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Review Article

Space–brain: The negative effects of space exposure on the central nervous system

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Abstract

Journey to Mars will be a large milestone for all humankind. Throughout history, we have learned lessons about the health dangers associated with exploratory voyages to expand our frontiers. Travelling through deep space, the final frontier, is planned for the 2030s by NASA. The lessons learned from the adverse health effects of space exposure have been encountered from previous, less-lengthy missions. Prolonged multiyear deep space travel to Mars could be encumbered by significant adverse health effects, which could critically affect the safety of the mission and its voyagers. In this review, we discuss the health effects of the central nervous system by space exposure. The negative effects from space radiation and microgravity have been detailed. Future aims and recommendations for the safety of the voyagers have been discussed. With proper planning and anticipation, the mission to Mars can be done safely and securely.

Key Words: Mars, microgravity, radiation, space travel

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INTRODUCTION

Throughout the existence of humankind explorers have taken great risks to discover new land for the advancement of tribe, science, commerce, and for the fulfilment of our inherent curiosity of the unknown. From seafarers' travels across unchartered ocean to the astronauts' trekking across the lunar surface, we have been triumphant in exploring our world and beyond. The next feat is Mars. Despite mankind's many successes, these journeys have been at the expense of significant morbidity and mortality of the explorers. While many of these pioneers were focused on learning about the techniques of exploration, they also learned about the unanticipated health challenges that came with it. Travel to Mars could suffer the same consequences. While NASA has made significant advances in the technology and engineering to make a mission to Mars feasible, the health concerns of the astronauts during this extended journey remains a significant presentiment.

While engineers ponder and develop the technologies to take us to the farthest galaxies, the health of the astronauts is of equal if not more importance. Machines sent from earth have already successfully landed on

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Mars, the question remains about feasibility of human interplanetary travel. Exposure to the space environment has been shown to affect all systems of human physiology and anatomy. Countermeasures to re-establish homeostatic states within the human body have begun, but the pathophysiologic mechanisms of space exposure on the neurologic system are still obscure.

Here, we summarize the current knowledge of neurologic compromise encountered or expected from space exposure, the most foreign environmental pressure to affect the human species.

Radiation exposure

The intrigue of deep space travel comes with inherent risks, and one that has recently come to light involves exposure to the ionizing radiation fields in space. In fact, exposure to these complex radiation fields in space has been identified as the primary risk to astronaut health as they venture from the protective magnetosphere of the Earth and beyond low Earth orbit en-route to distant worlds such as Mars.[11] As NASA prepares the necessary logistics and develops the technologies necessary for deep space travel, recent data has now emerged that highlight certain significant concerns regarding the adverse effects of radiation exposure on the brain.

For decades, clinical literature has informed health professionals that radiation exposure has certain unintended and adverse consequences.[34] In particular, cranial radiotherapy used to forestall malignant progression in the brain can cause progressive and debilitating effects on cognition, including learning, memory, processing speed, attention, cognitive flexibility, and executive function.[32] Such treatments also result in other behavioral disorders that adversely impact anxiety, mood, and depression.[3,48,51] New data from multiple laboratories have linked many of these radiation-induced disruptions in mood and cognition to reductions in the structural complexity of neurons,[37,38] changes in the microvascular bed,[9] and persistent neuroinflammation.[37] Studies where mice were exposed to space-relevant doses of radiation revealed increased presence of dense fibrillary proteins and β-amyloid within the cerebrum [Figure 1].[12]

While the clinical experience with radiation exposure has provided many important lessons regarding the radiation response of the brain, differences in total doses, dose rate, and importantly, radiation quality have confounded efforts to accurately predict how cosmic radiation exposure might disrupt central nervous system (CNS) functionality. Such prospects are of particular concern to NASA as neurocognitive complications arising from deep space radiation exposure may well compromise astronaut safety, mission success, and post-mission quality of life.[16]

As alluded to above, differences in radiation quality complicate efforts to estimate space radiation risks

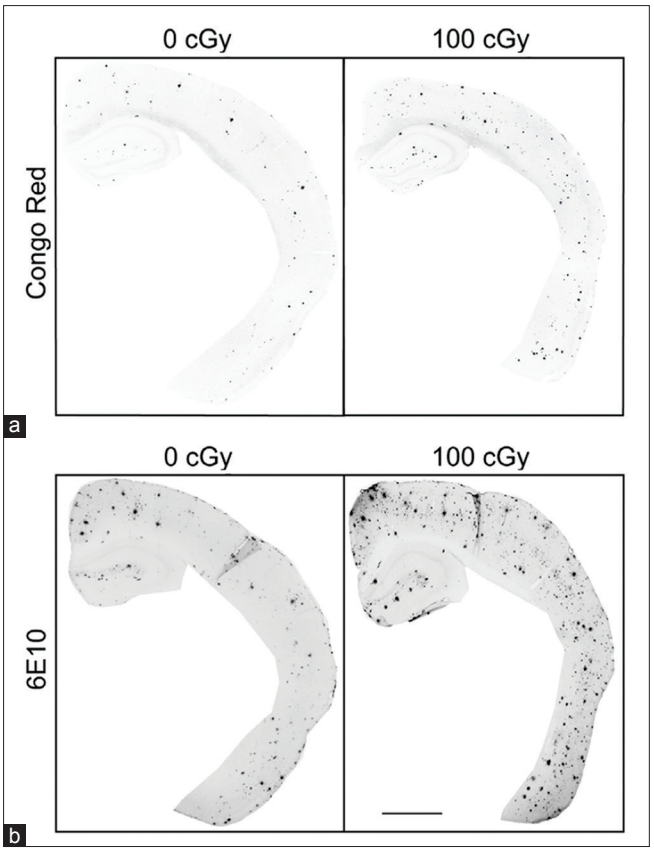

Figure 1: Immunohistochemical staining for Congo red and 6E10 increases after 56Fe particle irradiation. (a, b) Representative images of half male brains stained for Congo red (a) or 6E10 (b) 6 months after 0 Gy or 1 Gy 56Fe particle radiation. Scale bar is 1 mm. ***Reproduced from Cherry et al. Permission to reproduce open-source figure per Creative Commons 4.0. https://creativecommons.org/licenses/by/4.0***

