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Review article

The neurology of space flight; How does space flight effect the human nervous system?

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ABSTRACT

Rationale and Hypothesis: Advancements in technology, human adaptability, and funding have increased space exploration and in turn commercial spaceflight. Corporations such as Space X and Blue Origin are exploring methods to make space tourism possible. This could lead to an increase in the number of patients presenting with neurological diseases associated with spaceflight. Therefore, a comprehensive understanding of spaceflight stressors is required to manage neurological disease in high-risk individuals.
Objectives: This review aims to describe the neurological effects of spaceflight and to assess countermeasures such as pre-flight prophylaxis, training, and possible therapeutics to reduce long-term effects.
Methodology: A literature search was performed for experimental studies conducted in astronauts and in animal models that simulated the space environment. Many studies, however, only discussed these with scientific reasoning and did not include any experimental methods. Relevant studies were identified through searching research databases such as PubMed and Google Scholar. No inclusion or exclusion criteria were used.
Findings: Analysis of these studies provided a holistic understanding of the acute and chronic neurological changes that occur during space flight. Astronauts are exposed to hazards that include microgravity, cosmic radiation, hypercapnia, isolation, confinement and disrupted circadian rhythms. Microgravity, the absence of a gravitational force, is linked to disturbances in the vestibular system, intracranial and intraocular pressures. Furthermore, microgravity affects near field vision as part of the spaceflight-associated neuro-ocular syndrome. Exposure to cosmic radiation can increase the risk of neurodegenerative conditions and malignancies. It is estimated that cosmic radiation has significantly higher ionising capabilities than the ionising radiation used in medicine. Space travel also has potential benefits to the nervous system, including psychological development and effects on learning and memory. Future work needs to focus on how we can compare a current astronaut to a future space tourist. Potentially the physiological and psychological stresses of space flight might lead to neurological complications in future space travellers that do not have the physiological reserve of current astronauts.

Abbreviations

CNS,	Central Nervous System
SMS,	Space Motion Sickness
OCR,	Ocular counterroling reflex
HDBR,	Head-down bed rest
WMH,	White matter hyperintensities
SANS,	Spaceflight-associated neuro-ocular syndrome
LP,	Lumbar puncture
ICP,	Intracranial pressure
CSF,	Cerebrospinal fluid
IIH,	Idiopathic intracranial hypertension
SPE,	Solar particle events
GCR,	Galactic cosmic rays
HZE,	High-energy charged particles
LET,	Linear energy transfer
ROS,	Reactive oxygen species
AD,	Alzheimer's disease
ICE,	Isolated and confined environment

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1. Introduction

Humans have long explored challenging environments from the deep seas to outer space, searching for biotic factors capable of sustaining life. Space is one of these extreme environments. Space missions have become longer and increasingly frequent, posing a significant risk to the human brain. Astronauts are exposed to various external stressors in space, but the full effects on the central nervous system (CNS) are still unknown (Roy-O'Reilly et al., 2021).

Technological advances have made human spaceflight more accessible, leading to longer exploratory missions. Extended periods in space will increase exposure to stressors, affecting astronauts during missions and upon return to earth. As shown in Fig. 1, astronauts are exposed to reduced gravity (microgravity), cosmic radiation, prolonged periods of hypercapnia, isolation, confinement and disrupted circadian rhythms (Roy-O'Reilly et al., 2021; Clément et al., 2020). These stressors have the potential to cause long term neurological effects that can last for years.

Microgravity, the most studied stressor, causes vestibular and ocular structural dysfunction (Hupfeld et al., 2021). Cosmic radiation is linked to an increased risk of malignancies and neurodegenerative conditions. These stressors combined with isolation, confinement and disrupted circadian rhythm can have psychological implications (See Fig. 1).

As commercial space travel becomes more accessible and affordable, a thorough understanding of the effect of spaceflight on the human CNS is needed. Although currently the cost of space tourism is prohibitively expensive for the vast majority of people this is unlikely to be the case for long. A 90 min spaceflight with the company Virgin Galactic currently costs approximately $250,000, which although expensive, is in the same region of expense as a trip to the South Pole (approximately $100,000) or an expedition to Everest (approximately. $50,000) (Wang et al., 2021). The investments of multinational corporations such as Blue Origin and Space X into commercial space travel may eventually lead to the introduction of mass space tourism (Cheetham, 2018). This will increase the risk of neurological disease in this population. Space tourists might not have the same physiological reserve as astronauts, who must meet stringent health and educational criteria, making them more susceptible to neurological conditions. Therefore, it becomes essential to understand the common nervous system conditions of spaceflight and identify those particularly susceptible to developing post-flight neurological complications.

In this article, we look at the CNS effects of space flight and make suggestions on which nervous system disorders may preclude people from becoming a space tourist.

2. Vestibular complications of space flight

The effects of microgravity have been extensively studied. It results in numerous anatomical and functional changes which cause symptoms such as space motion sickness (SMS), spatial disorientation, and movement difficulty (Tanaka et al., 2017). On earth, the CNS assesses spatial orientation by interpreting inputs from the somatosensory, proprioceptive (the ability to sense movement) and visual systems. The vestibular system contains 3 semicircular canals and otolith organs, which detect angular acceleration and linear acceleration, respectively (Tanaka et al., 2017). The otoliths predominantly determine the body's position in relation to a gravitational source; in most instances, this is the earth's gravitational pull. However, the otoliths cannot distinguish gravity from other planes of accelerations independently and rely significantly on visual and peripheral sensory inputs (Harris et al., 2017). A measure of perceived orientation is the concept of perceptual upright, which is the fundamental way of recognising objects and people (Dyde et al., 2009). The perceived direction of up is fundamental to the human interpretation of the world (Dyde et al., 2006).

