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Research Article,

Central nervous system during human spaceflight missions to Mars. A Meta-Analysis

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Abstract:

Galactic cosmic radiation, which can harm sensitive neurons and structures, changes in gravitational acceleration that change the terrestrial synergies between perception and action, and a variety of factors (isolation, confinement, a different atmosphere, and mission parameters, including distance from Earth) that can affect cognition and behaviour are just a few of the environmental challenges that space travel presents to the central nervous system. In order to better understand and lessen the effects of these extended exposures, space-faring nations continue to invest heavily in research. Mars travellers will be subjected to these environmental problems for up to three years. The results of more than 50 years of space-related neuroscience studies on people and animals subjected to spaceflight or settings that are similar to spaceflight are reviewed in this article, along with their implications and the future work needed to ensure successful Mars missions. It also discusses basic neurophysiology reactions that are important for understanding and preserving human health and performance on Earth.

Keywords: Emotions, Loneliness, Vestibular, Microgravity, Space Radiation, Behaviour, Cognition, Confinement,

Introduction:

For almost 60 years, researchers have been studying the central nervous systems (CNS) of humans, cosmonauts, and animals before, during, and after spaceflight missions. With mission lengths ranging from a few days to more than a year, the majority of missions were carried out in low Earth orbit, around 200 miles above the Earth's surface. From 1968 to 1972, nine lunar missions took people beyond the Van Allen belts into deep space. Twelve crew members also landed and walked on the lunar surface at a distance of 240.000 miles for up to three days. The performance and health obstacles that space travellers have faced in their travels will be greatly outmatched by missions that are currently being planned to places like Mars. Each space traveller faces a unique set of risks (or stresses) depending on the specifics of their mission. Among these dangers are altered gravity (primarily microgravity with intermediate periods of hypergravity during launch and ascent into space and during descent and landing from space, as well as hypogravity on lunar or planetary surfaces), isolation and confinement, radiation-hostile closed environment, and distance from Earth. With missions to the Moon and then to Mars, which will subject space travellers to previously unheard-of levels of these dangers, the National Aeronautics and Space Administration (NASA) and other space organisations are ushering in a new era of deep space exploration. Crew members on board these missions will be exposed to unique dangers that researchers from a wide range of physiological, behavioural, and medical disciplines are presently attempting to reduce for 1,000 days or more at distances from Earth of 10 to 20 light minutes. Neurophysiologists have spent the first 60 years of human spaceflight concentrating on elucidating the effects of the altered gravity, including the transient high gravitoinertial accelerations (3–6 g) experienced during launch and return to Earth and the very low gravitoinertial accelerations (10 6 g) experienced throughout the orbital phase of space flight. On the surface of the moon, no neuroscience studies have been conducted with astronauts. Spatial orientation, sensorimotor coordination, and cardiovascular dynamics are temporarily impacted by microgravity exposure, whereas prolonged exposure triggers more robust neurological system responses and physiological adaptive responses in numerous homeostatic features of the cardiovascular, muscle, and bone systems. The major goals of space neurology research to far have been to examine the processes behind adaptive responses in humans or model organisms, as well as how extended exposure to microgravity impacts the health and performance of the crew members flying onboard those missions. The psychological impacts of isolation and confinement during spaceflight have also been the subject of neuroscience study. The neurological consequences of space radiation exposure have also been researched, mostly in ground-based models employing cosmic radiation simulation facilities. This study outlines the effects of microgravity, isolation and confinement, and radiation on the central nervous systems (CNS) of animals and humans, and it ends with recommendations for future neuroscience research that are required before humans may safely launch exploration missions to the Moon and Mars.

Studies on Sensory and Motor Control in Model Organisms

Early on in the space age, experiments on animals were done to see if people might survive brief space missions. Miss Baker, a squirrel monkey, became the first animal to travel on a US spacecraft and return alive on May 28, 1959. Even though Miss Baker's flight was short—only 16 minutes—it garnered media attention. Two dogs (Strelka and Belka), a rabbit, 42 mice, two rats, and fruit flies were the first animals to be successfully returned alive from orbit when the Soviet Union successfully launched Sputnik 5 (officially known as Korabl-Sputnik 2) a year later. Although the development of space travel offered the chance to investigate the basic biological principle(s) governing how an animal's central nervous system (CNS) reacts to weightlessness, we are still unsure of how the CNS adjusts to abrupt changes in gravity levels or whether animals and humans react similarly. The mouse has traditionally been employed as the main animal model to investigate the neurological impacts of spaceflight, but other species, including primates, birds, amphibians, fish, mollusks, and insects, have also been used to examine a variety of brain systems. The relevant outcomes of these experiments conducted on animals, as well as the possible reasons for the observed alterations, are discussed below. An overview of further behavioural and physiological findings in model species that may give insights into the underlying mechanisms impacting human brain processing in spaceflight is provided to interested readers in APPENDIX A. A novel kind of "floating" electrode that could constantly record the activity of neurons for a long period of time was created in the middle of the 1960s by Gualtierotti and colleagues (Gualtierotti and Alltucker 1966; Gualtierotti and Bailey 1968). This electrode was originally utilised to capture the bullfrog's otolith afferent activity during brief (20 s) weightlessness produced by parabolic flight. When the frog was subjected to weightlessness, its vestibular afferents immediately increased in activity, and when it returned to 1 g, activity returned to baseline levels (Gualtierotti and Gerathewohl 1965). The findings of Fiorica et al. (1962) that the cats' vestibular neurons are more active during free fall were supported by these observations. In order to record the activity of otolith fibres in the bullfrog both during launch and during centrifuge spins in orbit, Gualtierotti (1977) further modified the electrodes. The findings showed a hypersensitivity to an applied acceleration above baseline values starting around mission day three and a substantially higher periodic variation in back-ground discharge at rest than on Earth. The electrodes stopped working after these alterations in otolith activity lasted through day 4 of the mission and recovered to baseline values on day 5. (Bracchi et al. 1975). By utilising infrared telemetry to continually record the activity of a larger sample of otolith afferents in toadfish for the period of the Space Shuttle Program's STS-90 and STS-95 flights, which lasted 16 days and 9 days, respectively, Boyle et al. 2001 aimed to expand Gualtierotti's study. Unfortunately, the on-board countermeasures proved ineffective. However, the toadfish were brought back to the lab within 8 hours of landing, and during carefully controlled accelerations, the activity of the otolith afferents was monitored using conventional electrophysiological methods. In the first day following landing, the flying animals' average amplitude of response to an applied translation was three times larger than that of the control animals (Boyle et al. 2001). The otolith afferents' activity almost reached saturation with a 0.25 mm displacement (Fig. 1A).

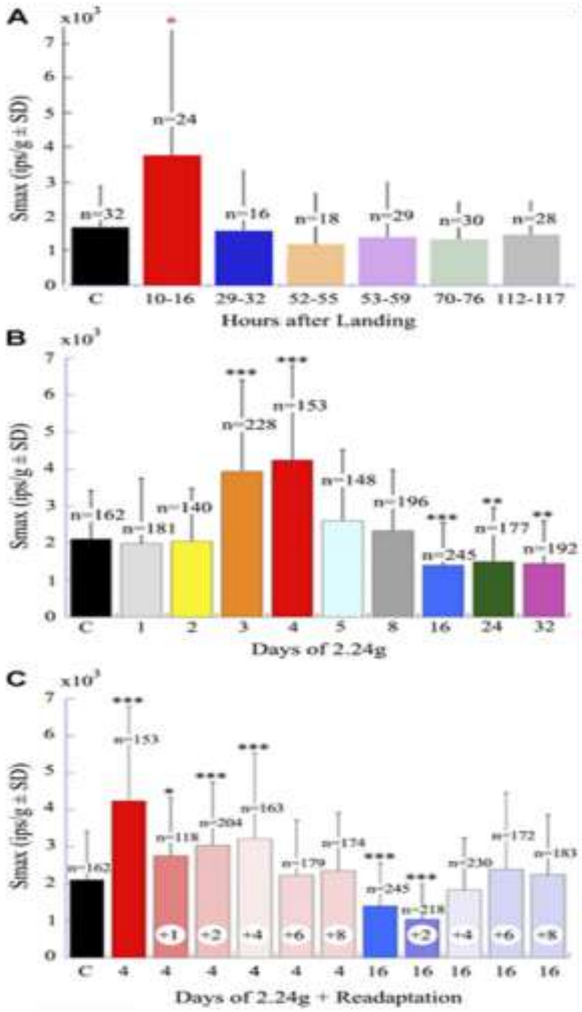

Fig. 1 shows the impact of reduced and increased gravity on the toadfish utricular afferents' maximum response sensitivity [Smax; measured in impulses per second per g (or 9.81 m/s2), ips/g]. A: Data from the STS-90 and STS-95 Space Shuttle missions that were collected after weightlessness exposure show the afferent Smax as a function of time after landing in hours from the first recording session (from 10 to 16 hours to the last, from 112 to 117 hours) [adapted from Boyle et al. (2001)]. Smax (red column) of fish subjected to an applied linear acceleration was substantially (*P 0.01) higher than for controls on the first day following landing (black column). The results taken in the same fish at various hours of delay after landing and shown by different colours showed that sensitivity restored to near normal values 30 h after landing. B: Plotting mean afferent Smax (ips/g SD) vs days of centrifugation at 2.24 g (data obtained from Boyle et al. 2018). The recording session started as soon as the centrifugation stopped. The standard translation's mean Smax of control afferents (C; black column) is 2,103 1,314 ips/g (n 162 afferents). At days 3 and 4, the orange and red columns, which each contained 228 and 153 afferents, and the orange column, respectively, exhibited significantly higher Smax values than the 162 control afferents (*P 0.0001). The afferent sensitivity returned to normal after the elevation for a period of 5 to 8 days, and then significantly decreased at days 16, 24, and 32 (blue column, n 245 afferents; green column, n 177 afferents; purple column, n 192 afferents; **P 0.005). Each group's total number of afferents is listed above its column in the SD error bar. C: After 4- and 16-day centrifugation exposures, afferent Smax in a normal 1 g as a function of the number of days (indicated by the number inside of each column). After four days of exposure, initial hypersensitivity was recorded, and it took four days for the levels to return to normal (red unmarked column). It took at least two days to recover from the subsequent hyposensitivity seen after 16-day exposures (blue unmarked column). The left column (C) in A–C contains the control response value, and the error bars indicate SD. Levels of significance when compared to control measurements are *P 0.05; **P 0.005; and ***P 0.0001.**

The toadfish reportedly enhanced their afferent sensitivity in order to regain their capacity to recognise acceleration when in weightlessness. As was already noted, on the first day after landing, these fish exhibited irregular behaviour when stimulated. On average, afferent sensitivity (and behaviour) returned to normal within 24–36 hours of landing, comparable to the recovery period for vestibular disorientation in astronauts when they return from space, despite the fact that certain afferents remained hypersensitive for days following spaceflight (see below). According to Pan et al. (2018), two possible mechanisms for these peripheral vestibular changes during changes in gravity levels are: 1) modifications to the hair cell transducer's sensitivity, such as rearranging the transmembrane channel-like proteins of the transducer pore; and 2) transient structural changes affecting the otolith's mechanoreception, such as a change in otolith-stereociliary coupling that modifies bundle deflection for a Ross (2000) offered data to support the theory that presynaptic modulation of synaptic strength in the hair cell may be the cause of weightlessness-induced hypersensitivity of the otolith afferent. In certain type II hair cells in rats, the number of synaptic ribbons rose by around

55% after being exposed to weightlessness, but type I hair cells were less impacted. Due to the fact that toadfish only have type II hair cells, an initial adaptive response to restore the lack of gravity detection may involve an increase in synaptic strength. This is then likely followed by the deletion of the extra synaptic bodies, which results in the restoration of normal function upon returning to a gravity environment (Graydon et al. 2017). Selected space-based brain investigations are summarised and interpreted in two important articles. Cohen et al. contributed the first tion (2005). Researchers tracked alert monkeys' ocular gaze and recorded the activity of central vestibular neurons while they were in space. Early on in the missions, the sensitivity of the vestibular neurons increased, correlating with results obtained using bullfrogs (see above). According to a recent study, astronauts' otolith-mediated reactions to centrifugation reduced right away after returning from a six-month space mission and recovered completely nine days later (Hallgren et al. 2016).