due to the different energy deposition patterns that distinguish charged particles found in space from more common terrestrial forms of radiation. Deep space travel subjects astronauts to exposures from potentially large, yet infrequent solar particle events amidst a very low but steady state background of galactic cosmic radiation composed highly energetic charged particles ranging from lighter protons and helium ions to heavier ions such as silicon, titanium, and iron.[35] The interaction of these particles with the tissues of the body, surface of a planet, or hull of a spacecraft can create fragmentation products of lighter ions including neutrons.[35] Charged particle traversals are also associated with significant amounts of delta rays that emanate from the particle track and can interact over distances that far exceed the size of average cells.[35]

Given this rather dubious backdrop, NASA has invested in research focused on estimating the risks of developing acute (i.e. mission critical) and chronic (i.e. post-mission) CNS deficits. As a result, recent and compelling evidence, based largely on rodent models, has confirmed significant adverse effects of space-relevant fluences of charged

particles on cognition,[7,9,10,17,20,29,41] and many of our studies, have linked functional behavioral decrements to the erosion of neuronal structure and synaptic integrity in specific regions of the brain.[37-39] Importantly, and somewhat surprisingly, these changes were found to persist over the course of 1 year, highlighting that acute exposures to various types of cosmic radiation caused relatively permanent changes in the brain that showed little or no overt signs of recovery, regeneration, or repair. Specifically, mice subjected to space relevant fluences of charged particles have been shown to exhibit significant cortical and hippocampal-based cognitive deficits using a variety of spontaneous exploration tasks designed to discriminate the capability to recognize novelty.[37,38] Deficits in recognition, episodic, and recency memory highlight some of the persistent behavioral impairments experienced by irradiated rodents. Additional tasks in mice have shown that elevated anxiety and depression are associated with impaired cognitive flexibility. Higher order deficits interrogated by more stringent tasks, such as a platform relocation task adapted from the traditional Morris water maze, or a fear extinction paradigm, point to problems in adaptive behavior or the capability to respond to a changing environment. In rats, elegant attention set-shifting paradigms have uncovered some fascinating effects pointing to marked interindividual variability in executive function,[8,10,19,29] while exhibiting a range of deficits likely to parallel human behavioral deficits. Given that multiple investigators armed with an arsenal of behavioral tasks have routinely found short and long-term deficits in cognition, it becomes increasingly evident that the radiation problem in space is a significant concern and will require considerable innovation to adequately resolve.

A deeper understanding of the underlying mechanisms responsible for space brain provides the most logical route for designing innovative strategies to overcome these looming complications associated with deep space travel. Several lines of evidence suggest that neurotransmission is impaired as a result of multiple pathologies persisting long after exposure. Because behavioral decrements can be predictive of structural alterations, we sought to determine whether regions of the brain interrogated by our cognitive tasks showed signs of damage or change. These studies have now revealed that hippocampal and cortical neurons exhibit significant reductions in dendritic complexity, dendritic spine density, and immature spine morphologies.[37-39] Additional data have now revealed that neurons in the entorhinal cortex exhibit the same types of reductions in dendritic spine density as that found in other brain regions (i.e. the hippocampus and prefrontal cortex) [Figure 2]. Mice subjected to low dose (5 cGy) exposure to either titanium or oxygen ions (400 MeV/n) exhibit nearly 50% reductions in the number of dendritic

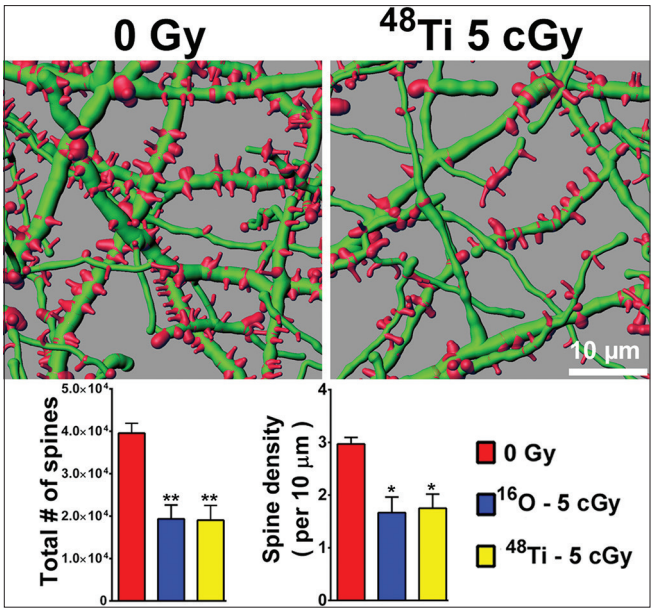

Figure 2: Persistent reductions in dendritic spine density in the entorhinal cortex 6 weeks following cosmic radiation exposure. Representative digital reconstructions of fluorescent dendritic segments (green) in the entorhinal cortex reveal marked reductions in dendritic spines (red) after exposure to titanium ions. Compared to controls, irradiation with either 5 cGy of oxygen or titanium ions reduces total spine numbers (left bar chart) and spine density (right bar chart) significantly (ANOVA). *$P < 0.05$; **$P < 0.01$

spines when measured 6 weeks after exposure [Figure 2]. These data corroborate past findings[37,38] and suggest that nearly any neuron in the brain is susceptible to similar cosmic radiation-induced structural plasticity.

Importantly, altered neuronal morphology coincides with poor behavioral performance as those animals showing the largest reductions in dendritic spines were found to exhibit the most significant decrements in recognition memory.[37,38] Interestingly, similar changes have been shown to underlie a host of neurodegenerative conditions that exhibit dementia,[6,24,44,47,49] and suggest that structure function relationships play critical roles in regulating the radiation response of the brain.