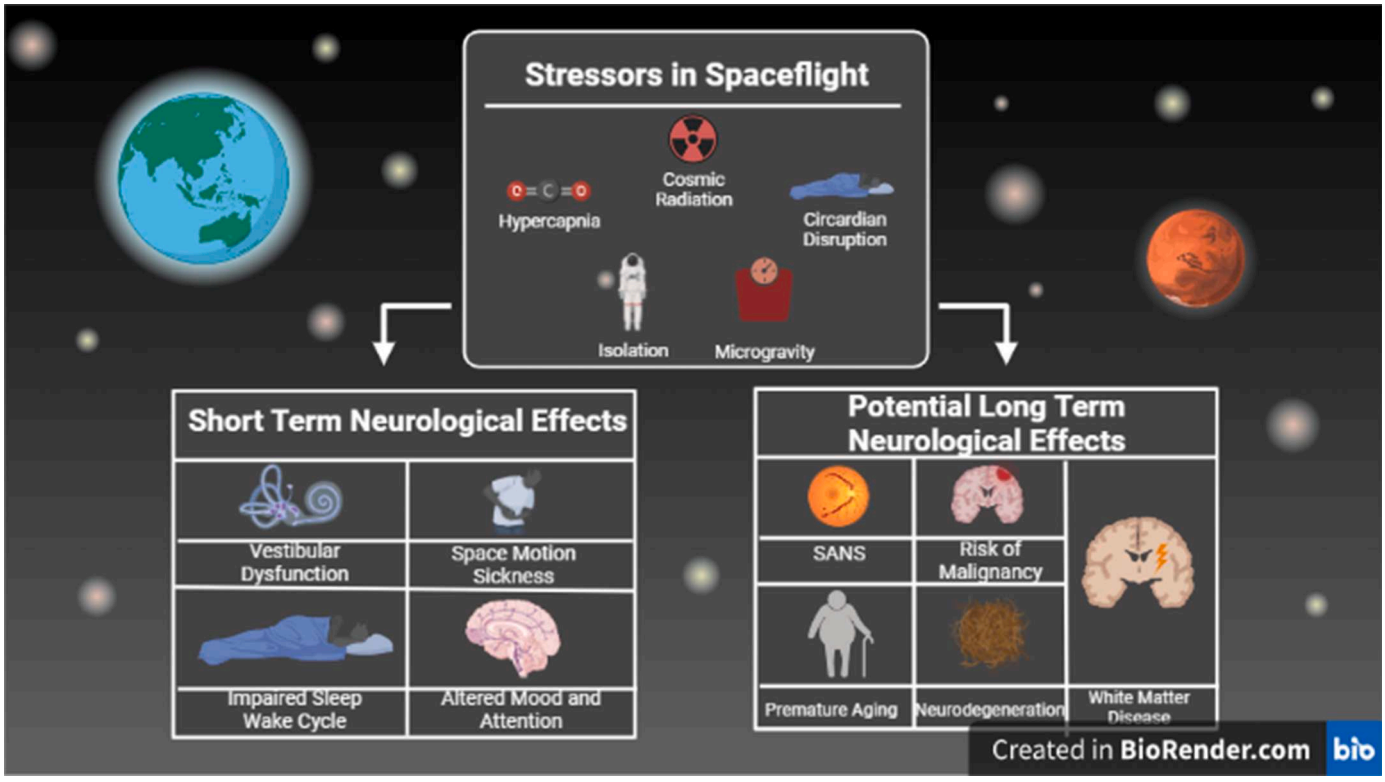

Fig. 1. Short- and long-term neurological effects of spaceflight stressors. The main stressors that affect the CNS are hypercapnia, cosmic radiation, circadian disruption, isolation and microgravity. The short-term changes such as vestibular dysfunction and motion sickness are well established due to microgravity. A combination of stressors contributes to the impaired sleep wake cycle. Although not well established, long term neurological effects of spaceflight include an increased risk of malignancies, premature ageing, neurodegeneration and white matter changes.

In space, the absence of gravity effectively unloads the otoliths due to the lack of a stimulus. Therefore, they cannot provide inputs about head positioning, leading to a greater reliance on other sensory inputs such as visual inputs (Paloski et al., 1993). Astronauts have difficulty determining the upright positions of objects and people due to the imbalance in sensory inputs. In 2006, Dyde RT *et al.* reported that vision contributed more to the perceptual upright in microgravity than on earth, as observed in subjects in supine positions (Dyde et al., 2009).

Studies in animal-based models have helped to better understand the effects of microgravity. Hindlimb and whole-body suspension of rodents is the standard method of stimulating spaceflight. Wise et al. (2005) showed that in mice exposed to 7 days of hindlimb suspension, there were significantly increased levels of reactive oxygen species (ROS), particularly in the brain stem and frontal cortex, due to a reduction in antioxidants. The hindlimb suspension method increases perfusion to non-weight-bearing bones, particularly the skull which increases the bone density of the skull, as seen in the study by Lafage-Proust et al. (1998). This increase in bone density is thought to be the underlying mechanism for the raised intracranial pressure (ICP) seen in this model system (Zhang et al., 2013).

Distorted otolith inputs initially cause incorrect perceptions of the upright position leading to spatial disorientation (Reschke and Clément, 2018). The disorientation results from whole-body rotation, during which the otoliths detect a change in position when there is no real change (Glasauer and Mittelstaedt, 1998). This phenomenon is seen in experiments conducted by Glasauer and Mittelstaedt (1998). These subjects could not determine their position close to the spacecraft in space, but a control group was successfully able to do this on earth. However, astronauts had better spatial orientation after 30 days in space, suggesting that the vestibular and ocular structures adapt to the microgravity with time (Glasauer and Mittelstaedt, 1998). The mismatch in sensory inputs contributes to SMS symptoms such as nausea, vomiting, fatigue and anorexia. Longer space missions allow astronauts to acclimatise to the environment effectively but are also linked to delayed readjustment upon returning to earth. Astronauts may have difficulty moving and feel unstable on their feet upon re-entry to the Earth. Dizziness during head and body movements may severely compromise the ability to perform mission activities required for a safe return. Similar to the transition from gravity to microgravity, returning to earth replaces the gravitational force, resulting in dizziness, disorientation, nausea and vomiting during the readjustment phase.

In 2016, Hallgren E *et al.* found a reduction in the ocular counter-rolling response (OCR) in astronauts who had returned from space; an otolith influenced reflex sensitive to head tilt in angular and linear accelerations (Hallgren et al., 2016). OCR is a method to evaluate the function of the otolith system. A reduction in sensitivities to head tilt in angular and linear acceleration was seen in astronauts who had spent six months or more in space (Dyde et al., 2006). The OCR returned to its pre-flight level after nine days (Lafage-Proust et al., 1998). The decreased post-flight OCR suggests that spaceflight beyond six months induces adaptive and structural changes that impair readjustment upon return to Earth. This delay in adjustment to Earth's gravitational field could impair the astronaut's decision-making in landing procedures, but no such events have been described. This may have significant implications for older space tourists, who are more vulnerable to falls and hip fractures secondary to dizziness, and drowsiness. They may also take longer to readjust to Earth's gravity.

Terrestrial space analogues have been utilised to mimic the space environment and better understand the effects of microgravity. Head-down bed rest (HDBR) is an established space analogue in which participants lie down at an inclined head-down position (-6 degrees most commonly) for a week, month or more extended periods. In 2016, Cassady K. *et al.* reported changes in functional brain connectivity, measured using functional MRI, of the vestibular and somatosensory networks in subjects exposed to 70 days of HDBR (Cassady et al., 2016). Functional MRI is a common technique used to assess the functional connectivity of different brain regions. These regions do not need to be connected anatomically but interact functionally when performing a cognitive task.

Functional connectivity as seen on functional MRI, increased during HDBR, followed by a decrease in the post HDBR recovery. This increase in connectivity is perhaps counterintuitive as a reduction in signalling and connectivity of sensory inputs is expected in a lower gravitational environment. However, this may represent an adaptive mechanism to HDBR. This adaptive response could be in the form of greater cortical reorganisation between the motor and sensory cortices that occur after completing complex tasks or adjustment to altered sensory inputs such as in space (Cassady et al., 2016; Lee et al., 2019).

Research in animal models has shown that microgravity could be countered with increased calcium carbonate crystals in the otoliths. As the sensitivity of otoliths is directly related to the biomineral content, an increase in calcium carbonate crystals may improve sensitivity in a zero-gravity environment (Balaban et al., 2011). However, the correlation between increased calcium carbonate crystals and a reduced adjustment time to microgravity is not scientifically proven. Such theories raise opportunities to study potential adaptation techniques that can be used before spaceflight to improve adjustment. These adaptation methods may accelerate the development of structural changes in the CNS. While these changes would allow astronauts to better cope with the space environment, there would be a significant readjustment challenge, as previously discussed in the findings by Hallgren et al. (2016). Structural and anatomical changes develop over extended exposure lengths and are unlikely to reverse rapidly upon return to earth.

