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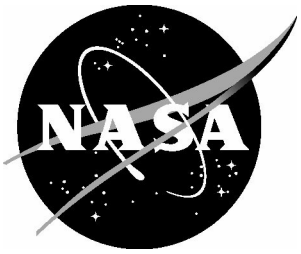

Brain Aging Hallmarks: A Primer for Future Studies on Space Radiation Effects

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#This work was prepared while Z.S. Patel was employed at KBR/NASA JSC. The opinions expressed in this work are the author's own and do not reflect the view of the National Institutes of Health, the Department of Health and Human Services, or the United States government.

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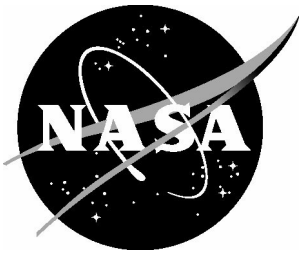

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Abstract

As humankind endeavors to travel farther away from Earth, many questions remain to be solved to ensure proper preparation for deep space. Multiple spaceflight stressors can elicit adverse health outcomes including exposure to space radiation. Space radiation exposure has been identified by the National Aeronautics and Space Administration (NASA) as an important contributor to cancer, degenerative tissue diseases including cataracts, cardiovascular disease, immune system dysfunction and possible central nervous system decrements. The complexity of the human central nervous system makes it difficult to adequately recapitulate in experimental model systems, which hinders quantitative description of associated decrements. The brain aging hallmarks, as introduced by Mattson and Arumugam in 2018, are measurable cellular and molecular hallmarks that generally contribute to the aging process, describe an aging phenotype, and are part of the etiology of age-related neurodegenerative diseases. These hallmarks include mitochondrial dysfunction, accumulation of oxidatively damaged molecules (oxidative stress), impaired lysosome and proteasome function, dysregulation of neuronal calcium homeostasis, compromised adaptive cellular stress response, aberrant neuronal network activity, impaired deoxyribonucleic acid (DNA) repair, inflammation, impaired neurogenesis and dysregulated energy metabolism. Cellular senescence and telomere attrition may also be considered, though more evidence is needed to regard them as brain-specific hallmarks of aging. Radiation exposure has previously been correlated with aging etiology; therefore, investigating the effects of radiation exposure within the context of the hallmarks of brain aging may provide insights into potential health risks facing NASA astronauts, and may provide a means to identify disease processes that may be important targets for disease prevention or intervention. This work describes the hallmarks of brain aging and serves as a primer for future investigation into how the hallmarks of brain aging may compare and contrast with outcomes associated with exposure to the space radiation environment. Further, it will be useful in future identification of hallmarks that may be appropriate to target for radiation countermeasures specific to the central nervous system.

1. Introduction

As humans actively work towards space travel to the Moon, Mars, and beyond, astronauts will experience many stressors of space travel including exposure to ionizing radiation, microgravity/altered gravity fields, long periods of confinement and isolation, potentially hostile and closed living quarters, and being far away from Earth for long periods of time, with associated communication and resupply constraints including limited access to medical resources (Patel et al., 2020). With current Mars mission duration expectations being approximately three years or longer, humans will be experiencing the major stressors of space travel for significantly longer periods of time than crews currently experience on the International Space Station (ISS) in low-Earth orbit. Therefore, it is important to quantify space radiation health effects on humans in the long-term.

In the past, NASA space radiation research has focused on three main risks to long-term health of the astronauts: radiogenic cancers, radiation-induced cardiovascular disease, and neurodegenerative conditions such as Alzheimer's disease and dementia (Cucinotta and Durante, 2006; Cucinotta et al., 2014; Patel et al., 2020). There is an expanding evidence base from occupational, clinical, and environmental exposures on Earth for the role of low-to-high dose radiation in development of cancer and degenerative diseases such as cataracts and cardiovascular disease (Ali et al., 2020; Baselet et al., 2017; Belzile-Dugas and Eisenberg, 2021). However, the effects of radiation on adverse outcomes in the central nervous system (CNS) are less defined,

especially at lower doses relevant to space flight. Large doses to the brain from radiotherapy can lead to cognitive disruptions including impaired memory and attention, and alterations in executive function (Haldbo-Classen et al., 2019; Makale et al., 2017). These changes depend on the dose received and clinical effects range from mild to severe, with potential for significant impacts on long-term quality of life (Greene-Schloesser et al., 2012; Lawrence et al., 2010). Radiation dose estimates for Lunar and Mars missions are significantly lower than typical therapeutic exposures. However, there is still concern that exposure to the particle radiation in space known as galactic cosmic rays may lead to cognitive and behavioral changes that could impact crew health and performance in mission, and lead to the development of neurodegenerative conditions later in life. Galactic cosmic rays exhibit increased biological effectiveness for many biological endpoints compared to typical photon (x-ray or gamma-ray) exposures on Earth (Bahadori et al., 2013), and have been shown to cause significant cognitive and behavioral changes in experimental rodent models studied on Earth using space relevant exposures (Britten et al., 2020; Cucinotta and Cacao, 2019; Howe et al., 2019; Raber et al., 2015). However, methods for translating the outcomes observed in experimental model systems to potential early and long-term CNS decrements in humans remains elusive. The main long-term outcomes of concern include the neurological conditions of Parkinson's disease, stroke, Alzheimer's disease and other forms of dementia (Cucinotta et al., 2014; Lopes et al., 2022; Pariset et al., 2020).