Normal brain function and the burgeoning field of neuroepigenetics have uncovered compelling evidence suggesting that persistent changes in DNA methylation may significantly impact learning and memory. In a recent report, cosmic radiation exposure increased levels of 5-methylcytosine (5mC) and 5-hydroxymethylcytosine (5hmC) in the hippocampus and correlated with persistent impairments in hippocampal and cortical memory.[1] Interestingly, inhibition of DNA methylation before or after irradiation reversed the adverse effects of exposure on cognition and normalized changes in DNA methylation to baseline levels.[1] These findings support the premise that neuroepigenetic aberrations contribute to cognitive deficits following space relevant radiation exposures, and that blockade of radiation-induced

hypermethylation protects against and mitigates those effects. Gene expression changes derived from epigenetic modifications could elicit several alterations in synaptic protein levels and contribute to neuroinflammation. Increased levels of post-synaptic density protein (PSD-95) and activated microglia are elevated routinely at nearly all times (days to months) following cosmic radiation exposure and show robust correlation with poor behavioral performance. Disruptions in PSD-95 can perturb synaptic integrity by disrupting the composition and distribution of proteins and receptors residing at the synaptic cleft,[25,40] and increased numbers of activated microglia could directly regulate structural plasticity by pruning dendritic arbors and spines.[50] Additional data have found that low dose exposure to charged particles elicits a persistent reduction in the glutamatergic readily releasable vesicular pool in synaptosomes along with reduced expression of glutamatergic NMDA receptor subunits.[30] Clearly, radiation-induced changes in synaptic proteins, receptors, and neurotransmitters could have a major impact on local and global circuits capable of altering the basal excitatory/inhibitory tone of the brain. More recent findings have identified surprisingly selective long-term plasticity of synaptic microcircuits in the hippocampus, where low-dose proton exposure decreased CB_1-dependent tonic inhibition of GABA release.[27] The prevalence of CB1 receptors in the brain suggest that pharmacologic manipulation of retrograde endocannabinoid signaling[26,46] may provide one potentially useful strategy for ameliorating the risk of adverse neurocognitive events during deep space travel.

In summary, as NASA plans for longer duration manned spaceflight, concerns have surfaced regarding the elevated risks associated with protracted exposure to the highly energetic spectrum of cosmic radiation. Animal models have revealed an unexpected sensitivity of multiple neuronal subtypes in the brain, with corresponding deficits in behavior. While data derived from rodents may be questioned for human relevance, they remain a useful resource for gathering critical information regarding the radiation response of the intact CNS.

Extrapolation of risk models across species will always be fraught with uncertainty but can be reduced through a deeper understanding of the neurobiological mechanisms. Biochemical, molecular, and cellular perturbations involving the release and availability of neurotransmitters, the redistribution and expression of synaptic proteins, the plasticity of neural circuits, and increased neuroinflammation likely converge to compromise neurotransmission at multiple levels. In the end, such factors may prove critical to small teams of astronauts where their capability to properly manage choreographed activities and respond to unexpected situations may be impacted adversely, confounded further by the increased autonomy inherent to prolonged deep space travel.

Anatomical effects on the brain

Subjective reports of blindness by astronauts and cosmonauts have been documented from even the earliest of space flights. Specifically, one astronaut reported a significant decline in visual acuity throughout his mission aboard the international space station (ISS).[2] Upon his return to Earth, an ophthalmologic examination revealed choroidal folds and cotton wool spots, which improved but did not resolve even 3 years following his mission [Figure 3].[2,31]

This finding heightened the awareness of ophthalmologic evaluations for astronauts and cosmonauts of future missions. Ophthalmologic examinations were performed on long-duration ISS crew members, which revealed similar ophthalmologic findings. This phenomenon led to the development of a named entity, "Vision Impairment and Intracranial Pressure (VIIP)" by NASA. Specific ophthalmologic findings included hyperopic shifting of up to 1.50 diopters in one or both eyes. Magnetic resonance imaging (MRI) discovered globe flattening. Lumbar punctures were performed in astronauts with evident disc edema, which revealed mildly elevated pressures (range: 21–28.5 cmH_2O).[2,31]

These symptoms seemed to follow a similar pattern for a different astronaut on a later mission. He had similar ophthalmologic findings, and an MRI was obtained 30 days after landing back on Earth, an MRI was obtained on a different astronaut with newly demonstrated optic disc edema [Figure 4].[2,31]

Following this MRI, a lumbar puncture was obtained, which was 28.5 cmH_2O. Cerebrospinal fluid (CSF) analysis was normal for the astronaut.

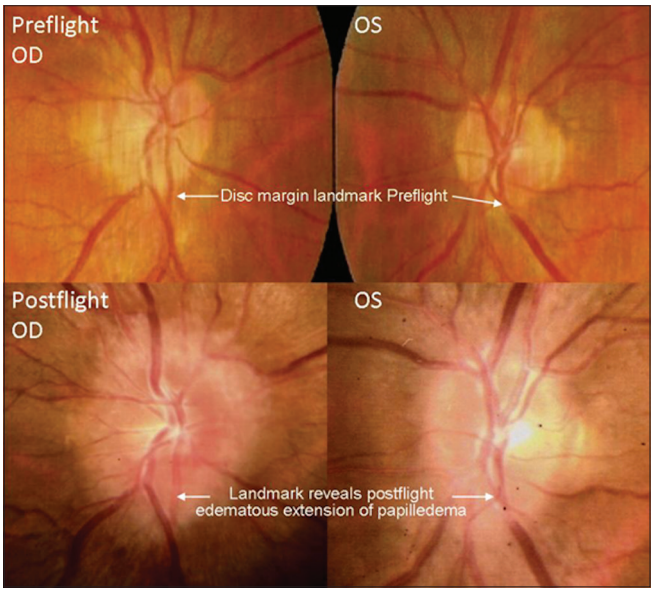

Figure 3: Fundus examination of the third case of visual changes from long-duration spaceflight. Fundoscopic images of the right and left optic disc showing profound grade 3 edema at the right optic disc and grade 1 edema at the left optic disc. *Adapted from Mader TH et al.*