Vestibular dysfunction and SMS remain critical obstacles to entry into space. Despite clinical trials of several medications to counteract SMS, promethazine is the only medication currently in use. Astronauts administer promethazine intramuscularly in space at the onset of their symptoms. However, it can cause sedation, impairing astronauts' concentration during the mission (Weerts et al., 2013). Due to these adverse side effects, other pharmacological agents such as Scopolamine and amphetamines are currently being assessed in clinical trials. Literature reviews have suggested that treatment with scopolamine, an anticholinergic drug co-prescribed with amphetamines, could significantly reduce symptoms of acute SMS (Dornhoffer et al., 2004). Co-prescription of stimulant drugs such as amphetamines is suggested due to the sedating effects of both scopolamine and promethazine (Weerts et al., 2015). Amphetamines are addictive, and long-term stimulant use may increase the risk of addiction and substance abuse of other drugs (Huang and Tsai, 2011). This would be more difficult to manage the longer the duration of a space mission. Amphetamines would need to be used with caution during space missions due to the risk of addiction for which there is no licenced therapy regimen for long-term stimulant use disorders (Chan et al., 2019).

Scopolamine has long been used to treat terrestrial motion sickness and therefore offers potential in the management of SMS. Scopolamine is a non-selective muscarinic antagonist that suppresses the muscarinic receptor signalling located in the semicircular canals. It is thought that conflicting signals from various sensory inputs cause SMS symptoms, and suppression of the semicircular canal sensory input may relieve SMS symptoms (Weerts et al., 2015). In 2015, Weerts A.P *et al.* investigated the efficacy of different methods of administering Scopolamine and found that intranasal Scopolamine was the most effective (Weerts et al., 2015).

Due to its non-selective antimuscarinic and anticholinergic properties, Scopolamine is used to induce cognitive injury in animals to better understand the changes in dementia and potential countermeasures (Yadang et al., 2020). Studies conducted in many species, including non-human primates, have shown memory and learning impairments. In particular, rats given intraperitoneal scopolamine showed deficits in learning and memory in the research by Heo et al. (2014). The underlying mechanism is related to a reduction in cholinergic transmission, similar to the changes in Alzheimer's disease (AD) and ageing

(Klinkenberg and Blokland, 2010). To mitigate the amnesic and cognitive side effects of Scopolamine, a study by Bartus (1978) showed that co-administration of the anticholinesterase physostigmine may reverse the effects of Scopolamine. The wide range of uses of Scopolamine provides a potential option in the management of SMS, provided that the side effects can be minimized appropriately in space. Alternatively, the chemical structure of scopolamine could be altered to reduce its side effect profile and improve efficacy; this approach is already used in drug discovery and repurposing fields (Pauwels et al., 2011).

Baclofen has been trialled to manage the effects of acute SMS as it directly acts on the vestibulo-ocular reflex, which stabilises the vision during head movements. Motion sickness originates from an increase in the velocity storage integrator, a central integrator of peripheral inputs and low-frequency rotations. A reduction in velocity storage activity is associated with a reduction in motion sickness (COHEN et al., 2003). Results have shown that Baclofen affects the semicircular canals, which may reduce these symptoms in spaceflight, given its effectiveness in the management of vertigo (Dornhoffer et al., 2004; COHEN et al., 2003)−. More conclusive evidence is required, but if Baclofen is deemed effective in treating SMS, it may revolutionise the adjustment challenge in space and the management of terrestrial peripheral and central vertigo conditions.

Adjustment and readjustment will likely be influenced by the duration of spaceflight and each individual's response. Astronauts may have increased adjustment periods depending on the length and depth of the missions. Astronauts travelling to space for short missions may only have minimal adjustment difficulties due to repeated exposure to the environment meaning that pharmacological intervention is inappropriate. However, in commercial spaceflight, general population members will likely face lengthier and tougher adjustment due to the lack of prior experience and coping mechanisms that astronauts would have developed as part of their training and exposure. Potential missions to Mars will inevitably result in more difficult adjustments due to the increased distance and potentially increased psychological stress due to the complexity and accuracy required for such a mission. Although pharmacological intervention for SMS has side effects, these side effects may be justified for longer commercial space missions.

In summary, astronauts in spaceflight are affected by SMS due to microgravity which removes the stimulus for the otoliths. As a result, the otoliths cannot detect spatial orientation in response to tilting the head and cannot detect the upright position of people and objects. Conflicting sensory inputs compromise spatial orientation and may affect mission performance. These symptoms are usually experienced for the first few days of spaceflight and upon return to earth but improve as the vestibular system adapts to the environment. People with less biological capacity are likely to experience SMS for longer periods. Intramuscular promethazine is the only medication that is widely used for SMS. Further trials are required to assess the efficacy of other pharmacological agents to provide more options for the prophylactic and symptomatic management of SMS.

3. Ocular pathologies and fluid shifts

Microgravity causes a redistribution of fluid from the lower extremities to the head which can contribute to vestibular dysfunction and affect the ocular structures and the brain parenchyma.

The redistribution of fluid causes significant structural changes to the brain, including increased grey matter and ventricular volumes (Roy--O'Reilly et al., 2021; Hupfeld et al., 2021). An increase in ventricular CSF volume can cause white matter hyperintensities (WMH), which are linked to small vessel disease in terrestrial patients. On Earth, WHM have been linked to cognitive impairment and an increased likelihood of developing dementia. In 2017, Alperin *et al.* highlighted a statistically significant increase in WMH in astronauts after long-duration spaceflight (Alperin et al., 2017). However, WMH in these subjects was restricted to the periventricular areas and resolved upon return to earth. The lack of deep WMH is thought to exclude WMH gained in spaceflight as a cause of cognitive changes seen in astronauts and is unlikely to be associated with long-term risks of small vessel disease or cognitive change (Alperin et al., 2017).

On earth, a postural change from a supine to an upright position generates a hydrostatic pressure gradient, which causes blood to flow down the pressure gradient and towards the feet (Tanaka et al., 2017). In space, the absence of gravitational force removes this pressure gradient and increases blood flow to the head (as shown in Fig. 2 with hypothetical blood pressures on Earth and space).

A study conducted by Taibbi G *et al.* compared the ocular outcomes in participants exposed to 14- and 70-day HDBR (Taibbi et al., 2016). Participants exposed to 70 days of HDBR had greater retinal thickening and optic disc swelling than those exposed to 14 days of HDBR, indicating that increased duration of microgravity exposure is linked to increased ocular changes seen in spaceflight.

The fluid shift increases the intracranial and intraocular pressure, producing an unusual combination of neuro-ophthalmic changes known as spaceflight-associated neuro-ocular syndrome (SANS) (Lee et al., 2020). These changes can include optic disc oedema (most commonly unilateral), globe flattening (flattening in the convex shape of the sclera), the appearance of choroidal and retinal folds, optic refractive error shifts or focal areas of ischemic change to the retina (Lee et al., 2020; Mader et al., 2021). In 2011, Mader *et al.* assessed seven astronauts before and after six months of spaceflight (Mader et al., 2021). Five astronauts reported decreased near vision (hyperopic shifts). Further assessment with specialised orbit imaging showed a combination of optic disc oedema, globe flattening, choroidal folds, and increased intracranial pressures demonstrated through a lumbar puncture (LP). Although vision was corrected in all seven astronauts, the structural changes persisted for months to years in some. In another more extensive study conducted by Mader *et al.* involving 300 astronauts, neuro-ophthalmic changes persisted for many astronauts years after fligh (Mader et al., 2011).