Like other radiation-associated risks to long-term health (cancer, cataracts, and cardiovascular disease), the neurological risks (Parkinson's disease, stroke, Alzheimer's disease, other dementias) occur most frequently in older adults and are associated with the aging process in unexposed populations (Campisi et al., 2019; Hou et al., 2019; Niccoli and Partridge, 2012; North and Sinclair, 2012; Reeve et al., 2014; Uwineza et al., 2019). This observation led to the suggestion that radiation exposure can lead to premature aging, and may function in disease development through the same mechanisms as those that predispose individuals to these chronic diseases during the course of aging (Giovanetti et al., 2020; Richardson, 2009; Tong and Hei, 2020). The aging process is multifaceted and results from interaction of numerous physiological changes that accumulate over time and degrade normal tissue homeostasis and lead to functional decline (Campisi and Sedivy, 2009). Common features are observed during aging that occur across a broad range of organisms and systems. These have been described as the hallmarks of aging (López-Otín et al., 2013). Research to uncover mechanisms associated with the hallmarks has been fueled by knowledge that the trajectory of aging is not fixed but instead is driven by processes that can be modified, which gives hope that it will be possible to identify routes for intervention that may alter the onset and progression of the range of chronic diseases associated with aging (Sierra, 2016).

More recently, a subset of hallmarks of aging that are specific to the brain have been identified. The hallmarks of brain aging, as described by Mattson and Arumugam in 2018, are a variety of cellular and molecular hallmarks that are observed in aging brains in both preclinical models and humans. These hallmarks include processes related to energy metabolism and adaptations to cellular stress, repair, and growth. Importantly, many of the hallmarks of brain aging have been implicated in age-related neurodegenerative diseases such as Alzheimer's and Parkinson's disease (Azam et al., 2021; Hou et al., 2019; Mattson and Arumugam, 2018). There are ten identified hallmarks of brain aging (**Figure 1**): mitochondrial dysfunction, accumulation of oxidatively damaged molecules (oxidative stress), impaired lysosome and proteasome function, dysregulation of neuronal calcium homeostasis, compromised adaptive cellular stress response, aberrant neuronal network activity, impaired deoxyribonucleic acid (DNA) repair, inflammation, impaired neurogenesis, and dysregulated energy metabolism. Cell senescence and telomere attrition have

also been identified as hallmarks of aging of peripheral tissues, though more research is necessary to determine if they are established hallmarks of the aging brain.

Here, the brain aging hallmarks and their processes are summarized. Understanding these hallmarks in the context of normal and pathological brain aging will serve as a framework for comparison with the effects of ionizing radiation exposure on the brain. Identifying the hallmarks can offer insights into potential health risks facing NASA astronauts and provide a means to identify disease processes that may be important targets for prevention or intervention.

2. Hallmarks of Brain Aging

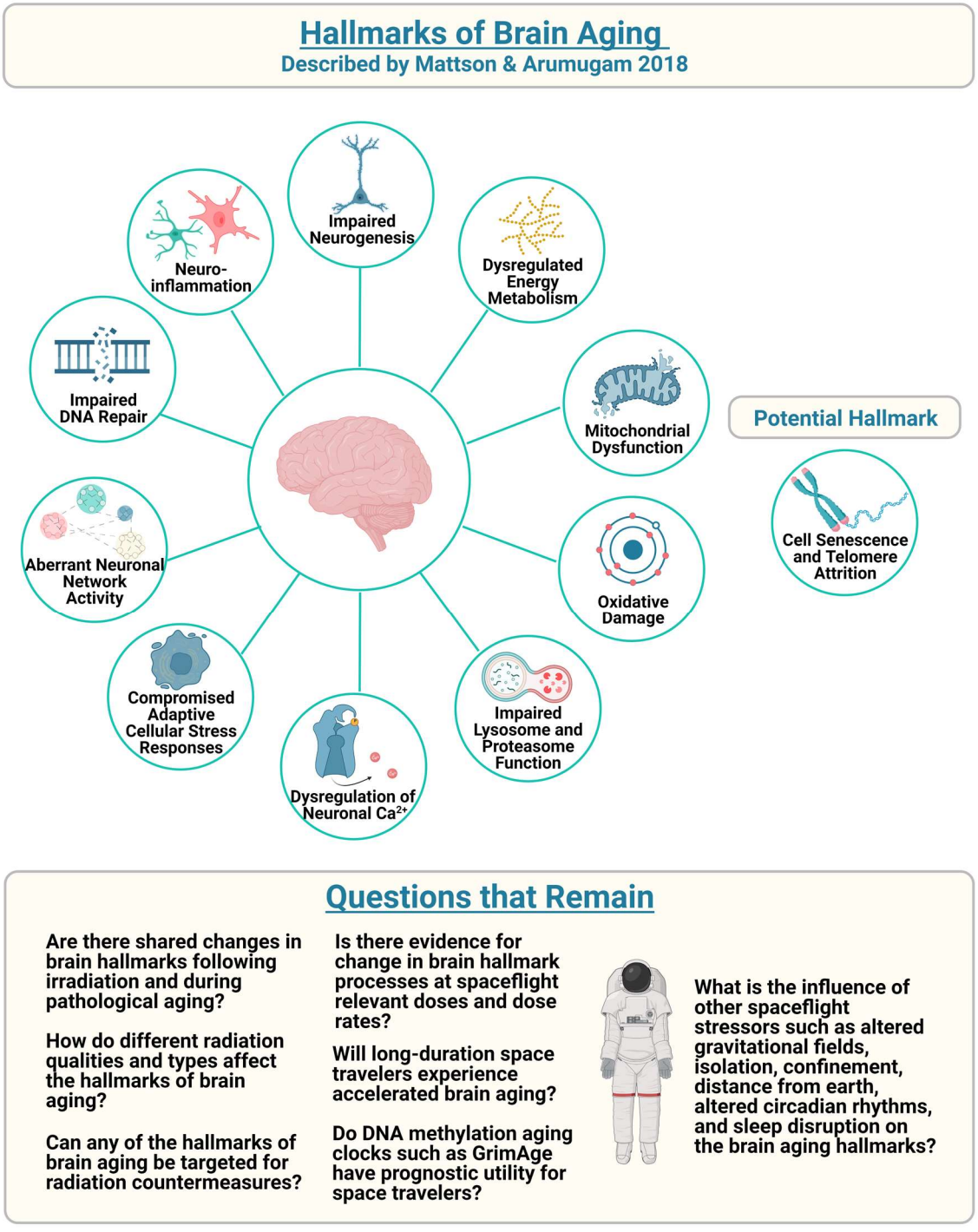

Figure 1. The hallmarks of brain aging and open questions regarding possible common pathways and overlaps with effects of space radiation exposure. The hallmarks of brain aging, described by Mattson & Arumugam in 2018, are cellular and molecular hallmarks found in aging brains that are part of the etiologies of many age-related neurogenerative diseases. Future studies can address how the brain aging hallmarks may be relevant in the context of space radiation exposure. Figure created with biorender.com[1]