The second book offers a thorough examination of the 16-day Space Shuttle Neurolab mission, which was focused on examining how the central and autonomous neural systems react to spaceflight (Buckey and Homick 2003). In total, 26 experiments were conducted as part of this mission to study the following topics: balance in humans, rats, and fish; integration of senses and navigation in humans and rats; neural development in rodents; blood pressure control mechanisms in humans and rats; and sleep and circadian rhythms in humans and rats. Hippocampal "place" cells in animals have been shown to preserve their three-dimensional spatial selectivity, suggesting that self-motion and external landmark signals may be resolved in such a new context (Knierim et al. 2000, 2003). In the adult rat cerebellar nodulus, which receives significant input from vestibular otolith afferents, structural changes, including the formation of lamellar bodies and evidence of degeneration, possibly the result of an overexcitation of otolith targets, were discovered using electron microscopy. While the lack of contextual contact in space was temporary in postnatal rats that spent 9 days in space, the absence of gravity during a 16-day space trip inhibited the maturation of motor techniques for surface righting (Walton et al. 2005a). On the day they returned from space, young rats raised in space from postnatal day 14 (P14) to P30 displayed altered swimming behaviour (altered posture in the water, swimming speed, and style), apparently as an adaptive response to weightlessness. Some of these characteristics persisted for 30 days after the mission (Walton et al. 2005b). Xenopus laevis, the clawed toad Xenopus laevis, cichlid fish Oreochromis mossambicus, and crickets Acheta domesticus and Gryllus bimaculatus are a few examples of species whose development of the vestibular system and other neurally driven behaviours have been studied during spaceflight and in ground analogues of spaceflight (Horn 2003; Horn and Ga- briel 2014).

The use of artificial gravity has been suggested as a remedy for the drawbacks of weightlessness. By placing one population of mice on the International Space Station (ISS) and continuously accelerating them at a centripetal rate while another population of mice was left in weightlessness alone, the Japan Aerospace Exploration Agency evaluated the viability of centrifugation as a method to counter the loss of gravity in 2016. (Shiba et al. 2017). Results showed that artificial gravity offers some protection from spaceflight-induced increases in retinal cell apoptosis and alterations in the expression of proteins linked to cellular structure, bone and muscle mass, immunological response, and metabolic function (Tominari et al. 2019). (Mao et al. 2018). Although hypergravity may be provided for extended durations in ground-based investigations, partial gravity can only be produced for limited periods on Earth. This can be used to test whether structures and their function respond linearly to gravity levels. Boyle et al. (2018) employed toadfish to examine how utricular afferents react to translational accelerations following STS-90 or STS-95, respectively, 16 or 9 days in orbit, and 1-32 days of 2.24 g centrifugation. Following centrifugation, the results are shown in Fig. 1B. The scientists predicted that the afferents would be hyposensitive under hypergravity since they were hypersensitive during spaceflight. Interestingly, the toadfish utricular afferents displayed hypersensitivity after three days of centrifugation. This hypersensitivity increased on the fourth day, recovered to normal levels during days 5–8, and subsequently occurred on days 16–32 (as was expected). It took more than 4 and 2 days, respectively, of exposure to 1 g for the initial hypersensitivity and subsequent hyposensitivity to return to control values (Fig. 1C). A consistent early neural response to a gravity challenge in either direction—weightlessness or hypergravity—might be reflected by the fact that the initial afferent response is elevated in toadfish during centrifugation, and that the afferent response is elevated in bullfrogs, the central vestibular neuron response is elevated in primates during the first days of spaceflight. Long-term hypergravity exposure causes afferent sensitivity to decline. Although the afferent response to extended weightlessness exposure is largely unknown, it may eventually become hyposensitive. This first response is consistent with astronauts' initial confusion during a space trip. Pre-synaptic manipulation of synaptic ribbons (or bodies) in hair cells has been mentioned above as a potential means of modifying the size of the touched utricular afferents' responses. In two distinct regions of the utricular macula of control fish and fish that underwent 4- and 16-day centrifugation, synaptic ribbons in utricular hair cells were detected. The number of ribbons per hair cell was equal in both groups despite the very considerable variations in the size of the afferent responses, proving conclusively that the number of synaptic bodies in hair cells does not directly correspond with their sensitivity to otolith stimulation (Boyle et al. 2018). In contrast to findings from a research in rats (Ross 2000), which showed synaptic densities increased in rats during spaceflight, Sultemeier et al. (2017) recently demonstrated that spaceflight lowers synaptic densities in the mouse extrastriolar utricle. Intriguingly, centrifugation had no effect on the fish's afferent sensitivity to rotational rotation (Boyle et al. 2018), and spaceflight had no effect on the synaptic densities of hair cells in the rat's horizontal semicircular canal.

Regardless of our best efforts, we have less information on the consequences of weightlessness on animal neuronal structure and function, and much less information on the long-term impacts of hypergravity in experiments conducted on the ground. The astronaut encounters similar difficulty with direction and equilibrium during their first few days in space, as well as for a while after returning from a very brief period of weightlessness. These issues are frequently observed in animals and people with vestibular disorders. After a few days, adaptive mechanisms, which may temporarily alter the transduction process(es) or synaptic strength, enable the astronaut to return to normal operation. Contrary to popular belief, vestibular illness sufferers are in it for the "long haul" and must learn new management techniques to control even basic habits. Long-term exposure to microgravity may have impacts on the CNS that entail more sophisticated adaptation processes. Some of these mechanisms may result in changes in neuron structure and connectivity that could be maladaptive when the organism is reintroduced into a gravity environment without adequate countermeasures, such as the use of continuous or intermittent exposure to an applied gravity via centripetal acceleration during the mission. The creation of procedures to measure the strength and duration of the applied gravity load can be sped up with the use of animal models. We must dive into the plethora of clinical and experimental data on the long-term effects of inner ear trauma on motor performance throughout the neuraxis in order to create new translational research that will clarify the scope and depth of the brain compensatory mechanisms. The behaviour and flexibility of synapse structure and brain function will be especially important for crew performance and health during space travel.

Control of vestibular and sensorimotor systems

The integration of sensory data from the vestibular, visual, proprioceptive, and somatosensory systems as well as a comparison of the actual sensory feedback to the anticipated feedback are necessary for the perception of direction and movement. The sensory signals coming from the vestibular system, in particular the signals from the otolith organs, are affected by a changed gravitational environment. Otoliths on Earth change the pattern of their output signals in response to gravitoinertial acceleration, which reveals information about head direction with respect to gravity. The otoliths are essentially unloaded in weightlessness and are therefore unable to offer valuable information regarding static head position. The CNS is therefore believed to perceive all otolith output signals during spaceflight as being caused by head translation, not head tilt, and this misinterpretation persists for many hours after the return to Earth. This concept is supported by changes in the regulation of astronauts' eye movements, posture, and gait following spaceflight (Young et al. 1993). According to a different theory, the CNS is no longer able to effectively predict the relative direction of gravity when in weightlessness, and this loss in capacity to assess gravity ultimately affects the CNS's ability to estimate linear acceleration (Merfeld 2003). The CNS of an astronaut must thus effectively adjust to these different inputs to the otolith organs in order for them to properly accomplish a job under variable gravity (Paloski et al. 2008). The ability of astronauts to execute sensorimotor activities, such as controlling the spaceship or making an emergency exit during a voyage to Mars, might be seriously hampered if they are unable to adjust to weightlessness. When sensory modalities stop transmitting information (due to illness or the absence of an effective stimulus) or when signals are improperly processed, sensory-motor disorders arise. Several sensory abnormalities affect astronauts during crucial phases of spaceflight, such as the transition into weightlessness and the landing back in Earth's gravity. Motion sickness, spatial disorientation, delays in eye-head synchronisation, and difficulties walking are examples of common sensorimotor problems. The nature and severity of these problems vary from person to person, depending on factors including frame of reference, sensory information weighting, rates of adaptation, and prior spaceflight experience. Astronauts suffer these sensory abnormalities more severely the longer they are in space, and full recovery might take weeks or months (Clément and Reschke 2008). Future long-duration space exploration missions, during which people would experience a variety of gravitational situations, will be hampered by this. Medication, self-assessment tools, and training are examples of countermeasures to avoid and mitigate the sensorimotor disorders brought on by spaceflight. Future research is anticipated to result in in-flight tools that will aid crew members in recognising and facilitating their own adaptation to various gravitational situations. The disturbances that the crews of Mars missions are likely to experience are discussed below, along with the countermeasures needed to preserve crew well-being and performance. Because the vestibular, proprioceptive, and haptic receptors are all extremely sensitive to gravitational stimulation, gravity plays a crucial role in spatial orientation. Astronauts first rely only on their vision in the absence of gravity. They encounter visual reorientation illusions as a result of mistaking their orientation in relation to the environment. Astronauts eventually adjust to weightlessness and find new methods to interact with the outside world (Oman 2010; Young et al. 1993). Spaceflight also has an impact on visual spatial cognition, which is crucial for astronauts to accurately judge distance and object size. Astronauts on the ISS frequently overestimate height and underrate depth and distance. A person's scale of size at eye height may shift when they are not standing on the ground, or these changes may occur because perspective signals for depth are less prominent in weightlessness (Clément et al. 2013). While in space, astronauts' ability to effectively conduct cognitive and sensorimotor activities, such as those involved in robotic operations, may be impacted if they perceive distortions of the visual world. Furthermore, this error will change how astronauts perceive the size of their housing and work area. Recent research reveals that spaceflight alters neuroplasticity, particularly in the vestibular and motor cortices (Koppelmans et al. 2016, Roberts et al. 2017, Van O mbergen et al.). The cortical regions linked to behavioural experience undergo both positive and negative plasticity, including reconfiguration and volume reduction. We've known for a while that the topographical arrangement of the brain is not set and that even adult brains can go through significant remodelling. These modifications take place as a result of skill acquisition (Karni et al. 1998), sensory deprivation (Kraft et al. 2018), or after a stroke as a result of coping mechanisms (Desmurget et al. 2007). Vestibular function and motor control may be compromised during Mars landing due to alterations in the cortical topographic arrangement of sensory and motor areas during long-duration spaceflight (Demertzi et al. 2016). To adapt to the changes in sensory impulses that occur in weightlessness, astronauts must modify their image of space and movement. In addition, astronauts will have to get used to Mars' lighter gravity during upcoming exploratory trips before having to readjust to Earth's gravity. Future human planetary exploration missions should take these factors into account, and further research should be done to build countermeasures. Visual or tactile tools that might assist astronauts in orienting themselves in relation to their surroundings and enable them to correctly steady the spacecraft after landing are examples of potential countermeasures. After a lengthy ISS journey, the astronauts' ability to manage the tilt of the spacecraft is hampered, and the frequency of mistakes they make reflects changes in how they perceive their own motion (Clément et al. 2018). Systems for tactile spatial awareness can aid astronauts in manoeuvring the craft. Small tactors that are affixed to the torso of these tactile spatial awareness devices vibrate as the body tilts in relation to gravity, alerting the patients to their body alignment. Using tactile feedback, astronauts have been able to manage their body tilt following spaceflight and have had their early post-flight performance returned to where it was prior to the trip (Clément et al. 2018). After the spacecraft has splashed down in the water, it's also feasible that a cockpit display that lines up the visual horizon perpendicular to gravity may show information that will aid astronauts in exiting the vessel. This idea is being examined right now. Gravity does not appear to affect the semicircular canals' fundamental reaction, according to the vestibulo-ocular reflex (VOR), which compensates for head motions in yaw under weightlessness (Benson and Viéville 1986; Correia et al. 1992). However, under weightlessness compared to 1 g, the time constant of horizontal nystagmus degradation is shorter (DiZio and Lackner 1988; Oman and Kulbaski 1988). Additionally, ocular counter-rolling, a response that causes the eyes to roll in the opposite direction of a head tilt, is absent in weightlessness and diminishes following spaceflight (Reschke et al. 2018a) (Hallgren et al. 2016). During spaceflight, astronauts' heads spin about the roll axis, causing torsional and horizontal nystagmus (Reschke and Parker 1987; Reschke et al. 2017a). These adjustments are most likely the result of gravity's effect on the velocity storage, which prolongs inputs from the semicircular canals after the cupula has returned to its resting position and directs the slow-phase eye velocity in the direction of the perceived vertical (Raphan et al. 1992).