The precise aetiology of SANS is unclear, but there are several potential theories. One of these is that these changes occur secondary to raised ICP. An increase in cerebral blood flow and thickening of the grey matter may impair drainage of cerebrospinal fluid (CSF), which may manifest as decreased near vision and ophthalmic changes such as optic disc oedema and globe flattening. These changes are similar to those seen in terrestrial patients with idiopathic intracranial hypertension (IIH) (Lee et al., 2020). IIH is a condition characterised by papilledema (pressure on the optic nerve) caused by raised intracranial pressure. The condition is often associated with obesity and treatment to relieve the optic nerve pressure is needed to stop blindness from potentially developing. IIH almost invariably presents with a headache and bilateral optic disc oedema secondary to raised ICP (papilledema), but these signs are not seen in astronauts with SANS. Although raised ICP has caused flattening of the posterior globe in some patients with IIH, this is rare. Whether the optic disc oedema in SANS represents papilledema or a finding specific to the condition is unclear. Furthermore, the pathophysiology of IIH does not arise from a microgravity environment or fluid shifts (Taibbi et al., 2016; Lee et al., 2020; Mader et al., 2021).

Evidence against the ICP hypothesis may be valid, as astronauts with clinical features of SANS did not have headaches, diplopia or the changes in vision, that are classically seen inIIH. Although astronauts with SANS had mildly elevated ICP (22–28 cm H_2O), ICP is usually significantly higher in patients with IIH (30–40 cm H_2O) (Lee et al., 2020; Mader et al., 2021; Mader et al., 2011). Other possible explanations include CSF collection in the optic nerve due to impaired exchange of CSF around the optic nerve and in the subarachnoid space (Mader et al., 2011). There is no clear pathophysiology of SANS, but a combination of these hypotheses will likely provide a better understanding of the onset and management of SANS.

There are currently no specific management options for SANS, but management options will be available as we better understand the

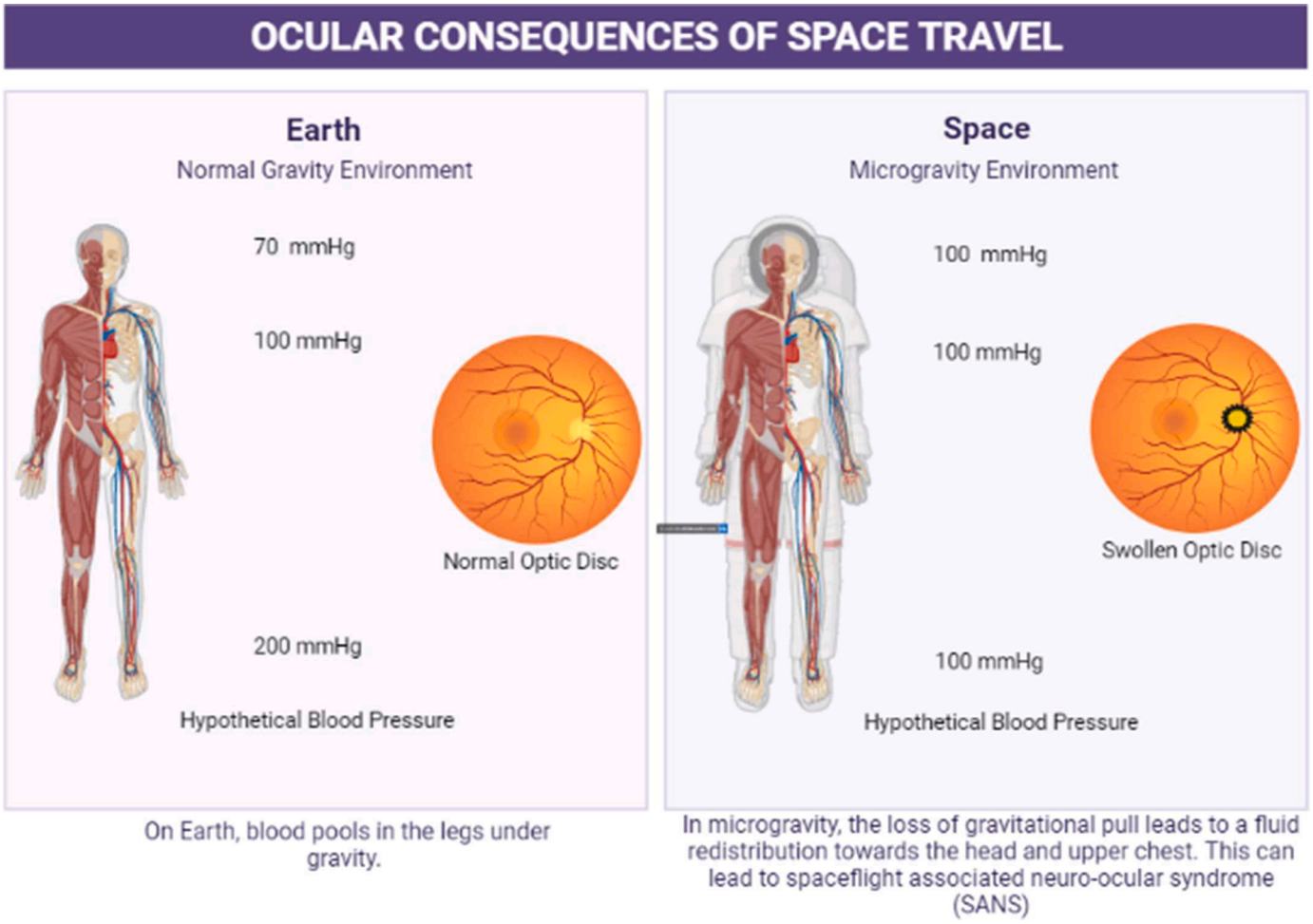

Fig. 2. The change to optic structures due to the redistribution of CSF in microgravity environments. The panel on the left shows hypothetical blood pressures on earth dependant on the effects of gravity. The panel on the right shows how in the microgravity environment there is a reduction in hydrostatic forces which leads to an equalisation of blood pressure throughout the body and hence fluid redistribution that an astronaut maybe exposed to.

condition. Due to the similarities with IIH, the management of SANS may be guided by the guidelines for the treatment of IIH (Mader et al., 2011). Acetazolamide, a carbonic anhydrase inhibitor, is the first-line management of IIH and works by reducing CSF production in the choroid plexus, reducing intracranial pressure (Millichap and Millichap, 2015). Although it has not been trialled in the prophylactic or therapeutic management of SANS, it could be used as part of a randomised controlled trial during pre or post-flight regimens.

The similarities between IIH and SANS may pose a risk for individuals with pre-existing IIH. Although the precise aetiology of SANS is unknown, it is suspected that individuals with IIH may be at a greater risk of developing SANS and its associated visual changes. Evidence suggests these individuals may be more susceptible to changes in ICP which may cause longer persisting visual changes and possibly a higher risk of long-term vision damage. Although it is difficult to clearly define if spaceflight should be contraindicated in individuals with IIH, it appears that spaceflight should be avoided in these individuals until further evidence about risks is available.