[1]*This is not an endorsement by the National Aeronautics and Space Administration (NASA).*

2.1 Mitochondrial Dysfunction

Mitochondria are organelles with their own genomes, mitochondrial DNA, and serve as the primary source of energy (adenosine triphosphate, ATP) in cells. The brain contains a high number of mitochondria, which are distributed throughout dendrites and axons of neurons (Grimm and Eckert, 2017). As a high energy-consuming organ, the brain is particularly reliant on mitochondrial function for ATP generation to support electrochemical neurotransmission and cell maintenance (Mattson et al., 2008). Interestingly, studies of neurons and astrocytes from young and old mice exhibited an accumulation of dysfunctional mitochondria with age (Ghosh et al., 2012). Accordingly, brain aging and neurodegeneration have been robustly linked to altered mitochondrial function including abnormal mitochondrial morphology, decreased levels of quality control (mitophagy), and increased oxidative damage to mitochondrial DNA (Kauppila et al., 2017; Magalhaes et al., 2021).

Mitochondria are interconnected through dynamic network structures modulated by balanced fission and fusion processes, which are dysregulated as brain tissue/synaptic cells age (Stauch et al., 2014). Aged brain tissue and neurodegeneration are associated with increased fission and decreased fusion, leading to mitochondrial enlargement and fragmentation (Chen et al., 2007; Morozov et al., 2017; Stahon et al., 2016). Additional studies have shown that the balance of fission/fusion is more important than isolated shifts in either direction, suggesting that precise regulation of fission/fusion may enable mitochondrial quality control as cells age (Sharma et al., 2019). Tissue-specific deletion of the genes that regulate mitochondrial fusion proteins in a transgenic mouse model affected synaptic transmission and memory function, while deletion of genes regulating mitochondrial fission led to mitochondrial swelling, impaired electron transport chain (ETC) respiration, and increased oxidative damage, resulting in cerebellum neurodegeneration (Kageyama et al., 2012).

Mitochondria are the site of oxidative phosphorylation for ATP production; as a result, oxygen radicals leaking from the ETC may contribute to molecular damage. Comparisons of young and aged mitochondria isolated from animal brain tissue revealed increased oxidative damage to mitochondrial DNA (Santos et al., 2013) and impaired ETC function (Pollard et al., 2016). Progressive decrease in antioxidants including mitochondrial superoxide dismutase, catalase, and glutathione activity was observed in the hippocampus and frontal cortex of post-mortem brain samples from individuals aged between 0.01-80 years, indicating a decrease in protection against reactive oxygen species (ROS) with age (Grimm and Eckert, 2017; Venkateshappa et al., 2012a). Accordingly, the amount of mitochondrial DNA mutations and deletions increase with age in brain tissue (Corral-Debrinski et al., 1992; Cortopassi and Arnheim, 1990). Mitochondrial DNA mutations and deletions increasing may be caused by lack of protective histone proteins and less-efficient DNA repair mechanisms for mitochondrial DNA, leading to susceptibility for impaired ETC and increased ROS, thereby sustaining a cycle of mitochondrial dysfunction and oxidative damage (Wiseman and Halliwell, 1996).

Mitochondrial dysfunction has also been implicated in the etiology of neurodegenerative diseases. Mitochondrial dysfunction occurs early in the disease processes, and many disease-specific proteins interact directly with mitochondria by altering energy metabolism or free-radical generation (Lin and Beal, 2006). Recently, promising therapies for neurodegenerative diseases have emerged that specifically target the mitochondria of neurons (Wang et al., 2020; Wu et al., 2019). Recent comprehensive studies of NASA astronaut cohorts and preclinical samples flown to ISS have uncovered mitochondrial dysregulation as a consistent phenotype of spaceflight, suggesting that the organelle may play a role in potential health detriments of the space

environment (Afshinnekoo et al., 2020; da Silveira et al., 2020). Understanding the role of space radiation in fostering mitochondrial dysfunction, considering mitochondrial morphology, mechanisms of quality control including fission/fusion, and oxidative damage to mitochondrial DNA, are important areas for investigation.

2.2 Accumulation of Oxidatively Damaged Molecules

Oxidative stress is the amalgamation of damage to a biological system caused by free radicals, including ROS or reactive nitrogen species (RNS) and/or a loss of antioxidant mechanisms. Free radicals, which are reactive due to their one unpaired electron, are formed as normal byproducts of cellular metabolism and are critical to the homeostatic environment. When concentrations of ROS/RNS fall below ideal levels, cellular processes such as cell division can be disrupted. On the other hand, raising levels of ROS/RNS past equilibrium can cause significant amounts of cellular and tissue damage (Finkel and Holbrook, 2000). Intracellular antioxidants such as vitamins A, C, and E are created by mitochondrial enzymes and reduce reactive oxygen species, and thus can mitigate the effects of oxidative stress. Additionally, antioxidant enzymes such as superoxide dismutase and glutathione peroxidase, as well as protection mechanisms such as protein refolding and degradation, base excision and repair of damaged DNA, and lipid turnover, can minimize the damage done by oxidative species (Wang and Michaelis, 2010).