Additionally, being exposed to weightlessness causes changes in the eye-head coordination needed to acquire targets. A combined saccadic eye movement (compensatory) and vestibuloocular reaction (anticompensatory), which adjusts focus onto a visual target, are required for coordinated eye-head motions toward an offset visual target. According to a recent research, Space Shuttle pilots took much longer after landing to acquire visual targets than they did previously. Increased latencies and lower peak velocities of eye and head movement compared to preflight values caused this delay in obtaining visual objects. After spaceflight, head movement has a decreased velocity and a longer latency, which requires a series of big compensatory eye saccades to bring the attention back to the target (Reschke et al. 2017b). who have developed to help in guiding the moving picture onto the retina (Reschke et al. 2002). However, ground-based research have indicated that the spatial targeting of saccades may be dependent on the gravity level. Few studies have demonstrated a direct influence of spaceflight on saccade gain. Such as particular, Wood et al. (1998) found that on Earth, ocular saccades consistently tilt as a function of head tilt, while Israel et al. (1993) found that during space travel, directional errors of saccades to recollected objects increase. Pilots will struggle to get data from instruments or have delays while capturing visual objects if they are unable to adjust their eye-head synchronisation to the changes in the gravitational environment. The danger is higher under circumstances like landing that call for continual attention, prompt action, and precise identification and positioning of a visual object. It is impossible to anticipate if these alterations are more prominent during long-duration exposure to weightlessness because the majority of investigations on the impact of spaceflight on vestibulo-ocular responses were carried out during short-duration Space Shuttle flights. Immediately upon their return to Earth, crew members have undergone tests for hand-eye-head coordination, active and passive visual-vestibular interaction, and computerised dynamic visual acuity (Clément and Reschke, 2008). However, cervical and ocular vestibular evoked myogenic potentials tests have not been carried out, and these vestibular tests are required to quickly acclimate astronauts to changes in gravity levels and to better understand the changes in otolith function.

Dynamic posture platforms that move or tilt the subject have been used to measure how spaceflight affects astronauts' postural stability. Other more advanced posture control techniques, such stabilising ankle rotation and/or vision, have also been tested (Paloski et al. 1993). NASA has been using computerised dynamic posturography (CDP) for the past 30 years to measure astronauts' posture objectively and learn how sensory input from the eyes, ears, and skin affects postural stability after spaceflight. The findings clearly demonstrate that postural stability is compromised regardless of the duration of spaceflight, although it is significantly more severe and lasts much longer following lengthy ISS missions (Fig. 2).

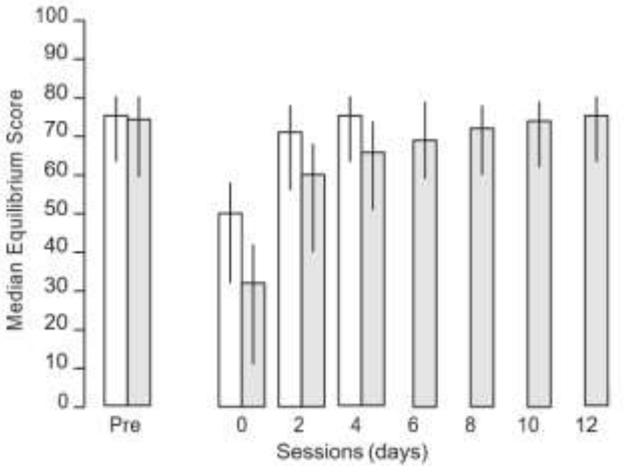

Fig 2. On the Space Shuttle (short-duration trips, generally 1-2 weeks) and International Space Station, computerised dynamic posturography (CDP) using the EquiTest has been utilised to evaluate the recovery of postural control in crew members after spaceflight (long-duration flights, typically 4 – 6 mo). In one of the sensory organisation tests (SOT5), CDP measures changes in centre of gravity (COG) when individuals stand with their eyes closed on a support surface that has been validated for postural sway. When visual signals are unavailable and somatosensory cues are unreliable, how the person uses vestibular cues will depend on this scenario. There are three trials that last for 20 seconds each. The maximum natural postural sway in the anterior-posterior direction (12.5°) and the estimated maximum anterior-posterior COG displacements are combined to get an equilibrium score. A score of 100 denotes absolute stability, whereas a score of 0 denotes loss of equilibrium. When compared to preflight, the median equilibrium score during SOT5 in astronauts drops significantly right away after landing (session day 0). (Pre). As weightlessness exposure duration grows, the severity of the disequilibrium worsens and recovery times lengthen. After open-column short-duration spaceflights (about 4 days) and long-duration spaceflights (about 12 days), postural control returns to baseline (shaded columns). 25% and 75% percentiles are shown with error bars. On postflight session days 0, 2, and 4, the equilibrium scores of short- and long-duration crew members are considerably different (unpaired t test, P 0.05). [Adapted from Wood and colleagues (2015).]

When the astronauts' eyes are closed and the support platform rotates in direct proportion to anterior-posterior body sway, the astronauts' posture is the most unstable. Vestibular feedback governs posture, but is altered when vision is removed and somatosensory feedback is interfered with (Paloski et al. 2006). Most ISS crew members found this test to be very difficult and did not even attempt it after landing when dynamic pitch head tilts were added to the postural assessments on the unstable platform (Jain et al. 2010). (Wood et al. 2015). The first week after returning from space, the majority of astronauts still struggled to stand when doing dynamic head tilts on the shaky platform, and some of them lost their balance while undergoing tests in the second week. These deficiencies imply that balance regulation during extended space travel also depends on a sensory shift in favour of somatosensory signals (Wood et al. 2015). Postural deterioration following spaceflight may potentially be attributed to changes in vestibulo-spinal reflexes. Although spaceflight significantly lowered the Hoffmann reflex, which measures alterations in otolithspinal reflexes, the difference between pre- and post-flight responses was not statistically significant (Watt et al. 1986). When astronauts experienced an unexpected drop during flight (a vertical fall to Earth while wearing bungee cords), Reschke et al. (1986) noticed a potentiation of the H-reflex that lasted for 40 minutes before dissipating after seven days. It is unknown how variations in the spinal reflex pathway's gain relate to preprogrammed muscle activity like posture maintenance, despite the fact that such changes in the H-reflex anticipate changes in this pathway's gain. The changes in the vestibulospinal and otolithocular reflexes, as well as the spatial orientation both during and after flight, may also be caused by a probable increase in otolithmass during spaceflight. While astronauts walk precisely and correctly in weightlessness once they have evolved to non-gravitational modalities of bodily locomotion, terrestrial patterns of locomotion are very gravity dependent. After landing, though, their balance control deteriorates, their gaze becomes erratic, they restrict head movements, and their step cycle changes (Bloomberg et al. 1997; Layne et al. 1997). Soon after returning from space, astronauts walk with a greater angle of motion at their knee and ankle, which improves their dynamic stability but slows down their walking speed (Bloomberg et al. 1997). After a long-duration space journey, it may take weeks to go back to preflight baseline values, even if astronauts regain their gait within the first 12 hours after landing (Mulavara). Because computational models only employ data from simulated gravity research, we do not know which walking methods will be preferred under

Martian gravity (Ackermann, Bogert 2012). The majority of astronauts also experience some degree of ataxia right away after leaving the atmosphere; they describe feeling as though they are turning when they try to walk straight, losing stability suddenly when they turn corners or experience unexpected disturbances, and losing orientation in unstructured visual environments. Additionally, some astronauts experience oscillopsia, an illusionary movement of their visual field when they move (Reschke et al. 2017c), which is similar to the symptoms of labyrinthine defects (Pozzo et al. 1991). This suggests a breakdown in head-trunk coordination as a result of conflicting sensorimotor input during the transition between gravitational environments. Additionally, astronauts leap differently than other people do; during the first three jumps, most people fell backward (presumably as a result of a potentiated stretch response), and they used their arms more to stay balanced. In fact, NASA has made CDP a medical necessity since the vestibular-induced alterations during lengthy ISS flights are so severe. Before NASA permits an astronaut to fly again, their CDP performance must reach the level it was at before the last journey. Additionally, following a long-duration space journey, astronauts must engage in 2 hours per day of vestibular rehabilitation therapy for 2 weeks as part of their "postflight reconditioning." By encouraging CNS compensation for inner ear deficiencies, this rehabilitation therapy involves specialised activities to remove or greatly reduce symptoms (Wood et al.2011). Until recently, astronauts and cosmonauts have been welcomed at landing by a large group of medical and operations professionals who have assisted them in exiting their vehicles and coping with readaptation, disori- entation, and cognition problems. This is with the exception of a few ballistic Soyuz landings. There won't be a landing greeting like this on the Moon or Mars, so NASA must come up with ways to lessen the disturbance to posture and gait that will be brought on by these long-duration trips. We must collect vestibulo-spinal data from each crewmember throughout varying gravity levels and during lengthy flights before these dangers can be recognised and minimised. Interacting with the environment or doing the activity repeatedly is a key element of brain adaptation to novel settings (or activities) (practice makes permanent). Thus, it has been suggested that regular head motions made by the astronauts during reentry might aid in their adjustment to Mars' gravity or readjustment to Earth's gravity (Wood et al. 2011). Due to practical limitations, it has not been able to systematically research this impact. Anecdotal information from Space Shuttle crew members suggests that gently increasing head motions help reduce oscillopsia and motion sickness. The astronauts performed these head motions while progressively inclining their heads, first in the yaw plane and subsequently in the pitch and/or roll planes. Systematic head motions are still advised to crewmembers during and after reentry despite the Soyuz's volume, greater g profile, and the arrangement of its passengers at landing making head movement more challenging than it was in the Space Shuttle (Wood et al. 2011).

The most clinically significant neurosensory condition that astronauts encounter is motion sickness, which they often suffer during the first few days of spaceflight and after landing on Earth. There are various signs of space motion sickness, including drowsiness, nausea, stomach awareness, exhaustion, and a decline in cognitive function. It is not possible to anticipate a subject's sensitivity to motion sickness in space based on how susceptible they are to it on Earth (Reschke 1990). About two-thirds of astronauts and cosmonauts experience motion sickness during the first few days of spaceflight. Different age groups, first-time or repeat flights, commanders and pilots, career or non-career astronauts, and mission specialists all experience the same occurrence (Davis et al. 1988). When astronauts enter the fractional gravity near Mars, their motion sickness will probably return. This might make it difficult for them to control sophisticated machinery during a Mars landing. Space motion sickness typically goes away three to four days after entering weightlessness.

