non-evacuated male and female residents compared to before the disaster (Ohira et al. 2016); observations that could be attributable to psychological stress. A higher systolic blood pressure and an increase in (albeit non-significant) anxiety symptoms were also observed in Three Mile Island residents (Davison et al. 1991). The role of hypertension in explaining a potential link between psychological stress and cognitive function (Figure 1, 'vascular inflammation') requires further examination, given that high blood pressure is associated with white matter lesions (Verhaaren et al. 2013), decreased cognitive functioning and accelerated cognitive decline later in life (Kilander et al. 1998; Knopman et al. 2001; Elias et al. 2003; Yamada et al. 2003; Emdin et al. 2016; Rouch et al. 2019). Although this may not be valid in the oldest-old (Richmond et al. 2011; Gottesman et al. 2014; Szewiczek et al. 2015; Corrada et al. 2017).

Behaviors associated with psychological stress such as cigarette smoking (Patten and Liu 2007; Phillips et al. 2009; McKee et al. 2011; Fluharty et al. 2017), excessive alcohol consumption (Keyes et al. 2012), and decreased sleep quality (Van Reeth et al. 2000) may also impact cognitive functioning (Figure 1, 'behaviors'). Psychological distress was observed to be a risk-factor for smoking initiation amongst Fukushima evacuation area residents (Nakano et al. 2018), while research elsewhere observed no association in exposed residents near the Semipalatinsk nuclear test-site, despite an increase in anxiety and somatic distress (Semenova et al. 2019). We are not aware of studies which have examined associations between cigarette smoking and cognitive functioning in populations exposed to IR, however it is known that cigarette smoking is associated with elevated levels of inflammatory markers (Levitzky et al. 2008; Khanna et al. 2013; McEvoy et al. 2015) and hypertension (Bowman et al. 2007; Halperin et al. 2008) which has been linked to dementia and cognitive decline (Anstey et al. 2007; Rusanen et al. 2011), and hippocampal atrophy (DeBette et al. 2011). Thus although it is unclear whether radiation-related psychological distress is associated with smoking, psychological distress may lead to smoking habituation in individuals

susceptible to smoking (Nakano et al. 2018), and contribute to accelerated cognitive decline. Regarding excessive alcohol consumption, an increased risk of alcohol-related mental disorders among clean-up workers (Rahu et al. 2014) and an increased risk of alcohol disorders among men having lived in the Chernobyl-contaminated zone has been observed (Bolt et al. 2018). Furthermore, an initial post-traumatic stress response in Fukushima nuclear workers predicted increased alcohol use post-disaster (Komuro et al. 2019), suggesting that psychological stress may be associated with excessive alcohol consumption. Psychological distress was also associated with continued drinking among newly-started drinkers post-disaster (Orui et al. 2017). Excessive alcohol consumption is neurotoxic (Kim et al. 2012; Caputo et al. 2012) and has been associated with cognitive decline and risk of dementia (Neafsey and Collins 2011; Sabia et al. 2014; Langballe et al. 2015). Thus, excessive alcohol consumption in at-risk individuals may also mediate cognitive decline. For sleep, an increased risk of insomnia has been seen in Fukushima nuclear (Ikeda et al. 2019) and Chernobyl clean-up workers (Laidra et al. 2015), although this association may not apply to general morbidity of sleep disorders (Rahu et al. 2014). Poor sleep quality due to worry may contribute to cognitive decline in those at risk of Alzheimer's disease. For example, evidence suggests that natural sleep may serve as a function to clear beta-amyloid plaques (Kang et al. 2009; Ju et al. 2013; Xie et al. 2013). Further, a recent meta-analysis concluded that insomnia was associated with Alzheimer's disease (Shi et al. 2018), while self-reported sleep disturbances have been associated with reduced cognitive functioning (Jelicic et al. 2002; Tsapanou et al. 2019) particularly in ApoE4 carriers (Virta et al. 2013).