The free radical theory of aging hypothesizes that biological aging is a result of accumulation of damage from oxidative radicals (Harman, 1992). Not only does aging lead to an increased production of free radicals, but antioxidant mechanisms also lose efficiency with aging, causing the damage created by ROS/RNS to accumulate. In the brain, increased oxidative stress can cause upregulation of neuroinflammatory pathways, cause vascular damage, and impair the function of proteasomes and lysosomes (Carvalho and Moreira, 2018; He et al., 2020; Picca et al., 2020; Zhang et al., 2017).

In age-related neurodegenerative diseases such as Alzheimer's disease, alterations in enzymes involved in oxidative phosphorylation, reduced energy metabolism, and sporadic mutations of mitochondrial DNA contribute to elevated oxidative stress (Wang et al., 2014). The accumulation of free radical damage is one potential mechanism that may accelerate the neurodegenerative symptoms of Alzheimer's disease (Smith and Perry, 1995; Tuppo and Forman, 2001). Furthermore, microglial cells, which are critical regulators of cellular homeostasis in the brain, change from resting to active states in response to exposure to oxidative stress. Glial cells in prolonged active states has been demonstrated in patients with Alzheimer's disease (Colton et al., 2000) and Parkinson's disease (Peterson and Flood, 2012).

Increased oxidative stress, including both elevations in free radicals and reductions in antioxidant capacities, are well known outcomes resulting from ionizing radiation exposure (Nuszkiewicz et al., 2020). In cell and animal model systems, there is a complex interaction between radiation type (i.e., particle radiation verses gamma radiation) and production of oxidative stress, which has been evaluated in multiple organ systems including the brain (Poulose et al., 2011; Suman et al., 2018; Tseng et al., 2013). Comparing and contrasting these data with evidence from brain aging research may provide useful insights into potential long-term outcomes associated with these changes.

2.3 Impaired Lysosome and Proteasome Function

Removing damaged cellular components to maintain protein homeostasis is essential for cell survival. The ubiquitin-proteasome pathway and lysosomal pathway are the two main systems that accomplish this by targeting and removing damaged proteins in cells. The ubiquitin-proteasome pathway targets and selectively degrades short-lived and misfolded soluble proteins that are specifically marked for elimination by ubiquitin. The lysosomal system can eliminate proteins with long half-lives, insoluble proteins or whole organelles by cellular autophagy (Bustamante et al., 2018).

With aging, the ability of neurons to maintain protein homeostasis declines. Compared with young neurons, aged neurons demonstrate greater intracellular accumulation of undegraded proteins and greater amounts of proteins that have undergone polyubiquitination, a sign of proteasome dysfunction (Graham and Liu, 2017). Studies using preclinical animal models have found that loss of autophagy may be linked to age-related neurodegeneration. Mice modified with Atg7 deficiencies and FIP200 deficiencies, two genes that are necessary for autophagy, demonstrate significant neuronal deficits and neurodegeneration, progressive neuronal loss, axonal dystrophy, as well as accumulation of ubiquitinated protein aggregates (Komatsu et al., 2006, 2007; Liang et al., 2010). In postmortem analysis of brains of individuals with Alzheimer's disease, mammalian target of rapamycin (mTOR) hyperactivity was present in the hippocampus which can inhibit cellular autophagy, and even more notably, the activity levels were correlated with the severity of the presentation of dementia (Perluigi et al., 2015). Decreased levels of autophagy (alongside lysosomal dysfunction) may also be implicated in the pathogenesis of Alzheimer's disease (Orr and Oddo, 2013). In addition, a mutation in the ubiquitin pathway, specifically the E3 ubiquitin ligase Parkin, is sufficient to elicit early-onset Parkinson's disease (Shimura et al., 2001). Several studies have evaluated the impact of space radiation on protein homeostasis (Shaler et al., 2020; Tidmore et al., 2021). Thus, future research could evaluate this work in the context of brain aging.

2.4 Dysregulation of Neuronal Calcium Homeostasis

Calcium plays a critical role in the nervous system. Calcium is necessary for both the synthesis and release of neurotransmitters, maintenance of the membrane potential, initiating phosphorylation of various proteins, activating transcription factors, and importantly, it plays a fundamental role in the firing of excitatory synapses (DeCoster, 1995; Kawamoto et al., 2012). Excitatory synapses increase the likelihood of further action potentials in neuronal connections. These connections are essential for neuronal plasticity and regulating learning and memory through processes of long-term potentiation and long-term depression which involve the strengthening and weakening of select synapses. Because of calcium's central role in regulating such processes, modest impairments in calcium homeostasis can cause profound changes in neuronal plasticity (Foster, 2007).

The calcium hypothesis of aging was introduced nearly three decades ago and postulated that a change in calcium concentration in the brain could contribute to cell senescence (Khachaturian, 1989). Essentially, the normal degradation and increased inefficiencies of calcium pumps leads to the increased concentration of calcium which can cause significant disruption to homeostatic equilibrium, ultimately leading to degradation of the pathways related to neuroplasticity, synaptogenesis, and dendritic function. It is also possible that age-related calcium dysregulation may contribute to the development of neurodegenerative diseases. It is hypothesized that in

Alzheimer's disease, amyloid beta metabolism leads to upregulation of calcium signaling, which may increase neuronal apoptosis and possibly impact long-term depression in neurons (Berridge, 2010). For example, the deposition of amyloid beta plaques demonstrably induce a calcium overload specifically in the region immediately surrounding the plaques (Kuchibhotla et al., 2008). Furthermore, experimentally reinstating neuronal calcium homeostasis can restore cognitive deficits in aged-rats (Gant et al., 2015).

Dysregulated calcium flux may be a potential parallel between ionizing radiation exposure and brain aging, as ionizing radiation can alter calcium flux in both target and bystander cells (Lyng et al., 2006; Shao et al., 2006). Furthermore, proteins related to calcium transport and signaling were upregulated after exposure to low-doses of ^{56}Fe irradiation (Britten et al., 2017). Whether space radiation exposure elicits similar changes in the calcium concentration as is seen in aged neurons, including degradation and inefficiencies of calcium pumps and sustained elevated calcium concentrations in neurons, is currently unknown.