After short-duration missions, 27% of astronauts feel motion sickness after landing, and 100% after long-duration flights (Ortega and Harm 2008). (Reschke et al. 2017c). Symptoms that occur after a flight are typically more severe than those that occur during it. When first experiencing weightlessness, female astronauts experience motion sickness at a somewhat greater rate than male astronauts. On the other hand, after returning to Earth, males report more severe motion sickness symptoms (Jennings 1998). Space motion sickness has been treated using a variety of medications. Although certain medications have shown some promise, no medication, or combination of medications, completely shields everyone from harm (Reschke 1990). For moderate-to-severe instances of space motion sickness, an intramuscular injection of 25–50 mg of promethazine is advised (Reschke et al. 2018b), whereas oral and suppository methods are advised for less severe symptoms. Promethazine has been shown to be useful in reducing space motion sickness (Graybiel and Lackner 1987), but it also has a variety of dose-dependent adverse effects, including as drowsiness, disorientation, and dizziness, which might make it difficult for an astronaut to steer a spacecraft during a Mars landing. After ingesting promethazine, those on Earth had significantly reduced alertness and coordination (Cowings et al. 2000). Promethazine may have an impact on fundamental vestibular function as well (Diaz- Artiles et al. 2017). Over the past two decades, a number of extremely potent antiemetic drugs have been developed, with considerably more benign side effects, to treat nausea and vomiting related to chemotherapy (see Navari 2009 for a review). These medications, the majority of which are serotonin antagonists, inhibit 5-HT3 receptors and may be used to cure motion sickness in space travel. An alternative strategy would be to take a medication that affects the brain's motion sickness-causing mechanism. The velocity storage integrator in the brain stem may have a role in motion sickness experienced on Earth, according to recent research (Clément and Reschke 2018; Cohen et al. 2008, 2019; Dai et al. 2003; Ventre-Dominey et al. 2008). It may be more effective to address the symptoms of motion sickness than to decrease velocity storage using GABA agonists like baclofen. If any of these alternative medications were to be taken into consideration as prospective therapies for space motion sickness, they would need to undergo thorough testing both on Earth and during parabolic flight, as well as careful characterization of any potential cognitive or motor adverse effects. According to Davis et al. (1988), Russian cosmonauts are just as likely as American astronauts to experience space motion sickness. However, the Russian space programme tests prospective astronauts for motion sickness resistance, whereas NASA does not. Additionally, the Russian space programme employs Coriolis (cross-coupled angular) acceleration as preflight vestibular training to mitigate or eliminate space motion sickness symptoms (Clément et al. 2001), despite the fact that this method has not been effective (Reschke 1990). According to Cowings (1990), autogenic feedback training greatly outperformed promethazine in terms of preventing motion sickness symptoms. However, the 6-hour training programme spread over 3 weeks was too time-consuming, thus this physiological training was stopped (Cowings et al. 2018). The impact of various mechanical devices in reducing space motion sickness symptoms has been investigated. These mechanical devices were created to combat deconditioning during lengthy missions and alleviate motion sickness symptoms during the initial days of flight, preventing the astronaut from fully acclimating to weightlessness. The neck pneumatic shock absorber, one mechanical device, includes a cap with rubber cords that provide pressure to the cervical vertebrae and neck muscles, stretching the user's neck muscles to maintain an upright head position and prevent any turning or tilting of the head (Matsnev et al. 1983). More recently, stroboscopic vision has been studied by NASA and the US Army as a straightforward and manageable postflight motion sickness remedy. In order to cure the symptoms of visual-vestibular conflicts, stroboscopic lighting avoids retinal slide. Passengers in cars and helicopters have found success using shutter glasses with a cycle frequency of 4 or 8 Hz and a short dwell duration (10–20 ms) to reduce their feelings of motion sickness (Reschke et al. 2007). It appears that the primary cause of postflight motion sickness is a visual-vestibular conflict (Reschke et al. 2017c). By lessening retinal slip, the stroboscopic shutter glasses may be able to reduce this conflict.

Countermeasures & Perspective.

The success of lengthy trips to the Moon and Mars depends on our ability to comprehend the effects of extended exposure to partial gravity. The operational implications of the vestibular and sensorimotor alterations brought on by spaceflight may be reduced if the effects of partial gravity were prevented, but this prevention has not yet been realised. Instead, restrictions are put in place to help astronauts adjust by limiting their activities once they change gravity levels. To decrease the danger of emesis in the spacesuit, astronauts are not allowed to engage in extravehicular activities until their third day in orbit. They are also not allowed to drive or fly until their third day after returning from a brief mission. The vestibular and sensorimotor systems of the astronaut may adjust to changes in gravity levels more quickly with adaptation training before flying and booster training while in flight. Ground-based research have revealed that the "learning to learn" strategy's greater adaptability lasts for up to a month after first training (Bock et al. 2001; Roller et al. 2001). For instance, the astronauts may practise on a treadmill that is affixed to a moving platform. The subject's gait stability would be put to the test by this system. A virtual scenario that exposes the participant to varied combinations of discordant visual information while they are walking on the treadmill might be used to impose more sensory diversity and difficulty. The person would be able to practise resolving difficult and contradictory novel sensory information through this encounter (Bloomberg et al. 2015). After receiving this training in sensorimotor flexibility, astronauts may be able to quickly alter their motor control techniques in the hours following landing (Igarashi et al. 1989; Seidler 2004).

It is conceivable that the exploration vehicles may be built to spin, generating centrifugal forces that would produce an artificial gravity environment within. Before putting this plan into action, NASA would need to figure out how gravity thresholds impact sensorimotor function in order to set the minimum gravity level necessary and to calculate adequate ground reaction forces that allow the astronaut to walk. A short-radius centrifuge in which people can exercise may be adequate to sustain gravity-dependent physiological systems, negating the need for large-radius centrifugation (Clément et al. 2015). The effects of gravity gradient, or the difference between the gravity experienced at the head and the gravity experienced at the trunk and the feet, would need to be clarified, as well as the minimum effective duration and frequency of artificial gravity exposure (Clément 2017). At the beginning of a space mission, astronauts' inner ear mechanisms are functioning normally as they transition into weightlessness. However, soon after, as gravitational stimulation to the otolith organs is lost, vertigo, spatial disorientation, and postural instability occur, which are symptoms shared by people with vestibular disorders on Earth. While in space and after returning to Earth, an astronaut must voluntarily and reflexively process the changing vestibular signals and initiate compensatory responses to better match the new environmental demands, just as a patient with a vestibular lesion must learn new strategies to improve day-to-day living. Balance, equilibrium, and motor control are some of the brain functions that are immediately impacted by the unfamiliar gravitational environment. These mechanisms adjust quickly and gradually. The overall goal of these procedures is to maximise performance in the space environment, but they may occasionally be unsuitable in a dynamic, rapidly changing environment, or they may even pose an immediate or long-term hazard upon return into a gravity environment. Without adequate safeguards, some of the mechanisms that develop during spaceflight to combat the loss of gravity signal may result in, among other things, structural changes in the inner ear and plasticity of interconnectivity between populations of neurons involved in perception and spatial cognition. It is expected that the vestibular, sensorimotor, and spatial orientation disturbances of astronauts will worsen the longer they spend in space. Less is known about the function of the vestibular organs in other functions, although there is a lot of clinical and experimental evidence on how inner ear trauma impacts motor control and orientation functions. For instance, we are aware that the majority of astronauts feel motion sickness while in orbit and shortly after their return, but we do not know if this response is brought on by changes in otolith bulk, vestibular neuronal activity, or utricular organ asymmetry. We also know that astronauts pick up on spacecraft manoeuvring rapidly and that this skill transfers over to later trips. Nevertheless, we are unsure of how the astronauts will modify their postural habits and orthostatic tolerance after they land on Mars' surface following a six-month mission in weightlessness (Paloski et al. 2008). The relationship between blood pressure control and vestibular adaptation is also significant, especially in light of the possibility that it is connected to postflight orthostatic intolerance. Furthermore, the spaceflight-associated neuro-ocular syndrome (SANS) problem, which almost certainly depends on the dose of microgravity (Mader et al. 2011), may be caused by prolonged fluid shifts, affects the visual system, and may lead to changes in the brain that could have long-term effects on the person—a blurring between neural and cardiovascular function. The vestibular signals must be effectively integrated with processes in other brain regions to remove the ambiguity of this new input-output situation (Reinagel 2001). The adaptation processes of the sensorimotor, oculomotor, postural, and cardiovascular systems are largely or entirely independent of one another and probably change over a variety of periods. Their fate will depend on how effectively the astronauts adjust to the unfamiliar surroundings.

Studies of Cognition and Behavior in Model Organisms

The obstacles to crew members' behavioural health and performance on future exploration trips will be far higher than the difficulties they presently experience while working and living on the International Space Station. Deep space missions will have previously unheard-of lengths, distances, confinements, and levels of autonomy; these pressures, together with protracted durations of exposure to microgravity and space radiation, may have an impact on an astronaut's cognitive abilities. Although many performance indicators may be directly assessed in people, there are few data on human epidemiology from space-like radiation. To investigate the consequences of neurochemical, functional, and structural changes in the brain and to evaluate how these changes relate to operationally important performances related to radiation exposures equivalent to spaceflight missions, NASA must rely on translational models. The processes behind the adaptation of complex behaviours (such as learning and memory, social interaction, anxiety, and sleep) during spaceflight have been studied using a wide variety of animal species. However, rats have been the main models used to evaluate the behavioural impacts of space flight and spaceflight analogues. A few months of observation in rodents is equivalent to several years of observation in humans since a lot of mice can be carried on a single spacecraft and mice have significantly shorter lifespans than people. Researchers may undertake ground-based research of the effects of hypogravity without the constraints imposed by spaceflight by suspending rats by their tails to imitate the mechanical unloading and cephalic fluid changes brought on by spaceflight. The combined effects of radiation and other spaceflight stressors must be assessed using animal models and behavioural constructs that can bridge the gap between the radiation-induced effects observed in animal models and the predictions of human performance changes in space in order to conduct a thorough risk assessment and manage health risks for astronauts of future exploration missions. Rodents subjected to several spaceflight stresses had structural and functional alterations in their central nervous systems (CNS), which suggests that fundamental information processing mechanisms are affected. Affect, learning, memory, and cognitive flexibility may all suffer as a result, which might have a detrimental effect on performance that is operationally important.

The most often studied spatial learning and memory processes have been used to investigate behavioural alterations brought on by spaceflight stresses. Contextual fear conditioning, mazes, novel object and place recognition, object in place recognition, and object recognition have all been used to assess memory that is hippocampus-dependent and strongly correlated with the cortex. Operant conditioning, attentional set sorting, and psychomotor vigilance tests can be used to measure cognitive activities that are connected to the frontal brain. Open field tests, raised plus mazes, and zero mazes are frequently used to measure anxiety and dread, while forced swim and tail suspension tests might reveal depressive-like symptoms. However, behavioural effects in animals are difficult to measure, and results vary depending on the species, strain, age, sex, and evaluation technique utilised (Buckner and Wheeler 2001). To accurately translate the impacts of animal behaviour on human behaviour and determine the implications of the findings for astronaut performance during a Mars trip will be the next challenge.

Gravity shifts influence anxiety levels, as well as memory and learning activities, according to several mouse studies. Rats were tested using the Morris water maze and shuttle box after two weeks of hindlimb unloading (HLU), which simulates the effects of weightlessness (Qiong et al. 2016). Rats' behaviour during parabolic flights, which produce various partial gravity levels, changed according to the gravity level: between 0.01 g and 0.15 g, they extended their hindlimbs, whereas between 0.4 and 0.2 g, they displayed startle response and crouching (anxiety-like behaviours). This suggests that there may be different thresholds for emotional behaviour and balance- or posture-related effects (Zeredo et al. 2012). After two weeks of rotation at 2 g, rats' performance in the radial arm maze significantly deteriorated for five days before returning to normal. This finding suggests that although animals require a constant gravity reference to maintain performance, they are capable of adapting to changes in gravity (Mitani et al. 2004). However, it is crucial to highlight that difficulties might be created when centrifugation is employed as a model of hypergravity: in one research, rats had symptoms of "rotation sickness" that worsened with the amount of rotation and partially recovered after 12 hours (Cai et al. 2005). Three Gy of 137Cs gamma rays on day 7 and 1.5 Gy of a broad energy spectrum of protons on day 14 of radiation exposure to young rats resulted in 14 days of HLU, but neither had any effect on spatial memory. The results from the open field and raised plus maze, however, showed reductions in anxiety-like behaviour (more time spent in the field's centre or in open arms) (Kokhan et al. 2017).