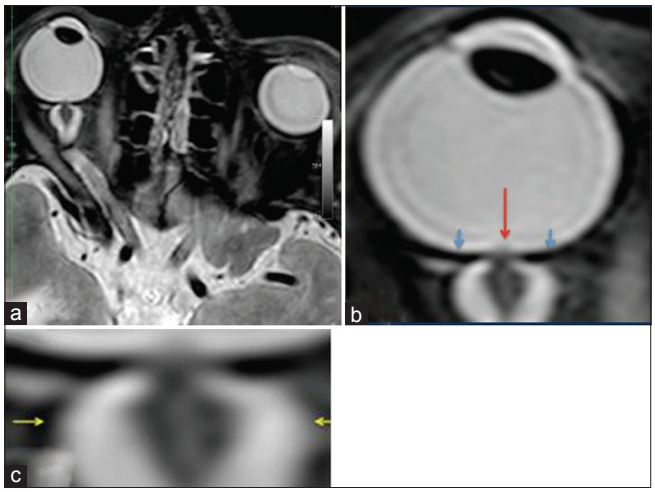

Figure 4: MRI (R + 30 days) of the fourth case of visual changes from long-duration space flight (a). There remains bilateral severe optic sheath dilatation. The right optic sheath diameter measures 10–11 mm (b, c); and the left optic sheath diameter measures 8 mm. These numbers are similar to the R + 3 examination. There is evidence of papilledema on the right eye only. There is residual flattening of the posterior globes. The optic nerve remains thickened bilaterally measuring up to 5 mm on the right and 4 mm on the left. There also remains bilateral tortuosity of the optic nerve sheaths with a kink at the optic nerve sheath approximately 1.1 cm behind the posterior margin of the globe. Red arrow depicts the optic-disc edema, blue arrows show the flattened globe, and the yellow arrows illustrate the distended optic nerve sheath. *Reproduced from Mader TH et al.*

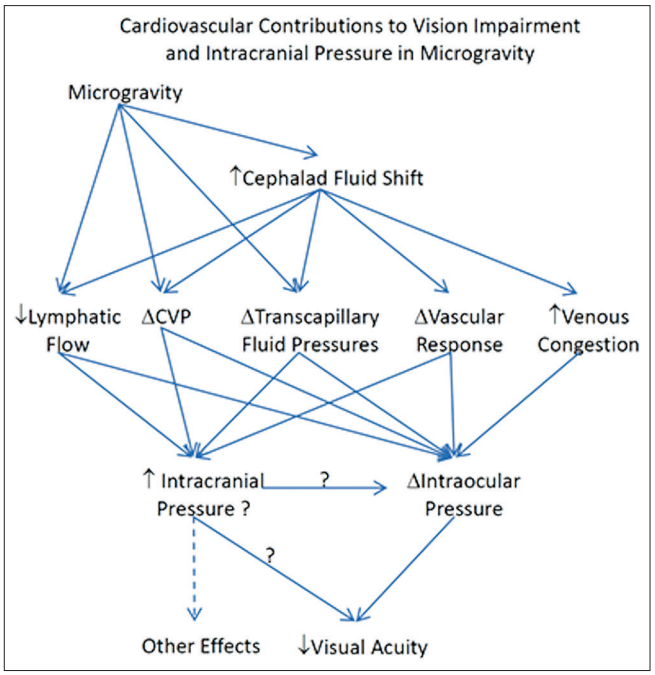

Figure 5: Known, investigated, and hypothesized cardiovascular contributions to vision impairment, ICP, and IOP in microgravity. Reproduced from Alexander *et al.*

These phenomena of visual changes associated with anatomic disfigurements of the globe and optic nerve were consistent with the pathophysiology seen in patients with increased intraocular and intracranial pressure.[2] This was postulated by NASA that the overarching etiologic cause of this was due to a cephalad shift of interstitial fluid during microgravity. The effect of microgravity was suspected in triggering a host of cardiovascular responses, leading to increased intracranial and intraocular pressures [Figure 5].[2]

Fluid shifting between the intravascular and extravascular spaces have been attributed to physiologic changes in the brain; however, studies remain inconclusive of their effect on the overall electrolyte balance and physiology on the body as a whole. The anticipation and biologic plausibility of decreased intravascular volume due to microgravity was made well-known in early space-flight experiments. However, recent experiments have failed to detect any significant changes in the renin-angiotensin-aldosterone system for short-term missions.[45] Aberrations in antidiuretic hormone, atrial natriuretic peptide, and sympathetic hormone activation have not been demonstrated in similar space-flight experiments.[45] However, the study administrators warn that the data on short-term space missions may not be generalizable to long-term missions such as a space flight to Mars.

The vestibular side effects of weightlessness and space have been well-studied. Aside from poor balance and proprioceptive properties of an impaired vestibular system, there are more serious, downstream effects of an improperly functioning vestibular system.[14,53,54] Vestibulo-autonomic effects, specifically the direct and indirect connection between the vestibular system and the autonomic centers of the brainstem have been well established.[14,53,54] An impaired vestibular system can lead to impairment in heart rate, blood pressure, and breathing patterns. The behavioral effects of dysautonomia can precipitate anxiety disorders, panic attacks, and agoraphobia.[2] Pathophysiologically, an impaired baroreceptor function can cause orthostatic intolerance. Naturally, the disequilibrium of impaired vestibulation can lead to nausea, vomiting, and downstream effects of hypovolemia and fatigue.[2]

Oculomotor aberrations have been recorded following prolonged space flight.[2,13] Observations of oscillation, jerk nystagmus, and rebound nystagmus were noticed on post-flight neurologic evaluations. These findings normalized after 1–2 weeks, but some took up to 4 years to resolve. More intensive testing of ocular movement with vertical head movement was performed on astronauts, which demonstrated incongruences between eye movement, head movement, and gaze fixation.[2]

Biological effects on the brain

In addition to the untoward effects of radiation on astronaut's neurobiology, microgravity has been suggested as an instigator in space-related neurologic dysfunction.