2.5 Compromised Adaptive Cellular Stress Responses

Both intrinsic (i.e., normal electrochemical activity) and extrinsic (i.e., physiological and psychological stress) factors may contribute to changes in metabolic, ionic, and oxidative stress in neurons. Stressed neurons demonstrate increased ATP consumption, calcium influx, and ROS production. In a healthy cell, these processes can activate multiple mechanisms that mitigate immediate stressors and strengthen defenses against future cellular stress. These adaptive mechanisms include improved regulation of energy metabolism, improved regulation of cellular waste and autophagy, and repair of potential DNA damage (Mattson and Arumugam, 2018). In addition, cellular stress in healthy neurons can cause upregulation of neurotrophic factors, which are biomolecules that enhance the survival and growth of neurons. Common neurotrophic factors include brain derived neurotrophic factor (BDNF), nerve growth factor (NGF), and insulin-like growth factor one (IGF-1). A healthy cellular stress response allows neurons to maintain stability, provide protection against future stressors and aid in their growth and survival. However, when the pathways to mitigate cellular stressors are impaired, neurons are more vulnerable to injury and neurodegeneration (Stranahan and Mattson, 2012).

With aging, there is evidence of altered stress response signaling and adaptation in neurons. As described in previous sections, aging is associated with declined calcium pump activity (Mata and Sepulveda, 2010; Zaidi et al., 1998), impaired calcium handling (Gareri et al., 1995; Nikoletopoulou and Tavernarakis, 2012), impaired mitochondrial dynamics (Jiang et al., 2015; Khacho and Slack, 2018), and lowered antioxidant defenses (Venkateshappa et al., 2012a, 2012b). Importantly, aging is associated with a reduced expression and signaling of neurotrophic factors such as BDNF, NGF, and IGF-1, which normally mediate neuronal growth and survival by promoting neuronal plasticity (Mattson et al., 2004; Molinari et al., 2020; Neidl et al., 2016; Schliebs and Arendt, 2011; Tapia-Arancibia et al., 2008; Wu et al., 2020). Notably, altered levels of neurotrophic factors have been described in a number of neurodegenerative diseases including Alzheimer's disease and Parkinson's disease (Zuccato and Cattaneo, 2009).

Several studies have shown that ionizing radiation may cause alterations to neurotrophic factors linked to changes in cognitive function. For example, 30 Gy of whole brain radiotherapy in rats resulted in cognitive impairment and decreased BDNF levels three months post irradiation (Tong et al., 2018). In addition, reduced levels of cortical BDNF were observed in male but not female mice following exposure to 200 cGy of a three-ion sequential particle beam (Raber et al.,

2019). Understanding the role of low-to-moderate dose ionizing radiation and high energy and charge (HZE) ions in modulating the adaptive cellular stress response, specifically the expression and signaling of neurotrophic factors such as BDNF, NGF and IGF-1, could provide insights into long-term outcomes of space radiation exposure.

2.6 Aberrant Neuronal Network Activity

The cerebral cortex consists of a complex system of interconnected neurons and supporting cells forming higher-order neuronal networks. Dendrites and axons reach toward one another, electrical synapses speed down myelinated paths, and neurotransmitters move along in synaptic clefts. The brain is made of grey and white matter, the former of which is composed of neurons, and the latter of which is composed of myelinated axons that form white matter tracts for inter- and intra-hemispheric communication (Schmahmann et al., 2008). Biochemical messengers known as neurotransmitters also contribute to the neuronal network, which allow communication between common excitatory glutamatergic neurons and inhibitory gamma-aminobutyric acid (GABA) interneurons (Hyman, 2005; Tremblay et al., 2016). The cohesion and balance of this system is crucial for optimal brain function.

With aging, both glutamatergic and GABAergic signaling pathways are impaired. Both glutamate and GABA levels, and signaling of their respective receptors, decrease with aging (Heise et al., 2013; Roalf et al., 2020; Segovia et al., 2001; Wenk and Barnes, 2000). Neuroimaging also reveals age-related changes in neuronal networks. Changes in white matter structure with age are common, as aging is associated with a loss of white matter integrity (Davis et al., 2009). Functional neuroimaging suggests that neuronal network activity is perturbed with aging, and perturbations are exacerbated in cognitively impaired older adults (Leal and Yassa, 2013).

Neurodegenerative diseases have been associated with aberrant neuronal network activity. Individuals with Alzheimer's disease demonstrate significant impairments in glutamatergic signaling specifically due to excessive activity of glutamatergic receptors (Wang and Reddy, 2017) and amyloid beta plaques inhibiting the re-uptake of glutamate (Fernández-Tomé et al., 2004). Risk for Alzheimer's disease has been associated with lower white matter integrity, whereby the structure of the white matter fibers have reduced myelination and disrupted microstructural organization of the fiber tracks, suggesting that declines in white matter integrity may be part of the etiology of the disease (Gold et al., 2012). In addition, studies in rodent models suggest that neuronal networks measured with functional neuroimaging are disrupted in animals with cognitive impairment, compared with cognitively unimpaired animals (Ash et al., 2016; Hsu et al., 2016).

Several studies suggest a role for space radiation in altering neural network activity in experimental models. Misalignment of GABAergic and glutamatergic signaling may be associated with space radiation, as 60 cGy of ^{56}Fe particle radiation altered glutamatergic signaling in the rat hippocampus (Machida et al., 2010). Likewise, recent studies report alterations in rodent hippocampal network properties associated with mixed ion exposures (Klein et al., 2021). In astronauts, changes in white matter microstructure associated with spaceflight have been observed (Lee et al., 2019), though future research will be needed to elucidate which space flight stressors contribute to these changes.