Rats were flown aboard the biosatellites Cosmos 605, 690, 782, or 936 for spaceflights lasting between 19.5 and 21.5 days before undergoing a set of spatial memory tests. The rats' spatial memory was found to be impaired in radial arm maze (Lachman-type) protocols conducted 2 days to 4 weeks after the flights. This effect was exacerbated when the animals were given higher workloads, suggesting this effect may have been related to fatigue or a lowered cognitive reserve (Gurovsky et al. 1980). The development of rats' spatial cognitive navigation systems appears to be minimally affected over the long run by the lack of gravity. Rats who endured 16 days on a Space Shuttle trip beginning at postnatal days 8 or 14 had their cognitive mapping skills tested. Only slight variations were noticed in search patterns, which vanished within a few days, and the spatial learning and memory behaviour of the flying rats in the Morris water maze, radial arm maze, and open field paradigms was identical to that of the Earth-bound, age-matched control rats (Temple et al. 2003). Additionally, when the offspring of rats exposed to 5 days of weightlessness on the Cosmos 1514 mission during gestation days 13 to 18 were tested when they were 1 to 4 months old, there were no maze-based cognitive deficits; however, in an open field paradigm, their exploratory behaviour was decreased and their grooming was increased, which together suggest increased anxiety (Apanasenko et al. 1986). After testing the 8- and 14-day-old rats for a month following their 16-day Space Shuttle Neurolab voyage, Temple et al. (2002) found that the spaceflight had no effect on the rodents' memory, spontaneous activity, or anxiety levels. Although it took them longer to reach the platform in the water labyrinth, the rats did swim faster for a brief period of time than they did before taking flight.

In order to determine whether transgenic mice were more resistant than wild-type mice to the damaging effects of microgravity on bones, three transgenic mice that overexpress pleiotrophin (a cytokine that is upregulated in tissue injury and wound repair, and is involved in bone formation, neurite outgrowth, and angiogenesis) spent 91 days on the ISS in 2009. The transgenic animals showed less grooming (a displacement activity) than the wild type, indicating that the strains use different procedural and emotional coping mechanisms to adjust to weightlessness. In water, rodent floating behaviour is typically associated with passive behaviour, anhedonia, and stress response. In space, it could reflect adaptation to the environment (Cancedda et al. 2012). Unfortunately, due to payload or health issues, only half of the mice made it through the 91-day flight. After the mission, the brains of the three remaining mice—two transgenic and one wild type—were examined, and it was discovered that flying animals had lower levels of nerve growth factor in their hippocampus and cortical regions than ground-based control animals did (Santucci et al. 2012). Although the source of this behaviour could not be determined from the films, aggre-gative conduct (huddling contact) near the feeder was seen to be more frequent in 45 male mice throughout the 30-day unmanned Bion-M1 mission compared to the behaviour of similarly housed ground controls. Individually housed mice were flown for 35 days on the ISS, and observations of their behaviour during that time revealed that they floated freely within the habitat and utilised their tails to keep their posture straight when sleeping (Shiba et al. 2017). Female mice that were 16 and 32 weeks old were recently seen on camera within the NASA Rodent Habitat on board the International Space Station. Younger flying mice had higher levels of physical activity than identically housed ground controls, and this activity followed the circadian cycle. Only a small portion of an animal's movement included free floating; instead, they evolved a guided coasting behaviour, utilised their tails to stabilise their positions, and walked on their front paws. Younger (but not older) mice exhibited characteristic circling or "race-tracking" behaviour within 7–10 days of launch, which later developed into group activity (Ronca et al. 2019). This race-tracking behavior may represent an attempt by the animals to self-generate artificial gravity via self-motion. Male gerbils (Meriones unguiculatus), in contrast to mice, wandered incoherently during the course of a 12-day flight (Foton-M3) and never tried to reposition themselves by grabbing onto the wire mesh of the cage system (Il'in et al. 2009).

Rhesus monkeys were trained to touch their hands to lights on a horizontal display screen that were positioned at various angles around the animal in order to evaluate the precision of eye-head-hand motions and reaction times during spaceflight. Although performance did improve during the second week of the 14-day Bion 11 mission, early in the flight the monkeys completed the coordination task up to 60% slower and up to 40% less correctly than when they performed same activity before the trip (Antsiferova et al. 2000). Furthermore, Washburn et al. (2000) found that training rhesus monkeys to move computer screen cursors over randomly appearing objects within predetermined time intervals, choose options from a five-choice menu, or use a joystick to track moving targets was degraded by spaceflight. Both the ground control monkeys and the flying monkeys in this study had reduced performance, but the flight animals' impairment was far more severe. The personalities and desire to cooperate of the monkeys was a confusing problem.

Space radiation & its effects

How to shield astronauts from sporadic solar particle events (SPEs), which are mostly made up of low- to medium-energy protons, and from chronic, low-dose-rate galactic cosmic rays (GCRs), which are mostly made up of high-energy protons (85%) and high-energy and charge (HZE) particles, is a problem that needs to be addressed (Nelson 2016). When HZE particles enter tissue, they may leave a trail of highly radioactive and potentially injured cells in their wake. It's possible that these tracks might cause significant harm to the CNS. DNA damage occurs in clustered, repair-resistant patterns, and it's also plausible that specific tissue-level kinds of damage develop as a result of the spatial connection of damage tracks with brain cell configurations. During a Mars mission, the maximum yearly radiation exposure from GCR is estimated to be in the range of 20 cGy, with less than 50% of the dosage from HZE particles (Cucinotta et al. 2014). According to recent research, HZE particle exposures of less than 10 cGy can cause structural and behavioural alterations. Many of these findings are detailed in two recent reviews (Cekanaviciute et al. 2018; Kiffer et al. 2019).

Overall, results from studies on animals show that space-like radiation produced by particle accelerators causes persistent, measurable changes in the CNS's functional status that are similar to those brought on by ageing and some neurological conditions involving oxidative stress, neuroinflammation, and dendritic disorders. During a Mars mission, the maximum yearly radiation exposure from GCR is estimated to be in the range of 20 cGy, with less than 50% of the dosage from HZE particles (Cucinotta et al. 2014). According to recent research, HZE particle exposures of less than 10 cGy can cause structural and behavioural alterations. Many of these findings are detailed in two recent reviews (Cekanaviciute et al. 2018; Kiffer et al. 2019). Overall, results from studies on animals show that space-like radiation produced by particle accelerators causes persistent, measurable changes in the CNS's functional status that are similar to those brought on by ageing and some neurological conditions involving oxidative stress, neuroinflammation, and dendritic disorders. Although the dosage responses can be complicated and nonlinear, some researchers have hypothesised that systems for repair or compensation may be activated at levels greater than those that directly cause harm. Space-like radiation induces quantifiable behavioural impairments that may manifest acutely or over the course of many months, according to observations of hippocampus-dependent memory formation, frontal cortex-dependent executive function and cognition, and amygdala-dependent anxiety and fear in rodents. However, little is known about the mechanisms underlying these cognitive changes. Age at assessment and irradiation, as well as sex and genotype (such as ApoE allele, hybrid strains vs. inbred), all have an impact on the behavioural reactions to accelerated particles (Rabin et al. 2012). Males' social interaction and memory were lessened than those of females, and their anxiety, microglia activation, and synaptic loss were larger. (2018b) demonstrated that charged particles generated a range of sex-specific reactions in mice, and females were more radioresistant. Some irradiated rats maintain a level of spatial memory performance comparable to that seen in the sham-irradiated rats (Britten et al. 2012), indicating that some rats are able to mitigate the negative effects of the GCR while others are unable to do so. There is a significant interindividual variation in the susceptibility of Wistarrats to develop neurocognitive impairment. Furthermore, rats chosen for their suitable or superior baseline performance and consistently exercised are less vulnerable to the negative behavioural effects of radiation exposure than rats chosen at random. In transgenic mice that overexpress the human Alzheimer amyloid precursor protein, exposure to low doses of HZE particles accelerated the development of age-related electrophysiological properties, decreased cognitive function (contextual fear conditioning and novel object recognition), and accelerated amyloid plaque pathology, including deposition and clearance (Cherry et al. 2012; Vlkolinsky et al. 2010). Hippocampal-dependent learning and memory, such as new object identification and spatial recall, show substantial impairments in rodents exposed to HZE particles at concentrations expected for a Mars trip. The extraordinary sensitivity of these processes may result from low levels of neuronal precursor cell death, particularly in the dentate gyrus, as well as the disruption of other functional processes, particularly synaptic plasticity. According to some data, these alterations and the sex-specific variations they cause may be mediated by changes in microglial activity (Krukowski et al. 2018a). After receiving 5 or 30 cGy of helium radiation for 6, 15, and 52 weeks, C57Bl/6 male mice exhibited memory impairment, an increase in anxiety and depressive-like behaviours, and a loss in cognitive flexibility. Increased microglial activation, as determined by CD68 antibody, was also seen along with these alterations (Parihar et al. 2018). At doses as low as 10 cGy, novel object recognition and spatial memory retention in mice were impaired two weeks after Fe particle irradiation (Haley et al. 2013); however, there were no effects of irradiation on contextual fear conditioning or spatial memory retention in the water maze for the same animals. The effects of 0.1, 0.25, and 1 Gy of accelerated oxygen particles on 6-month-old male C57Bl/6 mice were recently studied by Carr et al. (2018). The short-term memory of the mice exposed to 0.1 and 0.25 Gy radiation was compromised, whereas memory in the animals exposed to 1 Gy radiation was unaffected. The levels of NR1 and NR2B N-methyl-D-aspartate (NMDA) receptor subunits, the presynaptic marker synapsin1, which were all markedly decreased, and type 1 glutamate (GluR1) -amino-3-hydroxy-5-methylisoxazole propionic acid (AMPA) receptor, which was increased at the lower doses, also displayed this inverted U-shaped dose response.

Britten et al. (2012) demonstrated using the Barnes maze test that 20 cGy of accelerated Fe particles caused a lasting impairment in rats' capacity for spatial learning. The reduction in spatial learning was not brought on by the rats' lack of motivation to escape the Barnes maze because the overall number of head pokes (and particularly incorrect head pokes) remained constant throughout the test period, despite it having been demonstrated that Fe exposures as low as 25 cGy can reduce rats' motivation and responsiveness to environmental stimuli. Low dosages of HZE particles also impair neurocognitive activities involving executive function, which are controlled by the prefrontal cortex and depend on the striatum and hippocampus. For executive function to work at its best, a number of more fundamental cognitive processes must be active. Executive function issues are undesirable in any situation, but they will be more harmful during a voyage to Mars since astronauts would be needed to carry out complicated tasks all during the mission. According to research by Britten et al. (2014), rats exposed to Fe particle levels smaller than those required for a Mars trip displayed impaired attention set-shifting performance (ATSET), a measure of executive function, 3 months after the exposure. Depending on the rat's age, the radiation dose, and the type of exposure, several types of impairments in ATSET performance existed (whole body vs. cranial irradiation). The readily releasable pool of neurotransmitters from isolated cortical synaptosomes, which have been shown to play a significant role in controlling the activity of the prefrontal cortex and suggest an important presynaptic site of radiation action, was found to be associated with behavioural declines.