It also has to be considered that if CSF flow is affected during long-duration space travel, there may be changes to CSF drainage of the brain with respect to protein metabolism. The pathology of diseases such as Alzheimer's and Parkinson's is characterised by abnormal protein deposition (Braak et al., 2003; Braak and Braak, 1991). There is emerging evidence that protein deposition may be affected by CSF clearance of protein in Alzheimer's disease (Li et al., 2022). Long duration space flight may therefore exacerbate protein accumulation in susceptible patients and lead to earlier cognitive decline.

Two upcoming studies at the University of Birmingham will investigate key gaps in the diagnosis and treatment of SANS (Research to boost astronaut health for future space missions 2021). The first will utilise high quality imaging modalities for the early diagnosis and monitoring of SANS whilst the second will study the effect of a glucagon-like peptide-1 (GLP1)-receptor agonist in the treatment of SANS. GLP1 has previously been implicated as a target in CSF dynamics that can be targeted in animal models of IIH (Botfield et al., 2017).

Finally, conditions that affect the flow of CSF throughout the nervous system, such as aqueductal stenosis and hydrocephalus, may also be affected by the fluid shift of microgravity environments (Kramer et al., 2020). Therefore, these conditions may be relative contraindications to space flight.

4. Cosmic radiation

One of the main concerns regarding spaceflight is exposure to cosmic radiation. The earth's magnetic field protects us against high energy radiation, but astronauts in space are not protected by this magnetic field and are directly exposed to high energy radiation (Townsend, 2005). In the past, the duration of space missions was limited by technological capabilities, human adaptability and funding, meaning that radiation exposure was insignificant. However, technological advances and increased funding have enabled longer and deeper space missions, significantly increasing exposure to different types of radiation.

Solar particle events (SPE), which make up the majority of low dose galactic cosmic rays (GCR), are made up of protons emitted from the sun. GCR are composed of high energy protons and high-energy charged (HZE) particles (Clément et al., 2020). These charged particles have a higher linear energy transfer (LET) than the ionising radiation (gamma and X-rays) used in medical imaging and cancer treatment. HZE is a form of high-LET radiation that can penetrate spacecraft and human tissue and deposit in the body to induce cellular and DNA damage. Due to the higher amounts of microscopic energy deposition and a large range in shielding and tissue, there are significant concerns about higher cancer risks and neurodegenerative changes as seen in both animals and humans.

Significant developments have been made in the understanding of short- and long-term effects through stimulated radiation in cellular and animal models using ^{56}Fe particles (Rabin et al., 2007). Irradiation, used in cancer treatment, has been shown to precipitate cognitive decline and memory impairment. The underlying mechanisms are likely to be a combination of inflammation, oxidative stress and radiation effects on differentiated adult neural stem cells and potentially neural progenitor cells (Acharya et al., 2011).

Evidence of altered neurogenesis in the hippocampus was seen in studies conducted by Rola et al. (2004) and Raber et al. (2004). In the study conducted by Rola et al., mice who received HZE showed a reduction in neural precursor cells in the subgranular zone of the hippocampus after two months. In a more extended study conducted by Joseph (2000), rats showed behavioural changes two years after exposure to HZE alongside reduced hippocampally related memory performance (Joseph et al., 2000). Further analysis of this rat's showed evidence of accelerated ageing. These studies show that high-LET radiation has a significant short- and long-term impact on the neurogenesis in the hippocampus.

More recent research has identified several other mechanisms that might contribute to cosmic radiation induced cognitive impairment, that do not automatically lead to altered neurogenesis. The expression of the glutamate transporter GluR1 is reduced within the brain when mice are exposed to radiation levels similar to that experienced in space flight (Wu et al., 2022; Krishnan et al., 2021). This particular neurotransmitter receptor is needed to allow long term potentiation within neurons allowing memory encodement. Age of exposure to radiation and radiation type are likely to be important in determining the effect of cosmic radiation on neurotransmitter receptor expression changes as other studies have reported alterations to NMDA receptors but not GluR1 when older mice are exposed (Shi et al., 2006; Peng et al., 2019). Several studies have highlighted the role of microglia activation in cosmic radiation induced cognitive impairment, and how inhibiting this activation prior to exposure can stop the development of cognitive impairment (Raber et al., 2016; Parihar et al., 2018; Rola et al., 2008; Krukowski et al., 2021; Krukowski et al., 2018). Interestingly, the mechanism by which microglial activation causes cognitive impairment when exposed to cosmic radiation is similar to changes seen in Alzheimer's disease (Rajendran and Paolicelli, 2018). Microglial activation leads to alteration in synaptic protein expression suggesting abnormal synaptic pruning (Parihar et al., 2016).

Several possible treatments have already been suggested to combat the inhibition of neurogenesis caused by cosmic radiation. Amitriptyline, a widely used anti-depressant medication, has been shown to stop neurogenesis loss by inhibiting sphingomyelin phosphodiesterase 1 expression (Guo et al., 2019). Allantoin and neferine compounds also thought to have anti-depressant properties have been shown to stop the over expression of transthyretin post radiation exposure which, when over expressed, inhibits retinol-induced neuritogensis (Kang et al., 2018). Table 1 highlights some of the more recent suggested cellular pathway changes caused by cosmic radiation.

High-LET radiation likely plays a vital role in the onset of cognitive decline, given the close relationship between hippocampus function and neurogenesis. These effects are particularly significant in younger astronauts who may be especially vulnerable to cognitive decline and premature ageing. However, there is a significant difference in cognitive development between humans and rodents. Therefore, the extrapolation of the findings in animal studies to humans should be approached with caution (Cucinotta et al., 2014).

HZE induces direct neuronal damage and acute injury to the brain,

Table 1
Cellular changes seen after cosmic radiation and cosmic-like radiation exposure.

Type of radiation	Amount of radiation	Pathways involved in altered neurogenesis	Reference
Ionizing	30 Gy	The radiation-induced loss of glutamate transporter, GluR,1 in the hippocampus reduces synaptic potentials, particularly dendritic and somatic depolarization (Wu et al., 2022).	Wu et al. (2022)
Neutrons	18 cGy	Chronic neutron exposure alters the homeostatic synaptic plasticity relationship by reducing and disrupting the relationship between long-term depression and potentiation secondary to the loss of post-synaptic protein, PSD-95, in the hippocampus and medial prefrontal cortices. Neutron exposure increases CD68+ microglia, which causes a prolonged proinflammatory period (Krishnan et al., 2021).	Krishnan et al. (2021)
Ionizing	45 Gy	Irradiated rats had higher levels of glutamate receptors, NR1 and NR2A in the hippocampal CA1 (Shi et al., 2006).	Shi et al. (2006)
Ionizing	2 Gy	Irradiation of mice induced impaired cell proliferation and neurogenesis in the subgranular zone measured using neurogenesis markers Ki67 and doublecortin (Peng et al., 2019).	Peng *et al.* (2019)
HZE and protons	0.5 Gy (HZE) 0.1 Gy (Protons)	Mice exposed to combined ^{56}Fe and proton radiation had increased levels of interleukin-12 and reduced levels of interferon-ɣ than proton-radiated mice. Interleukin-4 levels were lower in mice that received HZE compared to proton-radiated mice. Exposure to combined radiation also reduced macrophage-derived chemokine levels, correlated to the percentage of new activated microglia in the hippocampus (Raber et al., 2016).	Raber et al. (2016)
Proton	0.5 Gy	Proton irradiation affects the hippocampal perisomatic inhibitory circuits by altering the cannabinoid type 1 receptors signalling system with GABAergic neurons (Lee et al., 2017).	Lee et al. (2016)
Proton	100 cGy	Radiation-induced long-term changes at 6 and 8 months post radiation in microglia activation as measured by increased levels of CD68 and CD107a proteins, markers of phagocytic activity (Krukowski et al., 2018).	Krukowski et al. (2018)
^{4}He	5-30 cGy	Exposure to ^{4}He resulted in hyperpolarized resting membrane potential in the perirhinal cortex. Radiation is linked to pre- and post-synaptic changes as measured by the frequency of the excitatory cells (Parihar et al., 2018).	Parihar et al. (2018)