Gravitational influences have been observed to affect cells at the cytoarchitectural level.[18,21,22] Gravity contributes to the spatial relationship of the intracellular organelles and cytoskeletal structures, which also affects biochemical and biosynthetic pathways.[43] Consequently, DNA replication, RNA transcription, and protein transport can be negatively affected.

A study performed by He *et al.*[21] examined the cytoskeletal effects of simulated microgravity in the slime mold *Physarum polycephalum*. Following 40 hours of microgravity, cytoskeletal analysis of the actin architecture was analyzed. Actin cytoskeletal changes were seen, specifically showing fibers that were shortened, disordered, and depolymerized [Figure 6].

Another experiment by Gaboyard *et al.*[18] analyzed the cytoarchitecture of rat hair cells between ground controls and inflight experiments. The cytoarchitectural organization was found to be moderately disorganized in in-flight controls with normal gravity and found to be severely disorganized in in-flight experiments without gravity [Figure 7].

Experiments by Huang *et al.*[22] examined the morphological changes that occur with bone marrow stem cells in microgravity, control gravity (g), and hypergravity (2 g). Examination of microfilaments showed that these stem cells also had deranged and thinner microfilamentous structures compared to the control group. In hypergravity, the microfilament diameters appeared to be larger in caliber, and with retained microfilamentous architecture [Figure 8].

Huang *et al.* also carried out experiments to determine if gravity played a role in the differentiation of these bone marrow stem cells. Their experiments have proven that gravity plays a functional role in cardiomycyte differentiation [Figure 9]. This was contrary to experiments that determined increased differentiation of force-insensitive cells such as adipocytes under simulated microgravity compared to hypergravity and control experiments [Figure 10]. Overall, this shows that gravity (or lack thereof) can selectively contribute to stem cell differentiation preferences.

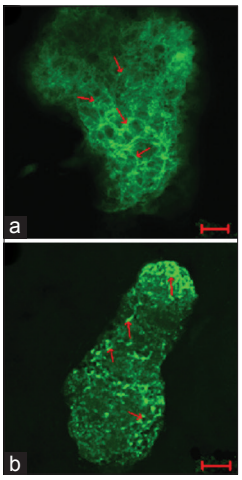

Figure 6:The actin cytoskeleton of G2 phase in ground control and test samples in altered gravity for 40 h and subsequent 1 g for about 10 h.The F-actin in Physarum spread on the coverslips was stained with FITC-phalloidin and the actin cytoskeleton was visualized by laser scanning confocal microscopy. Panel (a) showing the control group; panel (b) showing the test samples. Bar: 20 μm. *Reproduced from He et al.*

Oxidative stress within the hippocampus is known to be a problem with microgravity.[43] Such mechanisms of oxidative stress are likely related to heightened glucocorticoid-receptor activation within the hippocampus from a systemic, stress response to microgravity. Proteomic analysis of mice hippocampi in microgravitational environments performed by Sarkar *et al.*[43] showed that the exposure to microgravity decreased the presence of pyruvate dehydrogenase (PDK-1) and Synuclein β [Figure 11]. PDK-1 is a known enzyme involved in cerebral energy metabolism, and its decreased presence could be a result of increased oxidative stress within the mice's microgravitationally-exposed hippocampi. Synuclein β, a molecular chaperone, is known for preventing the aggregation of abnormal proteins compared to its alternative structure, Synuclein α. The decreased presence of Synunclein β could be due to the increased incidence of abnormal protein aggregations seen in microgravitational states.

Specific cells of the hippocampus that control cognitive maps are known as "place cells." These cells control the ability to translate visuospatial cues into a cognitive map of the subject's environment and surroundings. A study was conducted onboard a Neurolab shuttle mission utilizing mice and a three-dimensional "corner" that represented the floor, ceiling, and wall of a cage.[36] This apparatus rotated on different axes during parabolic flight. After a day of customizing the mouse to the apparatus, 0-g experiments took place, where the mouse was moved to a different façade of the apparatus. After a few days of experiments, the mice appeared to have lost directional-tuning and took longer to return to their original start point, appearing to be confused between what was the original wall, ceiling, and floor. Without the anchor of gravity, 3-dimensional visuospatial negotiation of place cells are difficult, if not impossible.

Cognitive effects

The known cognitive effects of space travel are mostly a product of radiation exposure as described previously. However, the absence of gravitational exertion can cause radiographic changes in similar neuroanatomic regions, independent of cosmic radiation exposure.

A radiographical analysis of the effects of microgravity was performed by Li *et al.*,[28] where healthy volunteers had been in − 6 degree head down tilt (HDT) bedrest