In one of the few studies on the effects of charged particles on nonhuman primates, Belyaeva et al. (2017) exposed rhesus monkeys to doses that are significantly higher than those that would be encountered on a Mars mission: 3 Gy of 170-MeV protons, followed 40 days later by 1 Gy of 160-MeV carbon ions. The "circle test" involved teaching the animals how to position a cursor over moving objects of various sizes using a joystick and computer monitor setup. While subsequent carbon ion exposure impaired cognitive performance in terms of test success rates and attempts, proton irradiation did not affect cognitive function. However, interindividual variations that were attributed to animal personality variations were seen. L-3,4-dihydroxyphenylalanine (L-DOPA) concentrations in the blood were increased one month after irradiation, but no biochemical effects were noticed right away following proton exposure. All of the dopamine metabolites examined in this study had dropped in concentration eight days after being exposed to 12C ions, with homovanillic acid showing the most dramatic reductions. Motor control and reward mechanisms might be impacted by altered dopamine metabolism and receptor expression. The majority of HZE particle studies have evaluated the impact of a single dose of a single particle type over a short period of time, which does not accurately reflect the long-term, low-dose-rate exposures to mixed particles that would occur in space. Recent mouse studies have demonstrated that sequential ion exposure may result in behavioural consequences that are not expected from exposure to individual ions (Krukowski et al. 2018b; Raber et al. 2016). The whole GCR spectrum as it would look inside the body of a female astronaut on a deep space trip behind vehicle shielding is being simulated in tests being carried out at Brookhaven National Laboratory by NASA to solve this difficulty (Slaba et al.2016). In order to combine a more precise radiation field with low dose rates on rodent timescales comparable to a three-year Mars mission, a simplified five-ion GCR field has also been used for higher throughput studies. Both of these fields can be delivered in daily fractions spread out over a period of six weeks, or six days per week. To address the dose rate issue, recent low-dose-rate neutron tests lasting six months were also undertaken (Acharya et al. 2019).

Human central nervous system and radiation effects & perspective

Patients undergoing radiotherapy get high (e.g., 50 Gy), localised doses of radiation that are far higher than what astronauts would experience. According to Greene-Schloesser and Robbins (2012) and Greene-Schloesser et al. (2012), this can have negative consequences on their CNS and cause them to frequently display behavioural abnormalities such chronic tiredness, cognitive decline, and depression. Adult survivors of childhood leukaemia display dose-dependent deficits in information processing speed, memory, attention, and learning when the disease is treated with fractionated whole body radiation exposures in the 20-Gy range (lower than the localised doses to tumours but still significantly higher than during spaceflight) (Armstrong et al. 2013). Low-to-moderate radiation exposure (2 Gy) caused memory and cognitive deficits in Chernobyl accident and atomic bomb victims, as well as greater frequencies of mental diseases and changed electroencephalographic patterns (Bromet et al. 2011; Lo- ganovsky and Yuryev 2001). No higher incidence of dementia was reported in a study of A-bomb survivors by Yamada et al. (2009), however some prenatally exposed offspring of A-bomb survivors were found to have mental impairment (Otake and Schull 1998). It is challenging to extend the findings from these A-bomb studies to the high-LET charged particle exposures experienced in space since they all involve low-linear energy transfer (LET) expo- sures, many of which were carried out on tiny cohorts. The "Million Man Study," which is now in process, will be the biggest epidemiological investigation of people who have been exposed to radiation. It will analyse occupational and unintentional exposures globally (Boice et al. 2018). The finest baseline for human exposures to date will be provided by it, which will include exposures from internally deposited alpha particle-emitting radionuclides that form high-LET tracks. In the hippocampal neural precursor cells destined to mature into neurons, astrocytes, and oligodendrocytes, space-like radiation can cause chronic oxidative stress and inflammatory responses that change the microenvironment of the brain. Low dosages of a variety of HZE particles have the potential to alter how the brain processes information by reducing the complexity of dendritic branches and the quantity of dendritic spines (and related synapses). Individual neurons' electrical and membrane characteristics are altered by space-like radiation, which also affects the strength of their connections after being stimulated and other synaptic properties including resting membrane potential, rheobase, and input resistance (e.g., long-term potentiation). Radiation exposure alters the amounts of several molecules involved in synaptic formation, as well as ion movements across membranes, inflammatory signalling, and cell survival. Most notably, these changes are linked to alterations in memory and cognitive function.

Less than 1 cGy of accelerated particles promotes oxidative stress in murine and human neurospheres, including both cellular and mitochondrial sources of reactive chemical species (Tseng et al. 2013). Furthermore, exposure to radiation in vivo is linked to an acute and long-term increase in oxidative stress, which may change the membrane characteristics and activation states of glutamate and GABA receptor ion channels (Derkach et al. 1991). Radiation causes long-lasting neuroinflammation, which affects immune cells, endothelia, and microglia as well as changing how cytokines and chemokines are produced and how their receptors work (Moravan et al. 2011). It has been demonstrated that temporary microglia reduction in mice exposed to helium particles preserves cognitive function (Krukowski et al. 2018a). Accelerated O and Ti particles at dosages as low as 5 cGy diminish dendritic spines in the medial prefrontal cortex and the hippocampus, as well as the amount of myelinated (but not unmyelinated) axons in the hippocampus (Carr et al. 2018; Chakraborti et al. 2012). (Dickstein et al. 2018). Acute alterations in presynaptic glutamate release, recurrent inhibition, synaptic effectiveness, and long-term potentiation have been seen in the hippocampi of radiotreated mice; these modifications are consistent with an imbalance between excitatory and inhibitory activity (Marty et al. 2014; Rudobeck et al. 2014; Vlkolinsky et al. 2010). According to a recent study, rats exposed to silica radiation saw changes in their frontal cortex neurons over time (Britten et al. 2020) Sokolova et al. (2015) found reduced excitability in CA1 pyramidal neurons as determined by hyperpolarized resting membrane potentials, decreased input resistance, upregulated persistent sodium current, and increased frequency of minia-ture excitatory postsynaptic currents in mice 3 mo after exposure to 1-Gy protons. Lee et al. (2017) have shown impaired connection probability in a hippocampal-frontal cortex microcircuit and have found differences in radiation responses for various inhibitory neuron subtypes. These small changes in passive membrane properties had a significant impact on computational model predictions of network function of the CA1 microcircuit. The behaviour of mice and rats as well as the underlying cellular and tissue-level CNS outcome measures have repeatedly been impaired in experiments using modest doses of high-LET charged particles that are similar to cosmic rays. After exposures of 25 cGy or more, the majority of the studied parameters exhibit statistically significant changes (often detrimental), while several parameters are sensitive below 10 cGy. Typically, changes may be seen 1 month after exposure, and many of them last more than 1 year. Executive function (including response time, vigilant attention, and impulse control), short- and long-term spatial and recognition memory, fear memory, anxiety, and depressive-like behaviours, and some sensory parameters have all been addressed using sensitive behavioural measurements. Reduced synapse number and dendritic complexity, altered intrinsic membrane parameters, impaired synaptic plasticity, reduced neurogenesis, and elicited neuroinflammatory responses like microglia activation and elevation of proinflammatory cytokines are just a few of the adverse responses at the tissue and cell level. Modified levels of neurotrophic factors (such as brain-derived neurotrophic factor, or BDNF), glutamate- and GABA-gated ion channels, as well as the expression of networks linked to proteotoxicity and neurodegenerative phenotypes, are among the molecular responses that have been seen. Although ongoing studies are now addressing effects of dose-rate reduction and responses to complex mixtures of particles and energies designed to better emulate the space radiation environment, the majority of data gathered to date were from studies of acute exposures to single species of charged particles. Overall, the evidence points to the likelihood that humans will experience cellular and tissue alterations brought on by spaceflight, and that these changes may impede accurate information processing or result in dysregulation of compensatory mechanisms. However, since humans have more cognitive flexibility and reserve than mice do, they will probably reduce the severity of performance limitations. To guarantee that astronauts perform at their very best, it will be crucial to keep coming up with preventative measures like training, exercise, and anti-inflammatory and antioxidant treatments.

Cognitive and behavioral effects in humans under space rediation & their prospectives.

The next major advancement in space exploration will be human space trips to Mars. We should, however, pay close attention to the intricate interaction of psychological and physical pressures that people would experience throughout these missions. In reality, the "most complicated component in the design of long-duration journeys into space" has been recognised as the human component (Ball and Evans 2001, p. 137). We need to comprehend and anticipate how adaptation to the intricate entanglements of physiology, psychology, and behaviour could alter an astronaut's capacity to perform an operational task in order to ensure the crewmembers are safe and perform adequately in the extreme environments associated with long-duration spaceflight (Kaas 1995). One causal relationship between space motion sickness, vertical orientation, and major disturbances of the fundamental components of perception and behaviour is demonstrated by the incapacitating effects of spaceflight-induced motion sickness and the accompanying impacts on astronauts' physiological, psychological, and performance (National Research Council 1998). The psychological difficulties of long-duration space travel are discussed here, along with the brain projections that connect psychological aspects, social contexts, and emotional states to the vestibular system. We pay particular attention to the dangers that integrated spaceflight poses and how crew members might adjust to them in ways that either directly or indirectly impair their performance and behavioural health. Both physically and mentally taxing, space travel. The physical requirements, which include noise, accelerations, weightlessness, and confinement, are beyond what a human being can tolerate. Many such physical stressors increase physiological adaptations (such as fluid shifts, spatial disorientation, lowered immune responses, muscle atrophy, and bone loss) as well as psychological stress (such as perceived mission danger, social isolation, monotony, restricted sensory stimulation, reduced activities, and autonomy). An essential first step in combating recognised stresses of spaceflight is to identify and choose astronauts who have traits that enable them to adapt to these high demands (Santy et al. 1993). For instance, contemporary selection programmes evaluate astronauts for crucial psychological traits as personality traits, ability to self-regulate, expeditionary attitude, autonomy, and psychiatric risk factors (Mittelstädt et al. 2016; Musson et al. 2004). (Santy 1994). Determine what has been referred to as the "right stuff" by considering interpersonal strengths and vulnerabilities, tolerance for linguistic and cultural differences, adaptability in leading and following, and the likelihood that any long-duration mission will also involve a multinational team (Kintz and Palinkas 2016). (Santy 1994). The disruption of circadian rhythm and resulting sleep loss, hor- monal alterations, and cognitive changes like longer reaction times are all examples of psychophysiological adaptations to spaceflight. Astronauts' sensory inputs are diminished during extended confinement within a spaceship, and these changed sensory inputs have an impact on their hearing sensitivity and ability to perceive motion and distance (Clément and Reschke 2008). Furthermore, "space fog"—cognitive and perceptual abnormalities that show up as attentional lapses, short-term memory issues, difficulty while executing dual activities, and psychomotor issues—is a regular occurrence for astronauts. Whether these stressors have additive or synergistic effects and how much of an effect may be due to workload, concomitant tiredness, or environmental variables such CO_2 levels, illumination, and noise are all difficult to ascertain. Additionally, the crew members respond to stress and environmental challenges in very different ways (Borle et al. 2017). Multiple elements will affect an astronaut's psychological health during a lengthy space mission. For instance, early ground research on isolation and space simulators found a strong linear dose-response rise in feelings of despair, anxiety, and anger toward others (Kelly and Kanas 1992; Rohrer 1961; Sandal et al. 1996; Santy 1994). This showed how crucial it is for astronauts to be able to control the range and intensity of their affective states and maintain an emotional state (i.e., mood) that does not impair or negatively influence their performance. Over the course of a lengthy mission, an entire spectrum of emotions, including joy, euphoria, tranquillity, worry, impatience, wrath, and grief, may manifest. The spectrum of these emotions (e.g., are they continuous or change frequently?) and whether they are relevant to thinking content must be given special consideration in research.

