Alex P. Michael · Christian Otto
Millard F. Reschke · Alan R. Hargens *Editors*

Spaceflight and the Central Nervous System

Clinical and Scientific Aspects

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Editors
Alex P. Michael
Neurological Surgeon
Mercy Clinic Neurosurgery
Saint Louis, MO, USA

Christian Otto
Director of Teleoncology
Memorial Sloan Kettering Cancer Center
New York, NY, USA

Millard F. Reschke
NASA Neuroscience
Johnson Space Center
Houston, TX, USA

Alan R. Hargens
Department of Orthopaedic Surgery
University of California, San Diego
La Jolla, CA, USA

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“To my parents, my brother, Jeff, and the girls in my life, Mary, Blaire, and Quinn. Ad Astra per Aspera.

—A.P.M”

Contents

History of Spaceflight and the Central Nervous System

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Alex P. Michael and Millard F. Reschke

Introduction

Early Discoveries

The concept of human space exploration dates to as early as the Renaissance with famous astronomers such as Nicolaus Copernicus and Galileo Galilei. With the help of the newly discovered telescope, they determined that outer space is an actual place filled with planetary bodies and stars. They questioned the widely believed geocentric dogma of Ptolemy and simultaneously challenged Christian religious ideals about humanities unique and exclusive relationship with God [1]. The visionaries Johannes Kepler and Cyrano de Bergerac conceptualized the idea of space travel and proposed the difficulties that may be encountered with interplanetary flight in the vacuum of space [2]. Science fiction writers of the nineteenth and twentieth centuries like Jules Verne, H.G. Wells, Edward Everett Hale, and Arthur C. Clark were able to incorporate sophisticated scientific principles to space travel and alien encounters making these works ever more exciting and plausible to the general public. Although only fictional tales, their intellectually sound writings about satellites and orbital flight around earth influenced a generation of scientist and engineers who went on to bring these fantasies into reality.

The dearth of research and technological feats over the past few centuries has helped us realize the celestial goals and aspirations of our predecessors. For the most part, each organ system has been extremely resilient to the extraordinary conditions this earth has placed upon them; however, they each function differently in the spaceflight environment. The effects of microgravity, acceleration, vibration, cabin pressure, carbon dioxide concentration, radiation, and extreme temperatures must all now be considered during spaceflight. This book will attempt to provide a comprehensive overview of the known physiologic and biochemical changes that occur in the human central nervous system during short- and long-duration spaceflight.

Early Rocket Science

At the end of the twentieth century, the study of the universe and speculation about the nature of spaceflight were not closely related to the technical developments of rocket aeronautics. This was until 1903 when Russian theorist and schoolteacher Konstantin Tsiolkovsky published his article "Exploration of Cosmic Space by Means of Reaction Devices." In it he laid out many of the principles of modern spaceflight using rocket propulsion. His future publications continued to develop sophisticated aspects of spaceflight including fundamentals of orbital mechanics, space vehicles, and space stations [3]. His pioneering work, though mainly theoretical, influenced modern rocket pursuits and served as the foundation of the Soviet space program.

Robert Goddard from the United States and Hermann Oberth, a German national, elaborated on rocket design, engineering, and propulsion often times in the face of harsh public criticism. Oberth's original doctoral dissertation on rocket-powered flight was rejected by the University of Heidelberg in 1922 for being too speculative. The work explained the mathematical theory of rocketry, applied the theory to rocket design, and discussed the possibility of constructing space stations and traveling to other planets. Goddard went on to patent, construct, and test his ideas on rocket components and liquid propellants.

In the 1930s and 1940s, Germany, Russia, and the United States were on the forefront of rocket development. Rocketry evolved from a theoretical discipline to incorporate large-scale experimentation and practical application. Although the prospect of space exploration was the primary motivation of many early engineers, international conflict and the inevi-

A. P. Michael (✉)
Neurological Surgeon, Mercy Clinic Neurosurgery, Saint Louis, MO, USA

M. F. Reschke
NASA Johnson Space Center, Houston, TX, USA
e-mail: millard.f.reschke@nasa.gov

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table weaponization of liquid fueled rockets caught the attention of military organizations. After World War II, the United States and the USSR were political and military competitors in what has become known as the Cold War. Both the countries prioritized the development of orbiting reconnaissance satellites for intelligence acquisition. Concurrently, the public and national governments became more receptive to the idea of sending humans to outer space.