2.7 Impaired DNA Repair

Proper DNA repair mechanisms are essential for cellular function. Two types of DNA lesions are single-strand breaks (SSB) and double-strand breaks (DSB), with the latter being more complex. SSB are repaired through nucleotide excision repair and base excision repair, while DSB, which have a higher likelihood of mutation, are repaired through homologous recombination and non-homologous end joining (Shimizu et al., 2014). In healthy cells, DNA damage is rapidly removed and repaired via the appropriate repair pathways. However, in aging neurons, more DNA damage accumulates (Lombard et al., 2005) especially following excitatory synaptic activity (Chow and Herrup, 2015; Yang et al., 2010). Further, the expression and activity of DNA repair proteins are reduced, resulting in increased inter-chromosomal translocations and intrachromosomal inversions (Mattson and Arumugam, 2018). Thus, aging causes an increased need for active DNA repair mechanisms, yet these mechanisms have reduced efficiency.

Dysfunctional DNA repair is also sufficient to cause premature and accelerated aging phenotypes, including Cockayne syndrome, Werner syndrome, and ataxia telangiectasia which are all caused by mutations in proteins involved in DNA repair and associated with cognitive dysfunction (Lombard et al., 2005). Additionally, abnormally repaired DNA may result in profound downstream consequences that include aberrant signal transduction, apoptosis, uncontrolled proliferation, and carcinogenesis (Jia et al., 2021).

One of the main mechanisms by which ionizing radiation causes biological damage is from damage to DNA (Mladenov et al., 2018; Sekhar and Freeman, 2015). The space radiation environment contains both high and low linear energy transfer (LET) components. Importantly, the propensity for DSBs are higher after exposure to high-LET irradiation compared with low-LET irradiation (Cucinotta and Durante, 2006), and high and low-LET irradiation can trigger different DSB repair pathways (Hill et al., 2004). Spaceflight itself may also impact DNA repair. During a yearlong stay on the ISS, chromosomal inversions and translocations were detected during the mission and continued to increase postflight, suggesting that DNA damage was persistent long term (Garrett-Bakelman et al., 2019; George et al., 2013). In the brain, decreased DNA damage repair was observed in rodents following relatively high dose exposure to ^{56}Fe ions suggesting the presence of aging-like pathology in these animals (Suman et al., 2013).

2.8 Inflammation

Acute inflammatory responses are natural and necessary in order to protect the brain from infection and injury. However, the sustained activation of immune cells in the brain causing chronic inflammation can be damaging to neural tissues (DiSabato et al., 2016). Resident glial cells, including microglia and astrocytes, are part of the primary inflammatory response of the brain. Microglial cells are macrophages that rapidly respond to tissue injury by providing surveillance to neurons, helping to maintain synaptic homeostasis, and releasing signaling molecules such as cytokines and chemokines (Zhu et al., 2022). Astrocytes critically regulate neurogenesis, synaptogenesis and blood brain barrier permeability. In response to injury, both types of glial cells can change phenotypes from resting to reactive states, termed gliosis, where they increase in size and number, upregulate macrophagic processes, and increase the release of pro-inflammatory secondary messengers (Lee et al., 2021). Effects of gliosis are beneficial and restorative in the short term, but can be damaging if sustained (Luo and Chen, 2012).

In the aging brain, glial cells increase in both number and immunoreactivity (Angelova and Brown, 2019). The chronic activation of microglial cells has been implicated in several age-related

neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. In patients with Parkinson's disease, the activation of microglia in the substantia nigra, as well as phagocytosis of degenerating neurons, is hypothesized to be key in the mechanism underlying the hallmark symptoms of Parkinson's disease (Kim and Joh, 2006). In patients with Alzheimer's disease, microglia are often located near sites of amyloid beta deposition, as they will attempt to engulf these amyloid beta plaques upon contact (Tuppo and Arias, 2005). However, their presence near the plaques and increased activity may contribute to neuronal injury. Therapeutics targeting microglial cells have been emerging as a strategy aimed at counteracting brain degeneration in age-related neurodegenerative diseases (Muzio et al., 2021).

In response to simulated exposure to the space radiation environment, mouse models demonstrate microglia reactivity, contributing to increases in neuroinflammatory markers, synaptic changes, and neurobehavioral deficits (Rienecker et al., 2021). Additionally, the depletion of microglia appears to mitigate the cognitive deficits that occur due to ionizing radiation (Allen et al., 2020; Krukowski et al., 2018). Therefore, there are potential overlaps between age-related neurodegenerative diseases and ionizing radiation exposure in their activation of neuroinflammatory pathways including glial cell reactivity.

2.9 Impaired Neurogenesis

Neurogenesis is the process of generating functional neurons from neural stem cells that occurs throughout life with decreasing capacity as aging progresses (Eriksson et al., 1998; Ming and Song, 2011). Adult neurogenesis is restricted to two brain regions: the subventricular zone (SVZ) of the lateral ventricle and the dentate subgranular zone (SGZ) of the hippocampus (Braun and Jessberger, 2014; Gage, 2000). Neuronal stem cells in the neurogenic niches of the SVZ and SGZ give rise to new olfactory bulb interneurons and hippocampal dentate gyrus granule neurons, respectively. These adult neurogenic stem cells provide a renewal source of functional neurons to support learning, memory, and spatial pattern separation (Ming and Song, 2011). The neurogenesis process ends with the successful integration of the newly generated neural cells into brain circuitry. Therefore, assessing synaptic plasticity and brain connectivity gives additional insight on functional neurogenesis.

Aging is associated with impaired neurogenesis, specifically decreased self-renewal, proliferation, and capacity for regenerating neurons to integrate into the central nervous system network (Cavallucci et al., 2016). Aging-associated reductions in hippocampal and olfactory neurogenesis contribute to corresponding cognitive and olfactory decline (Lazarov et al., 2010). In age-related neurodegenerative diseases such as Alzheimer's disease, individuals have markedly lower numbers of new neurons compared with age-matched healthy controls (Moreno-Jiménez et al., 2019). Furthermore, dendritic spine density is also reduced in Alzheimer's disease, suggesting a reduced ability for integrating any new neural cells into proper neuronal networks (Cochran et al., 2014; Dorostkar et al., 2015; Mijalkov et al., 2021).