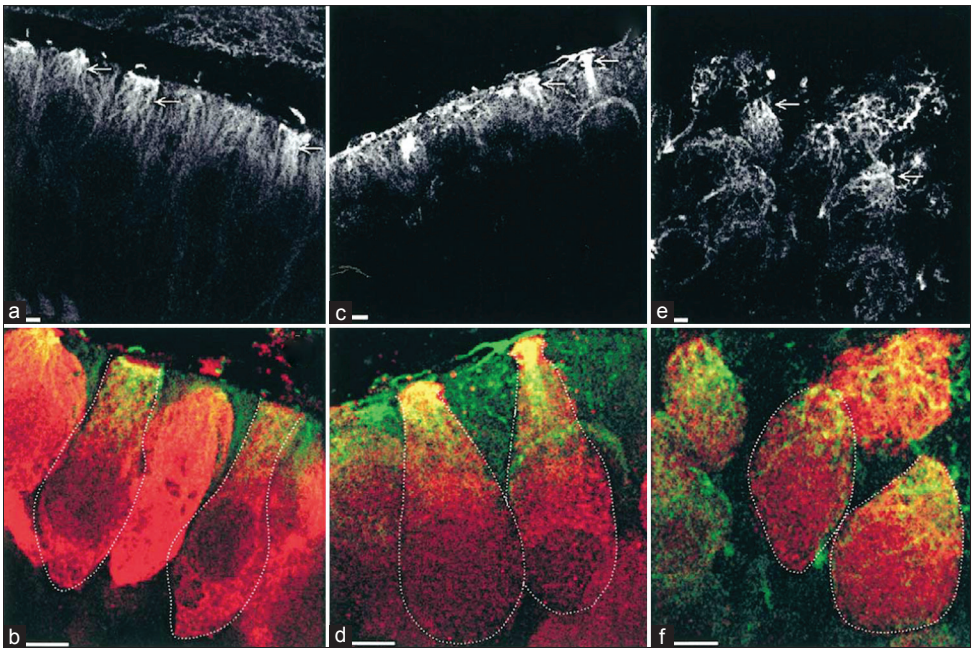

Figure 7: Comparison of cytoskeletal architecture (upper frames) and shape (lower frames) of hair cells between ground controls (a and b), C3 in-flight controls (c and d), and C3 weightlessness samples (e and f). α-tubulin staining (a, c, e) shows the organization of microtubules (arrows) in utricular sensory cells. Disorganization of cytoskeletal architecture is seen in weightlessness at higher magnification. (b, d, f), staining for calretinin (red) and a-tubulin (green) show the hair cell shape, demarcated by the dotted lines, and the location of tubulin in the upper part of the cells. Note the differences in hair cell shape between weightlessness samples and controls. Bar = 5 μm. *Reproduced from Gaboyard et al.*

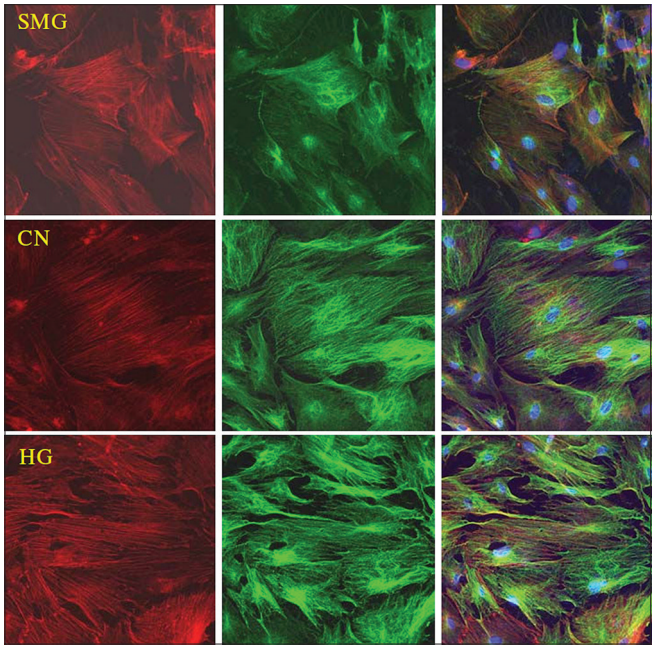

Figure 8: Effects of HG/SMG on the cytoskeleton of BMSCs. rBMSCs were cultured under HG/SMG conditions for 7 days, and then fixed with 4% paraformaldehyde and stained for microfilaments with Texas red isothiocyanate-conjugated phalloidin (red), microtube cytoskeleton with FITC--conjugated antibody (green) and nucleolus with DAPI (blue). In the SMG group, microfilaments appeared thinner and abnormally distributed, and microtubules appeared diffuse, compared with the control group (CN). In the HG group, the diameters of microfilaments and microtubules appeared to increase. Magnification × 63 oil immersion objective. *Reproduced from Huang et al. Permission to reproduce open-source figure per Creative Commons 4.0. https://creativecommons.org/licenses/by/2.0*

for 30 consecutive days to simulate the cephalad shifting of interstitial fluids seen in microgravity. MRI studies were obtained before and after this experiment. Analysis of the gray matter volume in the bilateral frontal lobes, temporal poles, insula, parahippocampal gyrus, and right hippocampus demonstrated significant volume losses following the 30-day experiment. In contrast, gray matter of the vermis, bilateral paracentral lobule, right precuneus gyrus, and left precentral and postcentral gyri increased following the experiment [Figure 12]. The neuroanatomical implications of these losses can limit the astronaut's memory and judgment – two cognitive faculties that are very important in prolonged space travel.

Li *et al.*'s experiment also discovered aberrations within white matter tracts as well. A decrease in the fractional anisotropy (FA) within the white matter tracts of the frontal lobe, temporal lobe, parietal lobe, occipital lobe, thalamus, brainstem, and cerebellum was observed [Figure 13]. This type of decrease in the FA is seen in cases of dysmyelination, axonal loss, or edema. These patterns of FA loss are also seen in the early stages of Alzheimer's dementia and mild cognitive impairment.

An alien environment

After landing on Mars, space travellers are at a continued risk of untoward neurologic sequelae. The terrain, atmosphere, and day/night cycle of Mars can interrupt the cognition and performance of space travellers. Aside

from the already disrupted circadian function from the rigors of space travel to Mars, specific aspects of Mars itself can attribute to a more accentuated disruption for newly-arrived space travellers.[52] A day–night cycle in Mars is only 40 minutes longer than on Earth. However, owing to the distance from the Sun and the degree of suspended atmospheric particles, the intensity of the Sun's brightness is about half that on Earth, thereby affecting circadian rhythm and the emotional benefits of the sun's exposure.[33] Suspended dust in the atmosphere also turns the Martian sky to a pink hue rather than the Earth's blue. This lack of blue color is known to affect circadian rhythms as studies have demonstrated the sensitivity of circadian rhythm to blue-color wavelengths.[5] Neuroendocrinologic implications for the circadian-timed release of growth hormone from the hypothalamus and melatonin from the pineal gland could play a role in the physiologic-pathophysiologic well-being of the space traveller. With these alien variables in mind, exercises in Martian-simulated environments have shown that performance and alertness are affected by a disrupted circadian rhythm of astronauts.[4]