Early Space Exploration

The Soviet Union

The Soviet Union initiated the modern space age with the Sputnik program (1957–1960) beginning with the launch of a low orbit satellite called Sputnik-1. Then, on November 3, 1957, Sputnik-2 carried the first living creature into outer space, a dog named Laika. This marked the beginning of a new era of biological and technological sciences. Soon after, the Vostok program (1961–1963), starting with Vostok 1, carried the first human into outer space, a Soviet cosmonaut named Yuri Gagarin. Gagarin made one orbit around the earth lasting 108 minutes. The original Vostok spacecraft was redesigned by the Soviets to carry as many as three persons and subsequently renamed Voskhod (1964–1965). There were two Voskhod missions, the second of which cosmonaut Aleksey Leonov became the first human to leave an orbiting spacecraft. The Soyuz program (1967–1971) brought about the Soyuz spacecraft which still remains in use to this day.

The United States

The National Aeronautics and Space Administration (NASA) was formed on October 1, 1958, in response to the Soviet Union's launch of Sputnik-1. NASA absorbed the National Advisory Committee for Aeronautics and several other research and military facilities to consolidate the efforts of all future US space exploration. President Dwight Eisenhower tasked the new administration to launch and retrieve a person safely from space. Project Mercury (1958–1963) went on to accomplish this on May 5, 1961, after the successful suborbital spaceflight of Alan Shepard. The Mercury program altogether yielded two 15-minute suborbital fights and four orbital missions of 5, 5, 9, and 34 h.

Soon after, the Gemini program (1961–1966) was designed to demonstrate the feasibility of long-duration space flight. Gemini in total exposed 16 astronauts to 10 orbital flights up to 14 days duration, similar to that of planned lunar missions. These first programs did not identify any medical or physiological problems that could prevent missions of 2 weeks duration or longer.

The Apollo program (1967–1972) was designed with important goals of advancing spaceflight technology, developing human capability to work in the lunar environment and carrying out a scientific endeavor to the Moon. It was the first time significant medical findings were identified in US astronauts including vestibular disturbances, post flight orthostatic intolerance, decreased exercise tolerance, cardiac arrhythmias, and decreased red blood cell mass and plasma volume [4].

The Apollo-Soyuz Test Project (ASTP, 1975) was a joint program between the United States and the Soviet Union with both practical and political agendas. ASTP tested systems for rendezvous and docking should a need for an international space rescue ever be needed. ASTP was followed by the Space Shuttle (or Space Transportation System, STS) program (1981–2011) uniquely using a reusable spacecraft and crew piloted landing. The Space Shuttle changed dynamics of space flight missions. Larger crew sizes enabled flight with pilots, responsible for flying and maintaining the orbiter, mission specialists responsible for experiments and payloads, and payload specialists to tend to specific onboard experiments. The shuttles had standard level atmospheric pressure and gas mixtures and the ability to fly dedicated spacelab modules to conduct scientific investigations in microgravity.

Early Space Stations

The development of a space station was originally an interim step in the US pursuit to land on the Moon. However, in 1961, President John F. Kennedy committed the United States to landing on the Moon before the decade was over, thereby expediting the Apollo program. In the mid to late 1960s, the US Air Force pursed a program called Manned Orbiting Laboratory (MOL) with advanced camera equipment to facilitate military reconnaissance [3]. MOL was canceled the same week as the Apollo 11 moon landing in 1969 was in favor of a NASA project called Skylab. Skylab, therefore, became the first US space station and afforded an opportunity to explore in-flight testing of the physiologic changes of long-term exposure to microgravity. It was also spacious enough for astronauts to freely move around and fully adapt to the spaceflight environment and first to provide a complex set of vestibular experiments [5]. Skylab flights 2, 3, and 4 housed crews in space for 28, 59, and 84 days, respectively (Fig. 1.1).

This show of technological adeptness at the height of the Cold War had several geopolitical underpinnings and raised the question of the military role for piloted spacecraft. The Russians began efforts on a space station in direct competition to the US endeavors. Almaz, the first space station program developed by the Soviets, was similarly intended more for military reconnaissance than for research. For secrecy, it was publicly designated Salyut (1971–1986) upon reaching orbit. Multiple manned missions were sent to Salyut using

Fig. 1.1 This image of Skylab in orbit was taken as the third crew (Skylab-4) departed the space station after 84 days in the orbiting laboratory (https://images.nasa.gov/)

the Soyuz spacecraft as the transport vehicle (Fig. 1.2). This was the first major step in creating a platform for a continued presence of man in space and allowed increasing long stays for crewmembers in outer space.

Salyut went through sophisticated engineering and multiple evolutions to accommodate more crew members. Additional docking ports were added so that long-duration resident crews could receive visitors. Salyut-7 was followed by the Mir space station (1986–2001) after the dissolution of the Soviet Union and the formation of the new Russian Republic. Mir contained a base block derived from the Salyut to function as the crews habitat and was capable of five additional units to carry out scientific pursuits [3]. The establishment of cooperative agreements between Russia and the United States allowed the US astronauts to serve as crewmembers alongside Russian cosmonauts. The NASA-Mir (1994–1995) and Shuttle-Mir (1995–1998) programs paved the way for future cooperation on board the International Space Station (1998–present). Mir was occupied from 1986 to 2000 hosting 100 people from 12 countries (Fig. 1.3).