Early on in the space programme, the most crucial psychological criteria for choosing astronauts were based on how they handled acceleration and deceleration and how they adjusted mentally

(Sells and Berry 1961). NASA acknowledged and stressed the significance of team dynamics, composition, and teamwork as missions became longer and started to involve three crew members (Kanas and Fedder- son 1971; Landon et al. 2016). The National Academy of Sciences emphasised the need of addressing the "negative psychological responses" that have an impact on social dynamics, group processes, and interpersonal relationships when astronauts are in space. They stated that "there have been cases of decreased energy levels, mood swings, poor interpersonal connections, flawed decision-making, and gaps in memory and concentration throughout the history of space travel" (Committee on Space Biology and Medicine 1998, p. 169). In the 2001 article Safe Passage: Astronaut Care for Exploration Missions by the National Academy of Science, the dangers of behavioural performance and psychology related with spaceflight were once more discussed (Ball and Evans 2001). Long-term space exploration missions will be independent and cut off from both terrestrial support and the social networks that underpin human welfare. It will be necessary for a spaceship to accommodate the crew's psychological and social demands as well as their greater integration and interaction with complex, more autonomous spaceflight technologies. This enhanced autonomy and isolation (McCandless et al. 2007). We must evaluate the intricate interplay between modifications of the vestibular and psychological/behavioral performance systems that are envisaged for long-duration space travel within this constantly changing need for human systems integration. It is necessary to describe any potential changes in neurophysiology before implementing countermeasures including technology, education, therapeutic interventions, and adjustments to the spacecraft's livable volume designs. There is conflicting evidence about how long-term spaceflight affects cognitive function. Strangman et al. (2014) examined a large body of cognition data from studies carried out in analogue and space environments and found no consistently predictable declines in cognitive performance for executive or higher order functioning, attention, memory, learning, or emotional and social processing. For longer trips, however, an astronaut's capacity for sustained attention will be more crucial because of the need for more autonomy due to the astronauts' great distance from Earth. It is evident that different tasks require different levels of attentional stability (Heuer et al. 2003; Manzey et al. 1995, 2000). Experimental simulations utilising analogues for spaceflight have shown performance-related alterations such decreased energy, altered mood, poor decision-making, and gaps in memory and concentration (Palinkas 1991; Palinkas et al. 1995). Methods that generate and/or sustain happy emotions are crucial mitigations strategies to assure effective completion of an operationally relevant task given that negative emotions are linked to a drop in task performance and motivation (Kanas 1987; Santy 1983). (Csik- szentmihalyi 1990). We do not yet understand how changes in motor control brought on by weightlessness affect task performance, i.e. how much gravity affects cognition and learning (Hanes and McCollum 2006; Smith et al. 2005). The consequences of exposure to weightlessness, radiation, confinement and isolation stress, as well as any potential synergistic effects of all of these stressors on physiological and psychological dysregulations are also unknown (Convertino and Tsiolkovsky, 1990). (Porte and Morel 2012). For instance, the hippocampus, which is particularly vulnerable to both stress and radiation, is crucial for memory consolidation and retrieval of long-term memories (Lupien et al. 2005; Monje 2008; Obenaus et al. 2008). As has been mentioned throughout this analysis, being exposed to weightlessness alters the otolith system's sensitivity. According to Bush et al. (2000), vestibular nuclei project onto the cerebral hemispheres, which presents interesting issues concerning the effects of vestibular alterations during a lengthy space flight: What degree of integration exists between the functional systems of emotion and vestibular modalities? How do the crewmember's emotions and social cognition benefit from the vestibular system adaptations? The possible relationships between vestibular physiology and behavioural health, performance, and cognition that are pertinent to prolonged space travel are identified here.

The gaze stability, postural control, verticality perception, navigation, and spatial memory processes all depend on the detection of linear and angular head movements by the vestibular system. In addition, the vestibulosympathetic efferents influence circadian rhythms, bone density, muscle composition, and postural blood pressure control (Besnard et al. 2018). It is widely established that vestibular stimulation by whole-body passive rotation causes autonomic alterations and that vestibular-induced nausea is caused by prefrontal limbic circuits (Golding and Stott 1997). According to neuroimaging, vestibular-induced nausea affects the same prefrontal regions of the brain that are linked to autonomic emotion control (Miller et al. 1996). (Demaree and Harrison 1997). The physiological adjustments to nonterrestrial gravity levels can cause dysregulations in the mood, affect, and arousal systems, according to research employing animals (Porte and Morel 2012). These results suggest that vestibular-induced motion sickness might stress prefrontal brain regions, which can alter autonomic systems. Relevant terrestrial research shows that individuals with vestibular impairment are more likely to acquire anxiety disorders than healthy controls (Best et al. 2009), and those with anxiety disorders typically report increased sensitivity to vestibular stimuli (Staab and Ruckenstein 2003; Staab et al. 2014). Accordingly, arousal and mood states interact with vestibular sensory function, which impacts autonomic systems including mood states, social cognition, emotion, perspective, and perception (Porte and Morel 2012). When evaluating the psychological risk concerns related to long-duration spaceflight, it is especially important to characterise how autonomic and vestibular demands interact with cognitive processes. In addition, there is evidence that the networks responsible for processing anxiety reactions and vestibular signals are functionally linked (Bednarczuk et al. 2018). It's interesting to note that a person's vestibulo-cortical hemisphere dominance level and anxiety level are correlated; people with right hemispheric dominance had the lowest anxiety levels. This shows a possible connection between anxiety and vestibular disturbances (Godemann et al. 2004; Pollak et al. 2003). Further investigation reveals possible connections between hostility and vestibular interactions. For instance, Carmona et al. (2008) rotated 20 healthy volunteers in yaw and discovered that the increased hostility was connected to the increased autonomic arousal. Additional research has demonstrated that vestibular stimulation can influence a person's perception of unfavourable emotional faces (Herridge et al. 1997), accurate understanding of emotional prosodic speech (Borod et al. 1992, 1998), inhibition during stressful vestibular challenges (Brandt 1999; Brandt et al. 2002), and reaction to appropriate sensory input (Sander et al. 2005). The interaction between the vestibular system and emotional components, as well as the expression, reception, and perception of unpleasant emotions, are located in the right hemisphere, which dominates the brain (Carmona et al. 2009). Loud noises and the way mission controllers spoke to the cosmonauts during the Salyut 6 and 7 missions caused them increasing amounts of discomfort (Grigoriev et al. 1988; Lebedev 1988). The need of addressing how feelings and vestibular changes brought on by spaceflight may influence crew health, performance, and safety is reinforced by this increased perceptual sensitivity. The crewmember's systematic neurobehavioral reactions and susceptibility to sleep deprivation are significant interindividual factors in operationally relevant performance (Van Dongen et al. 2004). According to Sletten et al. (2015), this variation is likely due to individual circadian differences, which are influenced by environmental factors (such as the amount and timing of ambient light; Czeisler et al. 1986) and play a role in biological processes like brain wave activity, the production of hormones, and cell regeneration. Despite temperature, noise, high CO_2 levels, emptiness, rumination, and hard workload diminish sleep in space (Hobson et al. 1998), vestibular alterations brought on by weightlessness may also impact the structure of sleep (Hobson et al. 1998; Mizuno et al. 2005). Sleep deprivation alters vestibular-related oculomotor responses, as demonstrated by research by Quarck et al. (2006). After sleep deprivation, the VOR gain rises after an unexpected head rotation, which might jeopardise postural balance. Additionally, there is a lot of proof that vestibular diseases cause sleep disruptions (see Besnard et al. 2018 for a review). As previously mentioned, there is evidence that the vestibular and emotional brain networks share comparable subcomponents because vestibular signals can modify affective regulation of emotions and decision outcomes (Preuss et al. 2014a, 2014b) (Carmona et al. 2009; Dodson 2004; Levine et al. 2012). For instance, emotional processing affects how well people complete cognitive activities (Buodo et al. 2002; Lindström and Bohlin 2011), but the vestibular system is crucial to the accuracy of one's movements when performing particular tasks. Thus, it is crucial to ascertain how the coordination of eye, head, torso, arm, and leg motions during task performance that must adjust to these settings is affected by microgravity (and other anomalous force environments) (National Research Council 1998). Crew members will be more independent on exploratory missions and will need to react to emergency circumstances. Understanding how the vestibular and emotional processing systems interact in hazardous or dangerous circumstances when vestibular perceptions can drive adaptive motor responses, such as during the "fight or flight" reactions, cannot be overstated. The crewmember would be signalled and made ready for action by emotional processes (Frijda 1986, 2007; Lang 1993), whilst the crewmember's motor reactions would be produced by vestibular processes. Given their shared goal, the vestibular and emotional systems' shared use of the insular and anterior cingulate cortex is not surprising (Carmona et al. 2009; Preuss et al. 2014a, 2014b).

It has been suggested that the brain's functional connectivity establishes the connections and interdependencies between the higher cognitive domains and the brain stem functions (Luria 1966). We need to pinpoint the neural pathways in the brain that connect the motor, somatosensory, and vestibular responses to mood and mood states in order to reduce the danger associated with an astronaut's mood and mood states during a lengthy expedition trip. Researchers will be able to evaluate how competition for common brain pathways relates to declines in operationally relevant performance as vestibular responses adjust throughout spaceflight using this integrated methodology. It is critical to determine if the unique impacts of each stressor on operationally relevant performance remain distinct when experienced together since crewmembers endure space radiation, solitude, and changing gravity all at once. According to the available data, each crewmember can handle all three stresses to a certain extent. Therefore, it is assumed that there is no interaction between the risks posed by each of these hazards. To fully characterise these risks, it is necessary to quantitatively determine whether combined exposure has additive or synergistic effects. After that, the stressors must be classified according to how they affect receptors, systems, or domains of action, whether they are observed singly or in combination. NASA's human spaceflight programme has recently moved its emphasis from 6-month orbital trips in low Earth orbit to longer-duration missions to the Moon and Mars. These missions will last 45 days, 14 months, and 30 months, respectively. The success of these missions depends on the astronauts' ability to operate at their very best under challenging circumstances. It is abundantly obvious that spaceflight can negatively impact an astronaut's capacity to operate complicated systems like vehicles. Accurate eye-hand coordination, spatial and geographic orientation awareness, and cognitive function are needed for these activities. After six months on the ISS, astronauts also show changes in posture and gait, including ataxia, muscle fatigue, hypo- or hypertonia of the major muscle reflexes, saccadic intrusion during smooth pursuit, and oscillopsia. These changes could make it more difficult for them to exit the spacecraft in an emergency. These symptoms persist even after the astronauts had engaged in intense physical activity during the trip, proving that the adaptation of the vestibular and proprioceptive systems as well as the central motor programmes is the primary cause of these deficiencies. Multiple transitions between different gravitational levels will be required for missions to the Moon and Mars (1 g on Earth to weightlessness, 0.16 g on the Moon, 0.16 g to weightlessness, 0.38 g to weightlessness, and 1 g on Earth), which will significantly broaden the range of difficulties and demands placed on astronauts. Additionally, extended exposure to seclusion, confinement, and harsh environments seriously jeopardises the mental and physical health of astronauts. The Belgian Antarctic Expedition of 1898–1899 demonstrated the risks of isolation; the crew's subsequent illness was documented in the logs by the ship's doctor, Frederick Cook, and the ship's first mate, Roald Amundsen (Stuster 1996). The Norwegian Fram expedition of 1893–1896, led by Fridtjof Nansen, was a more successful arctic voyage that provides crucial insights into the preparation for and survival from a protracted three-year space mission (Stuster 1996). Additionally, there is a chance that the crew will sustain CNS damage from exposure to the high-energy protons and charged particles in space or from secondary byproducts such neurons that might cause the crew more serious injury. These exposures have the potential to cause neurological problems, genetic consequences, acute radiation illness, alterations in cognition, motor function, behaviour, and mood, as well as acute radiation sickness.