which results in neuroinflammation. This process occurs due to the activation of astrocytes and microglia, resulting in reduced cognitive, behavioural and motor function (Cekanaviciute et al., 2018; Cucinotta et al., 2014). This neuronal damage results in mitochondrial dysfunction, production of ROS and expression of inflammatory mediators (Onorato et al., 2020; Nelson et al., 2016). ROS activate microglia and macrophages necessary for the clearance of waste substances from the brain, but can destroy synapses and brain parenchyma, if overactivated. High rates of ROS productions have been seen in neurons and synapses in the hippocampus from investigations in animal models exposed to space-like radiation. The oxidative stress can prevent the reproduction of neurons, which is necessary for consolidating memory and learning (Nelson et al., 2016). It should also be considered though, that ROS are active signalling molecules within the brain and have been shown to have a role in the development of long-term potentiation, the process thought to underlie the physiological processes that allow the brain to learn (Massaad and Klann, 2010). Destabilising the delicate balance in ROS production within the brain can have deleterious effects, which longer-term space flight may propagate.

Mechanisms to counteract ROS are currently being researched. Macronutrients with antioxidant properties effectively maintain the ROS balance within the brain. Selenium, a macronutrient, has received significant attention for its antioxidant properties (Kryscio et al., 2017). Selenomethionine, an analogue of methionine (a naturally occurring amino acid), has been shown to reduce ROS. Despite the lack of evidence of Seleniomethionine in post-spaceflight studies, terrestrial studies have shown that Selenomethionine and other synthetic antioxidants may replenish antioxidants in the body and prevent long-term degenerative changes (Kryscio et al., 2017). Trials in post-spaceflight astronauts are needed to match the promising evidence seen in terrestrial subjects. If Selenomethionine proves effective, it may be worth considering as part of the pre-flight treatment regime alongside other medication to reduce intra or post-spaceflight symptoms and complications of HZE exposure. Several other antioxidant supplements and therapeutics could be trialled in space flight which have evidence of improving cognitive performance on Earth. Higher vitamin E levels are associated with improved performance on cognitive testing, particularly in people of younger age (Beydoun et al., 2015). Chocolate, coffee and certain fruits and vegetables are thought to have positive effects on cognition through an antioxidant mechanism, although further research is needed in the area before the true effect of these foods' antioxidant properties can be confirmed (Baroni et al., 2021).

Neuroinflammation is thought to have a key role in the development of psychiatric and neurodegenerative conditions. In 2013, Cherry *et al.* reported that low dose HZE (100 cGy of Fe particles) accelerated the development of AD pathology in mice with a familial gene known to cause the condition (Cherry et al., 2013). The progressive cognitive decline is thought to occur secondary to a chronic neuroinflammatory process mediated by Intercellular Adhesion Molecule 1 (ICAM-1). HZE increases the expression of ICAM-1 which activates the endothelial cells of the blood brain barrier (BBB). This activation of the BBB reduces the clearance of amyloid from the brain leading to accelerated pathological aggregation and cognitive change. Damage to this BBB via this mechanism is important when considering space flight as several diseases in which cognition is affected have been shown to be linked to ICAM-1 and blood brain barrier dysfunction. Major depression and bipolar disorder have been associated with increased ICAM-1 levels meaning space flight may increase the prevalence of these disorders (Müller, 2019). There is still conjecture around the idea that long-term space flight causes chronic neuro-inflammation as animal studies often report higher doses of radiation than what astronauts may be exposed (Cherry et al., 2013). Animal research often focuses on specific particle types, which is not reflective of the heterogenous radiation exposure that astronauts receive on long-term space flight. Further work is needed to establish the link between the development of neuro-inflammation and long-term space travel.

The risk of brain tumours and cancer from spaceflight is currently being investigated by the National Aeronautics and Space Administration (NASA). HZE particles induce DNA change in numerous genes, which may be the initiating factor for tumours (Kennedy, 2014; Hong et al., 2016). There is currently limited evidence suggesting spaceflight HZE increases the risk of brain tumours. However, terrestrial sources of ionising radiation increase the risk of brain tumours. Atomic bomb survivors exposed to moderate to high doses of ionising radiation were at higher risk of brain tumours (Cucinotta and Durante, 2006; Preston et al., 2002). In the study by Ron et al., the risk of all subtypes of brain tumours was significantly higher, especially schwannomas, gliomas and meningiomas (Ron et al., 1988).

Cosmic radiation presents different challenges. GCR and HZE consist of ions and species that are more potent than the ionising radiation used in terrestrial settings. However, the nature of cosmic radiation alone does not translate to an increased risk of cancer so other factors such as age and the dose of radiation need to be considered (Ron et al., 1988). Although most tumours were benign, radiation-induced meningiomas displayed more atypical histological features than spontaneous meningiomas (Ballesteros-Zebadua et al., 2012). This is a cause for concern as tumours with atypical histological features may potentially become malignant in the future. The accumulation of radiation-induced damage and atypical histology may cause a rise in malignant brain tumours.

In 2012, Ballesteros-Zebadua *et al.* reported that pro-inflammatory mediators such as tumour necrosis factor-α, interleukin-6, and prostaglandin E2 are involved in the brain's response to ionising radiation in children who underwent radiotherapy for brain cancer (Ballesteros-Zebadua et al., 2012). In theory, the nature of space HZE may translate to a significantly higher risk of neural injury and inflammation than ionising radiation used in terrestrial situations. Due to this perceived risk, it may be appropriate to advise that children and pregnant women should be exempt from spaceflight. Children are more likely to experience short- and long-term effects such as demyelination and premature ageing (Ballesteros-Zebadua et al., 2012). However, more evidence is required with radiation that closely resembles that found in space in these populations to understand the long-term risks of ionising radiation exposure.

Positive effects of space-like radiation levels on cognitive performance have also been seen in mouse experiments. Work by Whoolery et al., (2020) has shown that when mice are exposed to space-like radiation there is improved performance in pattern separation tasks, and no detrimental change in rule-based, or object-spatial paired associates learning. Several theories are put forward by the authors to explain the improved performance on the pattern separation task such as alterations to the hippocampal functional network and the suggestion that HZE affects GABAergic interneurons in the dentate gyrus, which promotes brain network formation that supports this cognitive task. The dose of radiation used in most animal models to replicate space-like radiation is similar to what an astronaut would be exposed to on a 3-year Mars mission. Together these experiments suggest that multi-domain cognitive assessment throughout the duration of the space mission may be needed to assess the effect, which may be both positive and negative, that cosmic radiation has on astronaut performance. Research within this area may also help psychologists design appropriate cognitive stimulation for space travellers on longer space flights.