Fig. 1.2 View of the Soviet Soyuz spacecraft in Earth's orbit, photographed from the American Apollo spacecraft during the joint US–USSR ASTP docking mission in Earth orbit (July 18, 1975) (https://images.nasa.gov/)

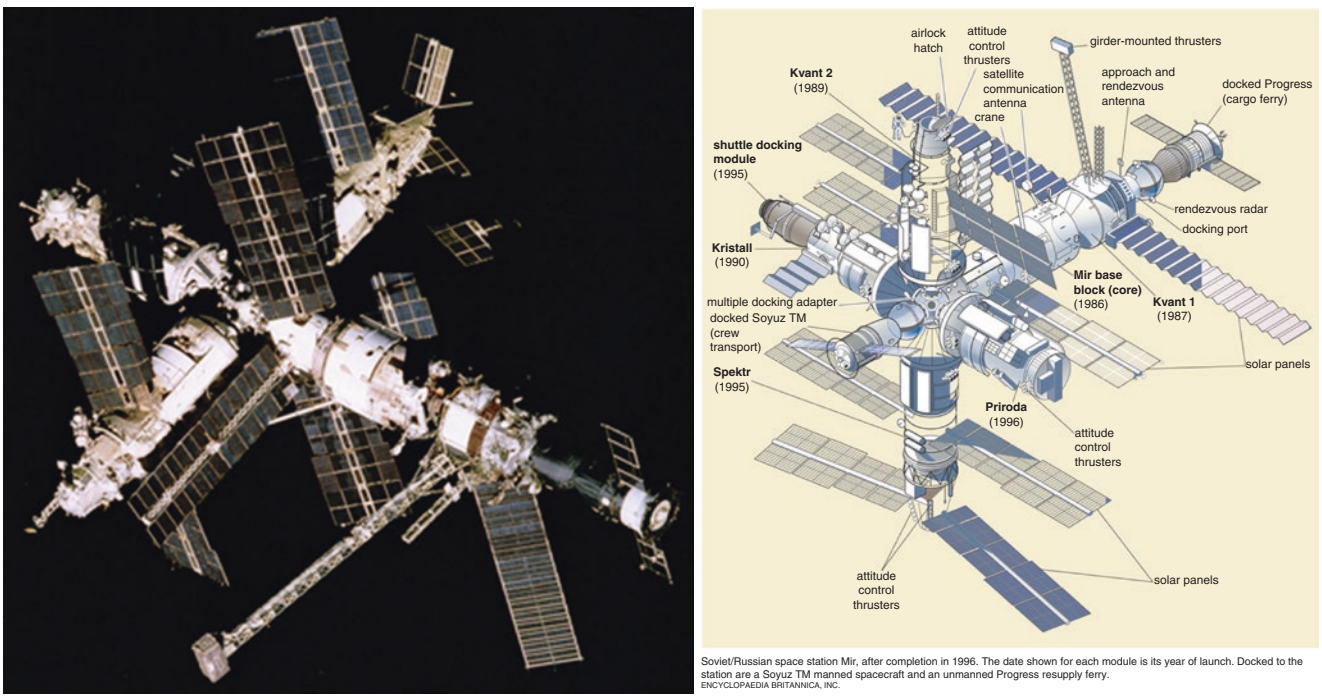

Fig. 1.3 Russian Mir space station photographed approaching space shuttle Atlantis (June 29, 1995) (https://images.nasa.gov/)

International Cooperation

Development of International Organizations

Unlike the United States, the Soviet Union had no publicly acknowledged space agency, instead relying on a variety of state-controlled organizations for conception and development of spacecraft. Rivalry between the various bureaus posed a constant obstacle to a coherent longitudinal vision for the Soviet space program. In 1992, after the dissolution of the USSR, Russia formed the Russian Space Agency to consolidate focus for the country's space policy and programs. It was later restructured and renamed the Russian Aviation and Space Agency in 1999 and then again as the Roscosmos State Corporation for Space Activities in 2004 [6].

In Europe, the French Space Agency (CNES), German Aerospace Center (DLR), the British National Space Center (BNSC), and the Italian Space Agency (ASI) were formed. In 1975, the European Space Agency (ESA) included 15 members—Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Norway, The Netherlands, Portugal, Spain, Sweden, Switzerland, and the United Kingdom. Since 1979, Canada has held the status of cooperating state within the ESA and has become tightly integrated into the institution. The Canadian Space Agency was established in 1990 and maintains a close partnership with many international space agencies.