These psychological stress effects on vascular inflammation, endocrine factors, and subsequently cognitive functioning, contribute to the complexity of the potential impact of low/moderate-dose radiation exposure. Neuroinflammation (Solleiro-Villavicencio and Rivas-Arancibia 2018) and vascular inflammation (Baselet et al. 2016) are both also thought to be associated with reactive oxygen species (ROS) and reactive nitrogen species, which are generated in excess by direct IR exposure (Figure 1, 'ROS/RNS and DNA damage'). In turn, they are thought to contribute to the adverse effect of exposure on cognitive function (for in-depth reviews see Hladik and Tapio 2016; Lumniczky et al. 2017). Firstly, IR-induced ROS may induce a pro-inflammatory response in the vascular system, which can lead to circulatory diseases (Borghini et al. 2013; Baselet et al. 2016; Baselet et al. 2017). Observational studies with exposed populations demonstrate this. For example, elevated inflammatory markers have been observed with increased radiation dose in A-bomb survivors (range = 0 to >1.5 Gy; Hayashi et al. 2003). Furthermore, associations between radiation dose and hypertension and cerebrovascular diseases have been observed in Chernobyl emergency workers (mean dose = 0.1 Gy; Ivanov et al. 2006) and Mayak workers (mean external dose = 0.66 Gy for males and 0.52 Gy for females, Azizova et al. 2011; mean external dose = 0.45 Gy for males and 0.37 Gy for females, Azizova et al. 2019). Although the available evidence is

limited to the high-dose range, this impact of radiation exposure on vascular systems may be important in cognitive dysfunction. For example, high-dose whole-brain irradiation (5.0 Gy twice weekly for four weeks) in mice results in cerebrovascular dysfunction coupled with decreased spatial memory performance persisting three months post-irradiation (Ungvari et al. 2017). Whether similar vascular effects occur at low or moderate doses in exposed populations warrants further examination, especially given that cognitive decline has been consistently associated with hypertension (Wiesmann et al. 2013; Knopman et al. 2018), ischemic heart disease (Deckers et al. 2017), and circulating pro-inflammatory cytokines (Trollor et al. 2012; Shibayama et al. 2019).

Secondly, in a state of oxidative stress, ROS mediates cell signaling which leads to microglia and astrocyte activation (Solleiro-Villavicencio and Rivas-Arancibia 2018). When activated, microglia and astrocytes secrete pro-inflammatory cytokines and ROS, which can aggravate further neuronal damage (Lumniczky et al. 2017). Studies suggest that this pro-inflammatory response has been implicated in IR-induced cognitive deficits at high doses (Lee et al. 2010; Jenrow et al. 2013; Acharya et al. 2016; Hladik and Tapio 2016). At low doses/rates (0.031 Gy; 0.0072 mGy/min), elevated levels of inflammatory response markers in human neural progenitor cells have also been observed (Katsura et al. 2016). Although other studies in mice observed no increased inflammatory response for doses below 2.0 Gy (x-ray and cosmic rays; Casciati et al. 2016; Cherry et al. 2012), and moderate/fractionated doses (0.3 Gy gamma rays) may even be associated with an anti-inflammatory response (Kempf et al. 2016). However, as outlined earlier, age at exposure is likely to determine microglia susceptibility to moderate doses of gamma exposure (Kempf et al. 2014). Overall, evidence for IR-induced neuroinflammation appears to exist at the high-dose range but less so for the low-dose range (for a detailed overview on direct effects on neuroinflammation see Betlazar et al. 2016). In addition to the oxidative stress caused by actual exposure, there is evidence that psychological stress (without actual exposure to IR) can also result in neuroinflammatory events. As such it is possible that both pathways (actual exposure and perceived exposure) contribute to neuroinflammation (Figure 1, 'neuroinflammation'). For example, there is research implicating the role of psychological stress in microglia activation and cytokine secretion in early life and adulthood (Calcia et al. 2016). Although glucocorticoids (e.g., cortisol as mentioned previously) are traditionally regarded as anti-inflammatory, its relationship with the CNS is complex and such elevated glucocorticoids may potentiate CNS pro-inflammatory effects (Duque E de and Munhoz 2016). In addition to microglial activation, stress-induced glucocorticoid secretion may also promote structural ramifications of microglia which exaggerates cytokine release following subsequent stressors (Walker et al. 2013). These neuroinflammatory effects are thought to underlie stress-induced cognitive dysfunction (Ohgidani et al. 2016) which has been observed following experiments with rodents designed to mimic chronic

psychological stress in humans (McKim et al. 2016). Therefore, it may be difficult to determine the extent to which neuroinflammatory effects can be attributed directly to actual radiation exposure.