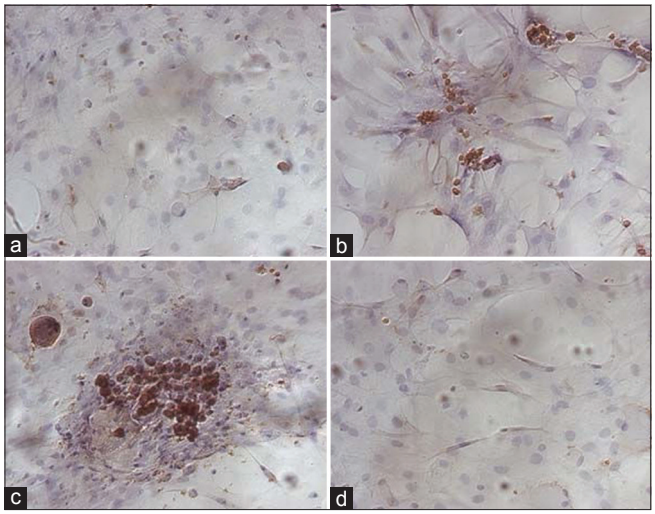

Figure 9: Immunocytochemistry analysis of cTnT in the cardiomyogenic differentiation of rBMSCs under HG/SMG conditions. (a) rBMSC group was used as a negative control. (b) rBMSCs treated with 5-aza only. (c) CH3 group strongly expressed cTnT. (d) CM3 group had few cTnT positive cells. Magnification ×200. HG increased the expression levels of GATA-4, β-MHC and cTnT in rBMSCs, whereas SMG decreased the expression levels. ***Reproduced from Huang et al. Permission to reproduce open-source figure per Creative Commons 2.0. https://creativecommons.org/licenses/by/2.0***

Humans will not be the only travellers headed to Mars. The space traveller's gut microbiome will also make the long journey to the red planet, and the effect of space travel has shown to have effects on them as well. The intestinal microbiome is a constant tug-o-war between healthy and harmful bacteria. A small tip in the scales can produce dramatic differences in this equilibrium. As space food have been prepared and packaged beforehand, there is a general sterility of their food for ease of storage and to prevent spoiling. However, helpful bacteria exist in the food we normally eat on Earth, and this reduced intake in healthy bacteria can tip the scales towards a proliferation of harmful bacteria. Moreover, in-vitro spaceflight experiments have shown that *Salmonella* and *Escherichia coli* species have been shown to have increased virulence, increased antibiotic resistance, increased resistance to environmental stresses, and increased survival in macrophages compared to ground controls.[42] The mechanisms behind this adaption is still unknown but may exist at the cell-signalling level, specifically involving the Hfq protein pathway, a known pathway for virulent bacterial activation.[15] Enhanced production of biofilms has also been demonstrated in in-flight experiments compared to ground controls. Biofilm production has been shown to be a protective mechanism for bacterial survival.[42] These changes in intestinal flora can have dramatic effects on gastrointestinal physiology, with secondary effects on all organ systems, including the nervous system.

A psychologic condition called the "Earth-out-of-view" phenomenon is a situation where pathologic behavioral changes occur when Earth is no longer in view due to prolonged space missions and journeys.[23] Psychologists fear that when Earth is out of view, space travellers might feel internally uncoupled with the behavioral norms of Earth and may begin to undergo maladaptive responses. Such adverse behavioral changes could include depression, anxiety, suicidal ideations, hallucinations, or

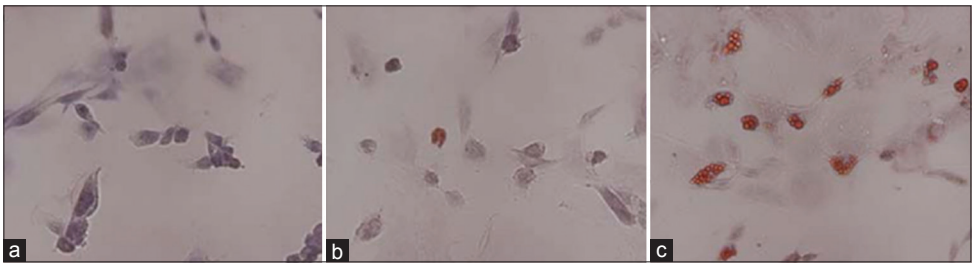

Figure 10: Oil red-O staining to detect the adipogenic differentiation of rBMSCs under HG and SMG conditions. (a) Control group. (b) AH7 showed few oil droplets. (c) AM7 group contained oil droplets in the cells. Magnification ×200. SMG conditions increased the expression of PPARγ2. ***Reproduced from Huang et al. Permission to reproduce open-source figure per Creative Commons 2.0. https://creativecommons.org/licenses/by/2.0***

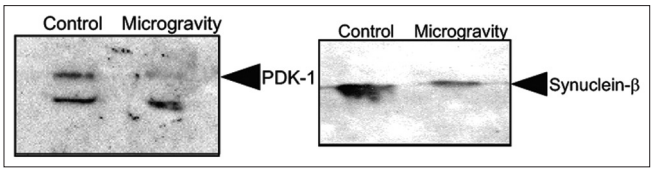

Figure 11: Western blot analysis of Synuclein β in control and in mice kept in simulated microgravity for 7 days. Western blot analysis of pyruvate dehydrogenase (PDK-1) in control and in mice kept in simulated microgravity for 7 days. *Reprinted with permission from Sarkar P, Sarkar S, Ramesh V, Hayes BE, Thomas RL, Wilson BL, et al. Proteomic analysis of mice hippocampus in simulated microgravity environment. Journal of proteome research 2006;5(3):548-553. Copyright 2006. American Chemical Society*

delusions.[23] Countermeasures to rectify this potential psychologic phenomenon are still under evaluation.