Impaired neurogenesis and impaired integration into neural circuitry resulting in cognitive deficits are shared outcomes of the aging brain and ionizing radiation exposure. Numerous studies have reported ionizing radiation inhibits hippocampal neurogenesis, suggesting depletion of radiosensitive neural stem/progenitor cells may be a contributor to radiation-induced cognitive decrements (Acharya et al., 2010; Mizumatsu et al., 2003; Raber et al., 2004), although the role of neurogenesis in mediating space radiation effects is complex (Whoolery et al., 2020).

2.10 Dysregulated Energy Metabolism

The human brain has uniquely high dependence on glucose utilization that accounts for 20-25% of total glucose consumption despite only being 2% of the body mass (Mink et al., 1981). Brain uptake of glucose from the circulation is driven by the energy demand of activated neurons rather than levels of circulating glucose (Cunnane et al., 2020). As such, glucose transporters are essential in shuttling glucose to region-specific brain cells with differing energy requirements. Studies of humans and preclinical models have clearly shown reduced expression of glucose transporters in the brain with aging, and changes in the expression of key enzymes involved in glycolysis and oxidative phosphorylation (Ding et al., 2013). Also with advancing age, circulating glucose concentrations increase in response to insulin resistance, as demonstrated by a compromised cell ability to increase glucose transport upon insulin signaling. For example, aging adults demonstrate progressive reductions in glucose uptake in the brain measured by positron emission tomography (PET) imaging of radiolabeled glucose (Goyal et al., 2017).

In elderly patients with mild cognitive impairment and Alzheimer's disease, glucose utilization in the temporal and parietal lobes is significantly reduced compared to cognitively normal adults (Kato et al., 2016). Remarkably, declines in cerebral glucose metabolism (hypometabolism) precedes the pathology and clinical symptoms of Alzheimer's disease and is more severe than hypometabolism observed in the normal aging brain (Currais et al., 2019). The finding that hypometabolism proceeds pathology suggests a decline in brain bioenergetics may not just be a passive consequence in neurodegenerative pathology. Glucose transporters, GLUT1 and GLUT3, are also reduced with Alzheimer's disease, and correlate with diminished brain glucose uptake and subsequent cognitive decline (Landau et al., 2010). Furthermore, dysregulated glucose metabolism attributed to brain-specific insulin resistance and diabetes mellitus are risk factors for dementia and Alzheimer's disease (Arnold et al., 2018; Diehl et al., 2017; Noguchi-Shinohara et al., 2021). In the context of spaceflight, significant alterations in the metabolome have been shown as a result of flights in low-Earth orbit (da Silveira et al., 2020). However, studies reporting brain-specific, radiation-induced metabolic alterations have been limited.

2.11 Potential Hallmark - Cell senescence and Telomere Attrition

Telomeres are stretches of repetitive DNA sequences and specialized proteins located at the end of chromosomal DNA. Telomeres function as a cap to protect the ends of chromosomes during DNA replication ensuring genomic integrity, and they also function to block recognition of chromosomal ends by the DNA damage response machinery, which avoids genomic instability and development of fused chromosomes (Shay and Wright, 2019). Telomerase (terminal transferase) is a ribonucleoprotein that exists in certain cells where it functions to add telomere repeat sequences to the end of telomeres, preventing telomere shortening. While there is a natural progression of telomere shortening during cell division— the Hayflick limit quotes average cell division between 40-60 times (Hayflick, 1965; Hayflick and Moorhead, 1961)— telomerase enables telomeres to continue replication with cell division through the lifespan of the cell.

Telomere shortening, or telomere attrition, is observed in humans throughout the lifespan and has been described as a hallmark of aging (Cawthon et al., 2003; López-Otín et al., 2013). Telomerase expression is silenced in adult somatic cells to prevent excessive cell proliferation and the development of tumors (tumorigenesis), resulting in the shortening of telomeres during the natural age progression. Additionally, as the telomere shortens, the ability of the associated cell to divide is impacted. As a telomere becomes critically shortened the DNA ends become exposed

and can activate DNA damage response pathways, which results in proliferative arrest. This ultimately leads to replicative senescence, where the cell loses the ability to proliferate and is permanently growth arrested (Campisi, 1997).

The role of telomere attrition and cellular senescence as brain aging specific hallmarks are not well established. Neurons in the brain are post-mitotic, therefore their telomeres do not shorten, and they do not undergo replicative senescence (Cheng et al., 2007). However, neurons can develop a senescence-like phenotype following DNA damage which can be observed by accumulation of telomere-associated DNA damage response foci in these cells (Rossiello et al., 2022). Furthermore, telomerase-deficient mice demonstrate impaired hippocampal neurogenesis and spatial learning and memory (Rolyan et al., 2011). Also, cell types in the brain other than neurons may have important roles in cognitive function. For example, glial cells in the brain can undergo replicative senescence (Cohen and Torres, 2019), and accumulation of these cells in the brain has been shown to be associated with initiation and progression of Alzheimer's disease in mouse models (Bussian et al., 2018; Liu, 2022). Also, telomerase reverse transcriptase (TERT) may protect against neurodegenerative diseases via mechanisms outside of telomere extension (Saretzki, 2022; Saretzki and Wan, 2021). This evidence suggests that there may be a role for telomere maintenance in the aging brain and in the prevention of neurodegenerative diseases (Sahu et al., 2022), but future research is needed to identify telomere attrition and/or cellular senescence as specific brain aging hallmarks.