In summary, cosmic radiation may increase the risk of developing neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. This may mean that space tourists who have these conditions, or are at higher risk of developing them, should consider the potential long-term consequences of their travel. Positive effects of cosmic radiation have been seen in animal models of space flight, but further work is needed to understand the balance between the negative and positive impacts cosmic radiation has on cognition. The exposure to cosmic rays and hence HZE may mean that a space tourist has a higher risk of developing a brain malignancy, especially in groups more susceptible to the effects of HZE such as children and pregnant women. This again may

suggest that advising against spaceflight in these groups is appropriate.

5. Psychological implications

The isolated and confined environment (ICE) of space is a significant stressor that affects the well-being of astronauts. As space missions get longer, astronauts will spend more time in isolation, confinement, and away from their families. With potential manned missions to Mars, astronauts may be socially isolated for up to three years (Kanas et al., 2009). ICE has been studied in expeditions to Antarctica to better understand the psychological pressures that astronauts face. Although Antarctica cannot replicate the microgravity and radiation exposure of space, it is an extreme environment that offers a realistic analogue for studying psychological stressors encountered by astronauts. Both environments require specifically designed technology for survival, lack standard circadian and weather patterns, and present physical and psychological challenges (Suedfeld, 2018).

Numerous studies have been conducted over varying periods, including the Antarctic winter, which represents some of the harshest conditions on earth. These Antarctic missions are associated with low mood, increased stress, interpersonal tension, reduced sleep and impaired concentration and memory (Tortello et al., 2021). The response to ICE is subjective, with varying psychological impacts from person to person. In most people, however, there is a common manifestation in the form of psychological stress characterised by an increase in sympathetic tone and activation of the hypothalamic-pituitary-adrenal axis (Choukér and Stahn, 2020). In the study by Palinkas L *et al.* (2008), stress presented as headache, sleep disturbances, cognitive impairment, low mood, anxiety and interpersonal conflicts in participants on a polar expedition. A smaller proportion of these individuals also suffered from a psychiatric disorder, most commonly seasonal affective disorder (Palinkas and Suedfeld, 2008). Mental health problems may also be precipitated by adjustment difficulties to the environment, particularly spatial orientation and motion sickness. Serious psychiatric complications such as bipolar disease and schizophrenia are rarer in spaceflight than in other extreme environments due to intense pre-flight screening but as space tourism becomes more common so might these psychiatric illnesses in space (Ephimia Morphew, 2001). Cultural and interpersonal stressors may also impact astronauts' mental health during spaceflight. As space crafts and the International Space Station are staffed by individuals from different countries and backgrounds, conflicts between staff will worsen mental health and impair mission performance (Kanas et al., 2009; Ephimia Morphew, 2001). Mission performance is dependent on the astronaut's ability to adapt and cope with the environment and work as a team. Social isolation and confinement can alter the group dynamics and create social tension (Tortello et al., 2021). ICE is a major source of interpersonal difficulties, particularly in longer missions. Astronauts from different cultures are likely to approach decision making and emergencies differently, which could impact collaboration during missions. Despite these potential challenges, multicultural staff may facilitate better collaboration between nations and space agencies, increasing funding and resources for spaceflight (Kanas et al., 2009; Ephimia Morphew, 2001).

Although spaceflight may be associated with negative psychological effects, the experience of missions and training can be beneficial and induce long-term positive effects. Pre-flight educational, physical and medical requirements are neuroprotective and reduce the risk of cognitive decline. Spaceflight, itself, may induce positive psychological effects, and effective countermeasures to inflight stressors are directly linked to personal gains (Suedfeld and Weiss, 2000). One of these positive psychological changes is salutogenesis which refers to the ability to emerge from stressors in a way that promotes long term personal growth and resistance to future stressors (Goemaere et al., 2016). Undergoing hardship and potentially traumatic experiences can result in psychological benefit and personal growth post-experience. Although the underlying mechanism is not well understood, it can protect astronauts from the pathological effects of stress (Ritsher et al., 2007). This process has been extensively studied in extreme, dangerous and isolated environments such as polar expeditions, submarines, spaceflight and combat situations. It results in personal growth and long-term positive changes in daily life, such as improved self-understanding and awareness, deeper relationships with family and a feeling of achievement of personal goals.

In a study conducted on twenty retired astronauts by Suedfeld *et al.* (2012), improvements were noted in all areas of personal growth, including new possibilities, general appreciation of life, spiritual change and personal strength. Similar findings were reported in naval crew who had more successful careers and fewer medical problems after a polar expedition (Palinkas and Suedfeld, 2008). Salutogenesis can result from a variety of factors. Firstly, a strong relationship between team members can promote teamwork, improve productivity and lead to an appreciation of the need for teamwork in achieving personal goals. Secondly, the development of personalised countermeasures to stressors enables easier adaptation and promotes more meaningful and enriching activities that have significance after the experience.

There are well-established physical benefits of astronaut training. Astronauts are required to meet physical fitness and educational requirements to be eligible for spaceflight. High levels of education, physical fitness and intellectual stimulation may mitigate the risk of neurological disease and are linked to reduced cognitive decline through slower deposition of β amyloid plaques in conditions such as Alzheimer's disease. In 1995, Ott *et al.* reported reduced rates of dementia in more educated individuals (Ott et al., 1995). Physical fitness and good cardiorespiratory health protect against cognitive decline, especially among the older population (Hillman et al., 2008). In patients with multiple sclerosis, aerobic conditioning increased grey matter volume in the prefrontal and frontal areas. These findings could be relevant to the general public as fitness-promoting public health policies may reduce the risk of cognitive decline. Acquisition of robotic, language and technical skills in preflight training is associated with positive brain plasticity. This was seen in increased grey matter density in areas that corresponded to the task being performed (Chang, 2014). Together this work may suggest that exercise on longer term commercial space missions may also help overcome some of the negative psychological experiences space tourists may be at risk of developing. Assessing the psychological consequences of spaceflight is essential for extended space missions and commercial space travel. In the future, there will be a greater emphasis on mental health during and after the spaceflight period with more stringent pre, during and post-flight routines. Methods are being developed to support astronaut health, facilitate efficient interaction between multicultural astronauts, and manage the stress of ICE. Improved coping strategies and greater collaboration in a multicultural group will better prepare the astronaut to cope with the social isolation of spaceflight (Kanas et al., 2009). It has yet to be determined the level of psychological assessment a future space tourist will undergo prior to their journey, but a basic assessment will likely be needed by all companies offering recreational spaceflight.

Spaceflight is a dangerous method of propulsion, so exposure to an extreme emotional event may be overwhelming. It may be that the social isolation of spaceflight leads to the development of psychological prodromes that precipitate functional neurological illness. The long-term success of spaceflight will require a better understanding of the interaction between the environment and astronauts. Findings in analogues such as long-duration Antarctic missions, submarines and sailing missions may aid in reducing psychological stressors and promoting positive changes such as salutogenesis. Rigorous psychological profiling may be needed prior to the mass introduction of spaceflight to the population, or that potential space tourists are at least warned about the psychological impacts of spaceflight. Table 2 lists conditions that may be relative contraindications to space flight, and what particular space flight stressor may exacerbate the condition.