The nervous system is impacted by a number of spaceflight environmental factors, as discussed throughout this review. It is possible that these effects could interact and increase risk to crew health and performance when the crews are cooped up, exposed to space radiation, and partially weightless during upcoming exploration missions (Greco et al. 1995). To evaluate and define how the cumulative impacts of spaceflight risks affect crew health and performance, an integrated method is required. Studies to better understand the scope and extent of neural compensatory mechanisms, which involve numerous systems (Smith and Curthoys 1989), as well as the crucial role the neurovestibular system plays in regulating the autonomic nervous system, which may affect mood and result in performance deficits linked to the proprioceptive (Keshner and Peterson 1995) and oculomotor systems, could be included in this integrated approach (Scudder and Fuchs 1992). In 1998, NASA collaborated with the National Institutes of Health, several American research organisations, five international space agencies, and others to fly the Neurolab project during a 16-day Space Shuttle trip as the centrepiece of the "Decade of the Brain" (STS-90). The Neurolab project's goal was to determine how space travel impacts the formation and operation of peripheral and central brain systems in both animals and people (Buckey and Homick 2003). Rats (adult and neonatal), mice, snails, fish, crickets, and humans were used in the 26 investigations that made up the Neurolab project. The various studies' findings gave an in-depth look at how the central and autonomic nervous systems adjust to brief spaceflight. The measures used in the studies included crew members' spatial orientation, vestibular function, and sensorimotor responses, as well as anatomical and structural changes in the vestibular organs. The first effort to present a comprehensive picture of CNS adaptation to space flight was Neurolab. Unfortunately, this strategy has remained a one-off since the Space Shuttle era came to an end. The roadmap for getting ready for Moon and Mars missions will offer beneficial chances to evaluate and reduce brain dysfunction in an integrated strategy that attacks basic issues by focusing on several peripheral and central neural structures utilising a variety of experimental instruments. To research changes in the CNS, including those to anatomy, electrophysiology, morphology, behaviour, cognition, and operational performance, we suggest expanding the Neurolab methodology to extended term spaceflight. NASA intends to test up to 30 astronauts on ISS trips lasting two months, six months, or one year, as well as volunteers who will spend four, eight, or twelve months in spaceflight simulators on Earth. Many of the outstanding problems in neuroscience research mentioned above will be answered by comparing the multi-system reactions of astronauts and volunteers over different lengths of spaceflight and spaceflight analogues. Since the 1998 Neurolab mission, neuroscience research has advanced significantly. The rapid evolution of omics has revealed previously unrecognised interactions among functions, molecular changes within and between tissues, novel methods of measuring outcomes, and noninvasive imaging, all of which could give us more insight into neurological mechanisms. Many recent discoveries have been fueled by the development and improvement of new genetic technologies. The opportunity to directly evaluate the difficulties outlined in this review in an integrated and unified manner would arise from a Neurolab-like mission to the International Space Station (ISS). This mission would use the new toolkit to specifically interpret and validate findings in the various areas. For instance, omic technologies could be used to identify genes, mRNA, and metabolites in healthy animals as well as in genetically modified animals lacking the ability to produce otoliths that were raised in 0 g or in an in-flight centrifuge that rotates intermittently or continuously at 1 g or at partial gravity (e.g., 0.16 g and 0.38 g). A variety of behavioural activities might also be evaluated before to, during, and following flight to better understand how each animal reacted. The same animals might be used to assess the anatomy and operation of many systems, including the inner ear, brain stem, central nervous system (CNS), baroreceptors, and muscles that carry and do not bear weight. These studies would answer fundamental questions in the fields of neural development, such as transduction processes in vestibular hair cells, control of antigravity muscles, and regulation of the cardiovascular system during changes in body posture and during regulation of sleep patterns, in addition to providing information to support crew health and safety. We will need to find suitable animal models that can be used to evaluate neuronal development under weightlessness across numerous generations in order to achieve these objectives. The coordination of complex human actions, like as reaching and locomotor motions requiring combinations of eye, head, torso, arm, and leg activity, might be studied using human participants in a Neurolab-like experiment on the ISS. The sensory, motor, and cognitive elements that affect the capacity to adjust to and maintain adaptation to various degrees of gravity might also be identified via this Neurolab-like effort. Astronauts may encounter certain orientation illusions due to alterations in the brain coding of spatial navigation that may be caused by variations in gravity levels. In concurrent investigations of people and animals employing onboard and ground-based centrifuges, body unloading paradigms, parabolic flight settings, virtual reality environments, and eventually lunar expeditions, researchers might explore how different gravity levels affect orientation and spatial localisation. The vestibulo-ocular reflex is mediated via vestibular pathways that go from the semicircular canals and otoliths to the vestibular nuclei and the ocular motor nuclei (a 3-arc neuron). Movements of the eyes and the head are coordinated by connections between the brain stem and the thalamus. Motion perception, spatial orientation, and cognition are all influenced by projections to multimodal cortical areas in the temporal-parietal regions and the posterior insula (Hitier et al. 2014). These regions in turn immediately project down to the vestibular nuclei, modulating the activity of the vestibular brain stem (Brandt et al. 2014). Additionally, the hippocampus and thalamus, which are involved in spatial memory and navigation, are connected to the vestibular nuclei via the thalamus (Phelps 2004; Vitte et al. 1996). Studies conducted on the ground have revealed that the cortical maps of both motor and sensory processes are extremely malleable and prone to quick rearrangement (Kaas 1995). Not just the cortex but also other CNS relay stations exhibit this plasticity. Long-term exposure to microgravity alters the hippocampus, sensorimotor cortex, and brain stem anatomically and structurally, according to pre- and postflight MRI studies (Koppelmans et al. 2016; Roberts et al. 2017; Van Ombergen et al. 2019). We are still learning about the functional implications and effects of this reconfiguration on Earth, let alone in space. Researchers would be able to assess the consequences and importance of these alterations in relation to an astronaut's performance before and after spaceflight through integrated neuroscience investigations aboard the ISS. To study the relationship between cortical plasticity and cognition in situ, near-infrared spectroscopy (NIRS) might be used to measure hemodynamic changes in the astronaut's cerebral cortex as they carry out cognitive activities in the spaceship. An astronaut's performance after they land on Mars may be impacted by the vestibular, sensory, and cognitive effects of the CNS rearrangement brought on by exposure to partial gravity, according to test procedures that may be developed. It is crucial that we comprehend how the crew will function during extended space exploration trips, especially in the hours immediately following their landing on Mars, since this knowledge may influence choices made about the mission's and the vehicle's design. For instance, the lander must be big enough for the crew to reside in until they acclimatise to gravity if they are unable to quickly put on a bulky spacesuit, open a hatch, and leave their landing ship. Knowing how long recuperation takes can help spacecraft designers scale a Mars lander appropriately or look for less dangerous solutions for the crew to transfer to a home. Mission management will also be assisted by metrics of crew performance right after landing in order to evaluate and prepare for emergency operations (Robinson etal. 2019). Individual data, however, do not fully convey the reality. At landing, the crew will work as a unit (and throughout the mission). Critical activities could be completed even if only one landing crew member has fully functional neuromotor and neurocognitive abilities. New methods for assessing team capabilities might thus result in more thorough evaluations of risk, which would then influence the assumptions and capabilities that would need to be included in mission and vehicle design. Additionally, the chance to properly examine crew performance for functional Mars duties from 0 to 24 h postlanding, or even longer, will be provided by crew members of long-duration ISS missions who arrive on Commercial Crew Program spacecraft. However, some of these human vehicles—such as the SpaceX Dragon spacecraft—will splashdown in the ocean, while others will land in American deserts (Boeing Starliner spacecraft). Ground landings provide a better comparison for crew performance after landing on Mars because water landings are expected to present major extra sensory obstacles (Robinson et al. 2019). By controlling a number of higher centres in the central and autonomic nervous systems, vestibular system stimulation can affect behavioural responses (Rajagopalan et al. 2017). Through ascending and descending channels, such as those leading from the vestibular nuclei to the locus coeruleus, the amygdala, the limbic brain, and the hypothalamus, the vestibular system affects vegetative activities (Balaban 2004). Motion sickness is developed by the amygdala and becomes used to it (Nakagawa et al. 2003). Clinical and physiological data indicate that the vestibular system contributes to autonomic regulation by inducing the sympathetic nervous system and activating the vagal nervous system (Holstein et al. 2014; Yates and Bronstein 2005). Changes in vestibular inputs during spaceflight are not just restricted to sensorimotor activities, but the hypothalamus is involved in thermoregulation and other essential endocrine functions. To determine the connection between vestibular adaptation during spaceflight and sleep cycles, hormonal and immunological changes, cardiovascular and pulmonary changes, muscle physiology changes, etc., an integrated neuroscience research project might be used. We will require sample sizes for these investigations that are sizable enough to confirm and describe the spectrum of individual differences. Finally, it is important to create appropriate animal models for investigating the physiological and morphological causes of postflight disorders.

Future aspects and conclusion:

Astronauts have had medically significant retinal alterations and changes to their visual acuity related with optic disc edoema in recent years while in long-duration space travel (Mader et al. 2011). These ocular alterations appear to be a byproduct of protracted cranial fluid movements, which might lead to axial brain shifts inside the cranial vault, thereby increasing pressure on the cortex (Roberts et al. 2017). Future one-year trips may provide light on the possible effects of protracted fluid shifts on neurological functioning as the ocular alterations appear to be reliant on the length of microgravity exposure. The hostile, enclosed environment of space is another risk that might make it more difficult to assess changes in CNS processes. It is challenging for any such system to keep the carbon dioxide (CO2) level in the crew compartment lower than 2 to 4 mmHg given the mass, power, and volume limits of spacefl vehicles. However, any human spacefl spacecraft must supply a crew with an environment similar to that found on Earth. The body controls CO2, a powerful vasoactive substance, using a number of mechanisms that include the respiratory and metabolic systems. The long-term effectiveness of these control systems in an environment with persistently increased ambient CO2 has not yet been determined. Identification of the CNS pathways involved in neuropathology and the response to radiation exposure is also necessary. The majority of investigations to date have been carried out in locations like the NASA Space Radiation Laboratory, which may mimic cosmic radiation. Since the ISS is in the magnetosphere, its radiation doses are not comparable to those in deep space (La Tessa et al. 2016). The threshold doses have not yet been established despite the abundance of cognitive data from rodents for acute doses of numerous individual particle types and energies. The majority of studies used doses that are much higher than those that astronauts on a Mars mission will experience (1 Gy), and very few took into account dose-rate effects or mixtures of particles that are typical of the GCR environment. We would be able to research the long-term consequences of mixed exposures to protons and highly charged particles along with lower gravity if a long-term colony of living systems were formed on the Moon. These colonies might contain a variety of biological systems, including tiny vertebrate animals, plants, and brain tissue cultures. These colonies could be checked for genetic changes, tumour development, and shortened life spans (Benaroya 2018). We must use translational models (such as rodents) to study the effects of neurochemical, functional, and structural changes in the brain and to evaluate how these functional, structural, and biochemical alterations relate to operationally relevant performances associated with radiation exposures similar to those of spaceflight missions because any study of radiation effects will be limited to animals due to the requirement to irradiate subjects. It is difficult to extrapolate findings from animal studies to practical implications for CNS health concerns in people, and this task is made more difficult by the many experimental settings used in radiobiological and neurobehavioral studies. The risk of being too distant from Earth on Mars missions grows as crew members travel farther. Under more autonomous operations, deep space missions will have previously unheard-of lengths of time, distances, isolation, and confidence. Additionally, there won't be any means of escape. When the Tracking and Data Relay Satellite (TDRS) system is in certain locations, communication between ISS crew members and ground support staff can be delayed for many minutes. This communication has a one-way delay of 0.25 seconds. Depending on where in the trajectory the mission is, this one-way time delay will rise to 1.25 seconds for Moon missions and between 4 to 24 minutes during Mars missions. Blackouts or whiteouts lasting up to two weeks may also occur during solar conjunctions. Therefore, compared to ISS crews, exploration teams will need to function far more independently. Medical evacuations from the ISS can be accomplished in 3.5 hours, however due to celestial mechanics, emergency evacuations for Mars missions have incredibly small windows of opportunity (Robinson et al. 2019). How the crew responds to a simulated medical crisis autonomously or with a significant communications delay might be tested in microgravity on the ISS in order to evaluate a medical event on a long-duration mission beyond low Earth orbit. To verify the existing livable capacity requirements for the Mars transit, the effects of isolation and confinement during deep space travel might be examined on the ISS. Furthermore, carrying out simulated operations on the Martian surface by astronauts returning from a 6-month mission on the ISS could verify crews' capacity to complete important ground tasks following a physiological adjustment period during the transit of Mars, and these tests could also help with the conceptual design of Martian structures.

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