It is unclear how telomere dynamics are impacted in the spaceflight environment; however, this is an active area of investigation. In a recent study of astronauts aboard one year or shorter missions to the ISS, telomeres were longer than baseline during spaceflight, then immediately shortened upon return to Earth (Luxton et al., 2020). Exposure to oxidative stress correlated with telomere dynamics. However, there were large interindividual variabilities (Luxton et al., 2020). There is evidence that ionizing radiation exposure can also affect both telomere dynamics and cellular senescence in peripheral cells (Loseva et al., 2014; Shim et al., 2014), and further evaluation of brain-specific involvement would be of interest.

3. Discussion

The hallmarks of brain aging are a set of biological changes that generally contribute to aging processes, describe an aging phenotype, and are part of the etiology of age-related neurodegenerative diseases. The purpose of this review was to describe the hallmarks of brain aging with the goal of serving as a primer for future work that can evaluate the overlap between the brain aging hallmarks and exposure to space radiation.

The brain aging hallmarks and their processes are as follows: mitochondrial dysfunction, which can be characterized by disrupted mitochondrial morphology, impaired mechanisms of quality control including fission/fusion, and oxidative damage to mitochondrial DNA. There is also the accumulation of oxidatively damaged molecules characterized by the formation of free radicals, the reduction in antioxidant capacities, and the use of antioxidants to mitigate oxidative damage. Another hallmark is impaired lysosome and proteasome function, characterized by decreased levels of autophagy or elevated levels of polyubiquitination. In addition, dysregulation of neuronal calcium homeostasis can occur, characterized by the degradation and inefficiencies of calcium pumps and sustained elevated calcium concentrations in neurons. Brain aging is also associated with a compromised adaptive cellular stress response characterized by the expression and signaling of neurotrophic factors such as BDNF, NGF and IGF-1. In addition, aberrant neuronal network

activity may occur, characterized by a misalignment of GABAergic and glutamatergic signaling, alterations in white matter, and changes in neural networks measured with functional neuroimaging. Another hallmark includes impaired DNA repair, which is characterized by DNA damage and activity of DNA repair mechanisms. In addition, inflammation is associated with brain aging and can be characterized by glial cell reactivity. Another hallmark of the aging brain is impaired neurogenesis characterized by neurogenic stem cell biomarker expression and dendritic density and complexity. Finally, dysregulated energy metabolism in the brain can occur with aging, and is characterized by glucose metabolism, transport, and uptake, expression of key enzymes involved in glycolysis and oxidative phosphorylation, and the presence of insulin resistance in the brain. Cellular senescence and telomere attrition were also discussed as they are hallmarks of aging, yet since neurons are post-mitotic, more evidence is necessary to identify them as brain-specific hallmarks of aging.

There are many questions that remain when considering the hallmarks of brain aging in the context of space radiation exposure (**Figure 1**). For example, it will be important to understand not only if the brain aging hallmarks are impacted by ionizing radiation but also to consider the doses, dose-rates, qualities and types of radiation that are applicable to the space radiation environment. In addition, it will be important to consider if changes in these hallmarks from space radiation exposure are related to the pathological aspects of brain aging. Another question that remains is regarding the use of the brain aging hallmarks as targets for radiation countermeasures. There are abundant research and development efforts focused on finding agents to mitigate aging in general (Gonzales et al., 2021; Paudel et al., 2020). Thus, identifying overlaps between aging and radiation phenotypes can assist in detecting potential candidates for countermeasures that support both anti-aging and radiation protection. Identifying radioprotective countermeasures will be key in reducing potential space radiation-induced impairments in brain function and decreasing risk for future development of neurodegenerative diseases. A further intriguing area for investigation is the possible application of epigenetic clocks in astronaut risk assessment, which were included in the evaluation of the Mars-500 ground simulation mission participants (Nwanaji-Enwerem et al., 2020). These calculators predict biological age based on DNA methylation signatures and have been shown to be useful for predicting the onset of a variety of neurodegenerative diseases (Grodstein et al., 2021; Sugden et al., 2022). It is unclear if these calculators are relevant for space travelers; however, if relevant, these calculators could help predict astronaut risk for age-related diseases.

Long-duration spaceflight will expose astronauts to a myriad of hazards to human health. It will be important to consider the influence of other spaceflight stressors such as altered gravitational fields, isolation, confinement, distance from Earth, misalignment of circadian rhythms, and sleep disruption on the hallmarks of brain aging. It is possible that various spaceflight stressors can combine with ionizing radiation exposure to induce synergistic biological effects. Furthermore, risk factors outside of space flight hazards such as sex, family history of disease, and genotype will be important to consider as they can influence risk for age-related neurodegenerative diseases.

4. Conclusions

The hallmarks of brain aging as described by Mattson and Arumugam in 2018 are a set of cellular and molecular hallmarks that are apparent in aging brains and part of the etiology of age-related neurodegenerative diseases. These hallmarks include mitochondrial dysfunction,

accumulation of oxidatively damaged molecules (oxidative stress), impaired lysosome and proteasome function, dysregulation of neuronal calcium homeostasis, compromised adaptive cellular stress response, aberrant neuronal network activity, impaired DNA repair, inflammation, impaired neurogenesis and dysregulated energy metabolism. Cellular senescence and telomere attrition are aging hallmarks, but more evidence is needed to consider them as brain-specific hallmarks of aging. Although the aging process is multifaceted and complex, these hallmarks offer a starting point for future research that can identify parallels between brain aging hallmarks and exposure to ionizing radiation. This work may provide insights into potential health risks facing NASA astronauts and provide a means to identify disease processes that may be important targets for disease prevention or intervention.

5. Disclosures and Conflicts of Interest

The authors have no conflicts of interest to disclose. Author contributions: Conceptualization (JLH); Investigation, writing original draft, visualization (VL, ARZ co-first authors, KLM, KBM); Writing review and editing (all authors); Supervision (KBM, RBN, ZSP, JLH); Project administration (RBN).

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