Path forward

Countermeasures to offset the deleterious effects of space on neurologic function have been conceptualized. Virtual reality systems have been implemented as a part of astronaut training programs to familiarize astronauts with the challenges of orientation and re-orientation when in space.[2] Artificial gravity in the form of centrifugal force and the acceleration generated on the astronaut have been conceptualized and studied.

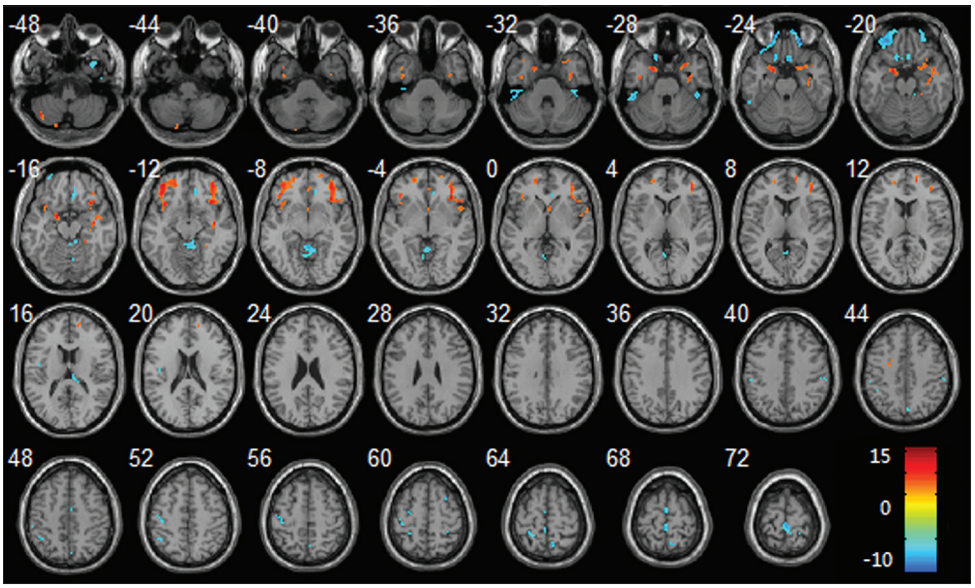

Figure 12: Regional changes of GM volumes after HDBR revealed by voxel-based morphometry. Three-dimensional slices depicting regions showing decreased GM volume (red) in the bilateral frontal lobes, parahippocampal gyrus, insula, right temporal pole, right hippocampus and increased GM volume (blue) in vermis, bilateral paracentral lobule, right precuneus gyrus, left precentral gyrus, left postcentral gyrus overlaid on a T1-weighted MRI anatomical image in the stereotactic space of the Talairach template. *Reproduced from Li et al. Permission to reproduce open-source figure per Creative Commons 4.0. https://creativecommons.org/licenses/by/4.0*

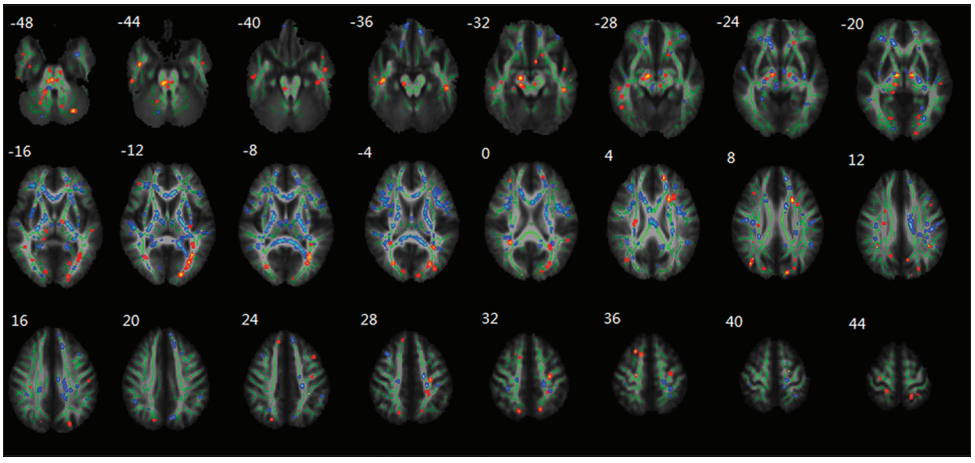

Figure 13: Regional changes of FA values as revealed by TBSS after HDBR. The group's mean FA skeleton (green) was overlaid on the mean FA images. The threshold of mean FA skeleton was set at 0.2; the regions with decreased FA after HDBR are red colored, and the regions with increased FA after HDBR are blue colored. *Reproduced from Li et al. Permission to reproduce open-source figure per Creative Commons 4.0. https://creativecommons.org/licenses/by/4.0*

Several questions regarding its utility, however, have been debated. Scientists are testing the impacts of intermittent versus continuous exposure to artificial gravity.[2] Arguments of microgravitational desensitization to adopt a dual-adaptive state have bolstered the claim that intermittent gravity is better. Studies are ongoing on whether intermittent gravitational states cause physiologic problems with pendulous interstitial fluid shifting and continual changes in the orthopedic effects of gravity and microgravity. A space suit whereby physical, haptic feedback is applied to the astronaut is being developed.[2] This feedback system can orient the astronaut on proprioceptive directionality in the disorienting environment of space. One cosmonaut with a known history of space motion sickness ran on a treadmill for an hour a day, while visually fixed on a TV screen 2 meters away.[2] His symptoms improved greatly following this new regimen, and this could be further investigated as a method to improve the neurovestibular side effects of space.

CONCLUSIONS

Maintaining neurologic function on long-term voyages through space exposure is vital for both the health of the astronaut and the security of the mission. Studies and previous observations from returning astronauts and cosmonauts from long missions aboard space stations have demonstrated significant unanticipated concerns. Countermeasures to protect the astronauts from space exposure require further exploration and are vital components in ensuring safe and reliable journey to Mars.

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Conflicts of interest

There are no conflicts of interest.

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