In summary, psychological stress has been associated with pro-inflammatory and endocrine effects which are thought to be associated with reduced cognitive function. This association may be further promoted by behaviors thought to be related to psychological stress such as cigarette smoking, excessive alcohol consumption and poor sleep quality. Based on the evidence provided, it is therefore apparent that pro-inflammatory mechanisms in the CNS and the vascular system may co-exist as a result of both direct IR exposure and psychological stress relating to perceived IR exposure. In addition, the possible effect on neurogenesis may also be impacted both by direct IR exposure, and from elevated cortisol caused by chronic psychological stress, further complicating the issue. Continuing along the line of the mixed exposure phenomena, it is worth examining whether psychological stress compounds the possible effect of direct IR exposure on cognitive functioning. Experimental research on this scenario is required. Interestingly, based on the evidence above, psychological stress may pose a greater threat to cognitive functioning specifically in the context of low- and moderate-dose terrestrial radiation exposures.

5. Societal relevance and implications

The totality of any direct and psychological stress effects of low/moderate-dose IR exposure on cognitive functioning has implications for policy and public health. For example, the International Commission on Radiological Protection (ICRP) which guides precautionary measures following accidental exposures, states that a dose rising toward 0.1 Sv will almost always justify protective measures (acute or annual dose; ICRP 2007). However when framed in context of the Fukushima nuclear disaster, precautionary measures such as forced evacuation may bring considerable unnecessary harm in low-dose scenarios (Cuttler 2012; Socol et al. 2013) through mechanisms described in this review. Further, the psychological stress associated with nuclear accidents may be further exacerbated through stigma and discrimination (Tanisho et al. 2016; Maeda and Oe 2017), and social change associated with displacement (Tanaka 2015; Kunii et al. 2016). Therefore effort is required at the community level to ameliorate these psychosocial consequences and prevent further psychological stress (Becker 1997). Consideration of such stress may also be relevant when considering other radiation-associated non-cancer effects. The term resilience is often used in disaster preparedness and is relevant to nuclear accidents where large numbers of the population are potentially exposed to low and moderate doses of IR. To account for the above, radiation protection guidelines could be developed to supply greater psychological guidance, which in itself could play a critical role in resilience. For instance, psychological effects can reduce the potential for resilience (Sandifer and Walker 2018), and indeed cognitive

dysfunction may also reduce this potential (Hunter et al. 2018) which may be especially relevant to older adults (Cloyd and Dyer 2010).

All of this is also relevant for occupational and medical exposure scenarios. As addressed previously, astronauts (Limoli 2017; Garrett-Bakelman et al. 2019; Cucinotta and Cacao 2019) and radiotherapy patients (Greene-Schloesser and Robbins 2012) are potentially at risk of altered cognitive functioning and could therefore benefit from a deeper understanding of radiation-related psychological stress. Although astronauts will be well-informed about radiation effects, they are already under considerable stress from the nature of space travel alone (Garrett-Bakelman et al. 2019). For conventional radiotherapy patients the relevance of psychological stress relating to radiation is less clear because the radiation is used to treat a current disease and the exposure is consented to. Nonetheless, some understanding to support possible anxiety directly associated with the actual treatment is warranted, since the importance of psychological interventions, particularly in cancer treatments, has already been established (Spiegel 2012).

6. Conclusion

It is generally agreed that exposure to relatively high doses of IR can impair cognitive functioning in adults, and more so in the developing brain. Although likely detrimental following prenatal and neonatal irradiation, the evidence for low- and moderate-dose photon exposure in adulthood appears inconsistent, based on the experimental data provided. The epidemiological evidence also appears inconsistent, but factors such as radiation type (high-LET vs. low-LET) are important to consider as well as level of dose, which makes comparisons between different exposure scenarios difficult. Further to any potential impact of low- and moderate-dose exposures, the considerable psychological stress associated with perceived or actual exposure may also impact cognitive functioning. Indeed, mechanisms for both direct radiation and psychological stress impacting cognitive functioning appear to overlap, particularly relating to pro-inflammatory effects. Therefore, such mechanisms for cognitive dysfunction may co-exist and should be accounted for in epidemiological studies to avoid overestimating the impact of IR exposure alone. Further for animal studies, the psychological stress resulting from restraint and transport of subjects must be planned for and addressed prior to IR experimentation. Overall, the current review suggests that psychological stress associated with low-dose exposures is likely to have a greater negative impact on cognitive functioning than the effects of actual exposure, specifically in the context of nuclear accidents. In other populations however (e.g., astronauts and radiotherapy patients), the significance of any psychological stress is not well documented and requires further examination. Nevertheless, efforts to understand and alleviate stress relating to radiation exposure are still warranted. Given the potential for such negative health consequences there is a pressing need to consider how information on risk is communicated to and received by

populations concerned about exposure to IR at any dose level, including where this is negligible.

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