Table 2
Conditions that may be contraindicated in spaceflight.

Nervous system condition	Space flight stressor
Vestibular Disorders	Microgravity environment
Severe motion sickness	Microgravity environment
Idiopathic Intracranial Hypertension	Microgravity environment
Visual impairment (such as short sightedness)	Microgravity environment
Syncopal Disorders	Microgravity environment
Hydrocephalus and CSF flow disorders	Microgravity environment
Increased risk of brain malignancy	Cosmic Radiation
History of Childhood Malignancy	Cosmic Radiation
Increased risk of neurodegenerative disease	Cosmic Radiation
A history of Psychiatric Illness such as depression	Social Isolation

6. Gender differences

Gender-based differences in neurological responses to spaceflight also need to be considered. Current evidence suggests that the differences in functional and anatomical structures of the brain in males and females can affect adaptation to space. Females are at a reduced risk of SANS and raised ICP, despite the significantly higher incidence of IIH in females, as seen in the findings by Lee et al. (2020). Although difficult to assess, research by Moriyama *et al.* (2007) on the human vestibular nerve from cadavers suggests that, on average, female vestibular nerves contain fewer myelinated axons than males. This potentially explains the higher incidence of vestibular dysfunction seen in female astronauts. These findings were reflected in the higher incidence of SMS in female astronauts in both short and long-duration spaceflight (Reschke et al., 2014). Studies by NASA cancer risk model indicate that overall, females are at higher risk of radiation-induced cancers when compared to males, but there is variation depending on the tumour site. Females were at higher risk of lung, liver, urinary and stomach cancers, but males were at higher risk of colon and brain cancers (Cucinotta and Saganti, 2022). Brenner *et al.* investigated the risk of CNS tumours in atomic bomb survivors (Brenner et al., 2020). The risk for all tumour subtypes was higher in males, including meningiomas which, are significantly more common in females (Preston et al., 2002). Due to the higher overall risk to females, the mission duration for female astronauts is sometimes reduced (Cucinotta et al., 2015). This poses interesting questions about developing self-sustainable colonies on planets such as Mars if female astronauts experience worse health outcomes on longer journeys. Gender-specific risks across different organ systems and diseases are not yet well established but may become more apparent as more people become space tourists.

7. Limitations

The major limitation of research into neurological consequences of space travel is that only a small number of individuals have been studied thus far. This problem is compounded by the inter-individual variation in physiological responses to microgravity.

Terrestrial analogues such as HDBR help to understand the mechanisms behind the brain pathologies caused by space flight but lack the realistic simulation of space missions. Several factors of space travel cannot be replicated in experimental settings, including cosmic radiation, impaired metabolism, nutritional changes, and sleep deprivation. Whilst studies in other animals have demonstrated the development of many of the pathological changes discussed in this review – extrapolation from mice to humans may be inaccurate.

In the long term, well designed clinical trials and observational studies will better indicate the long-term adaptive and maladaptive CNS structural and functional changes from space travel. Several leading multinational corporations are at the forefront of the push for space tourism. As such, private companies will have access to a wealth of information on the neurological sequelae of space travel. The data gathered in experimental protocols and databases must be accessible to regulators who can independently verify the safety and consequences.

8. Summary

In this article, we have highlighted the changes in the nervous system that occur due to space flight. Diseases that affect the vestibular and ocular pathways are already seen in astronauts who return from space and may lead to impaired balance and vision upon returning to earth. Specifically, neurologists must be aware of SANS in the future as this could easily be confused with IIH and may lead to the unnecessary investigation of symptoms.

Long-duration space flight poses real risks of neurodegenerative disease in previously well patients. An extensive neurological examination and neurodegenerative biomarker assessment may be required prior to spaceflight to identify the personal risk of neurological disease a space tourist may have. The risk of brain malignancy and the development of conditions such as Alzheimer's and Parkinson's disease should be thoroughly discussed with a person intending to travel to space. Patients with ataxia or other balance problems may be significantly affected by space travel. The confines of spaceflight and the potentially lonely nature of travel may also lead to an appearance of space-related functional neurological disease, which may mean that neuropsychological profiling prior to departure is essential.

As evidenced in this article, many conditions can affect the nervous system when undergoing space travel. As a result, it may be that as more and more people become astronauts, medical support in the form of a neurologist is needed in space. The space neurologist of the future is unlikely to be supported by the impressive armoury of tests and procedures that can be performed on Earth and therefore is likely to need excellent clinical diagnostic skills and an ability to diversify into different neuroscience specialities such as neuropsychology and possibly psychiatry.

There remain health and legal challenges that need to be considered before the initiation of commercial space flight. Despite the advancements in medical investigation, the sensitivity of current screening tests for spaceflight-associated neurological disease remains a potential issue in diagnosis and treatment. Furthermore, the risk of spaceflight must be categorised based on the duration and distance of space travel (low earth orbit vs deep space mission), as this will significantly influence the radiation dose and adjustment periods.

Commercial space travel is likely to need legal guidelines regarding accountability, roles and responsibilities, data collection, individual medical assessment and acceptance of the risk associated with the travel. The medical assessment may include genetic testing to assess personal health risks and for research purposes. There are several potential ethical issues related to genetic testing, particularly autonomy and confidentiality, especially for general research purposes. Genetic testing can also have unintended personal and emotional consequences that may have long-term impacts. As we progress to the era of space tourism, holistic consideration and continuous development of the nature of spaceflight, individual risk identification, and legal factors, are required

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Space is a complex medical setting due to the extreme environment and the physiological changes that occur due to environmental stressors. Medical equipment and resources are limited in space. The increase in deep space missions will increase the need for medical and surgical expertise and equipment. Currently, medical emergencies are extremely rare in space, and non-emergencies are usually treated with ground-based medical support. Most conditions that arise in space are due to adaptation and can be managed with the available medication. More complex non-emergency situations are often managed on Earth (Stewart et al., 2007). Ground-based medical support is not an option for deeper space missions due to the communication difficulties and limited movement of astronauts. Emergencies such as arrhythmias, myocardial infarctions, stroke, thrombosis, brain haemorrhages, renal colic and infection will require prompt intervention in space. Advanced medical

care will be a requirement for deep space missions with dedicated healthcare professionals trained in space medicine with more specialist equipment and technology. Future manned missions to the moon and Mars will require an onboard physician experienced in managing potential emergencies. As a result of limited resources and staffing, preflight training may include more intensive medical training to assist during an emergency. One avenue that could be explored for longer space missions in areas of medicine such as emergency surgery could be the use of medical robots. The da Vinci operative system would be one such technology that could be employed to allow trained surgeons on earth to perform complex operations in space (George et al., 2018; Sterbis et al., 2008). Although the transmissions of operative signals between the spaceship and Earth based surgeon would be delayed when greater distances are travelled, affecting the ability to use this technology during interplanetary travel.

As we continue to understand more about human adaptation to microgravity and the potential medical problems that may arise, the capabilities of healthcare must continue to progress to match the ambition of multinational corporations. In conclusion, there appear to be many factors that can affect the nervous system and lead to neurological diseases in people who travel to space. As space travel becomes more accessible to the general public these nervous system effects will need to become a staple of the future neurologist's clinical practice.

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