The China National Space Administration (CNSA) was created in 1993 after the Ministry of Aerospace Industry was split into the CNSA and the China Aerospace Science and Technology Corporation. The former was to be responsible for policy while the latter responsible for execution [7]. In 1998, the CASC was restructured into a number of smaller state-owned companies to be contracted out for operational requirements. China launched its first manned spacecraft in 2003, making it the third country to achieve human spaceflight.

Japan Aerospace Exploration Agency (JAXA) was formed in 2003 with the merger of three formerly independent space and aeronautical science organizations. Since its inception, it has been responsible for the development and launch of satellites and continues efforts toward independent space travel.

The International Space Station

The United States received presidential approval for Space Station Freedom in 1984 and invited US allies to participate in its development. A total of 16 countries and several space agencies came to be involved in the project, making it the largest ever cooperative technological undertaking. The first elements of the station, renamed the International Space Station (ISS), were launched and connected in space in 1998 (Fig. 1.4). Several modules and equipment have subsequently

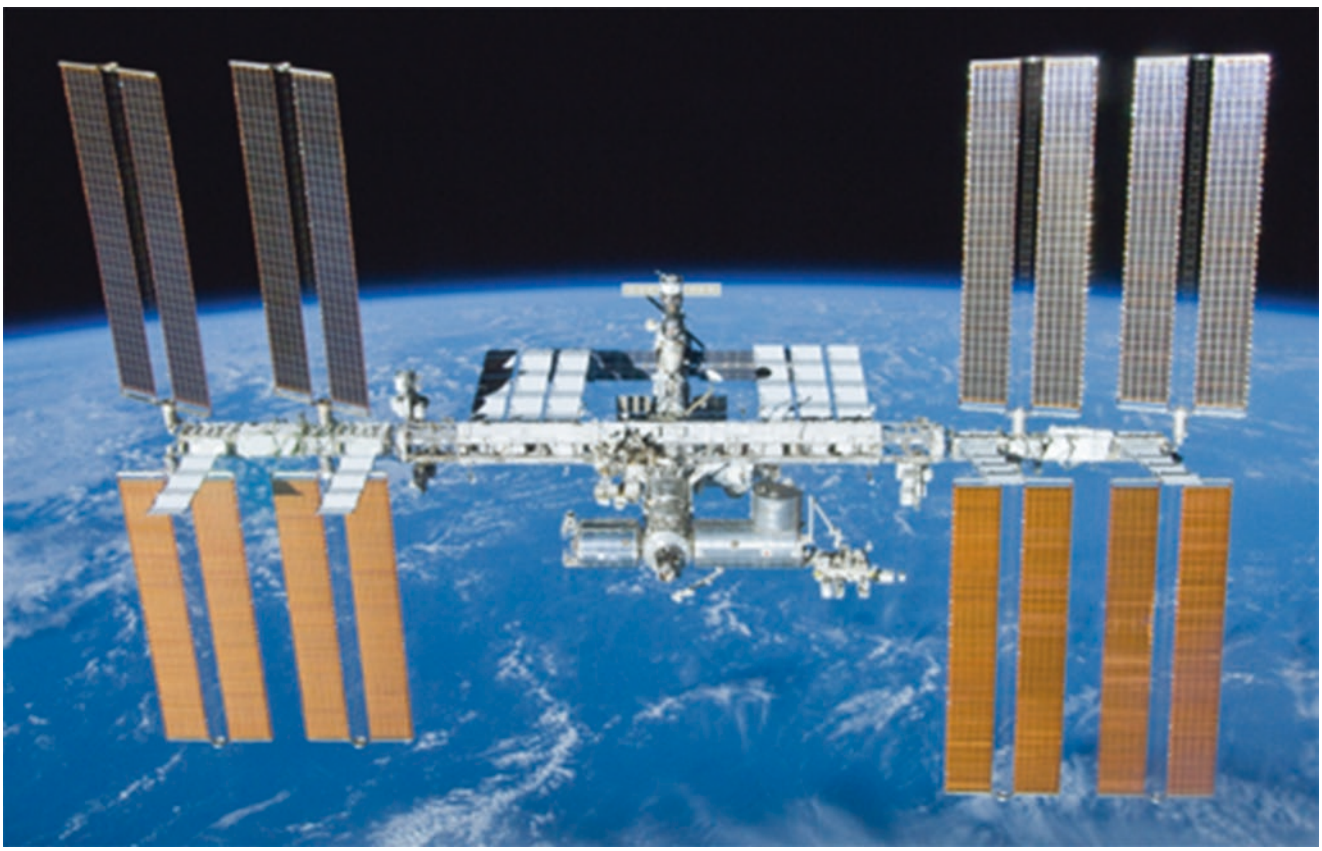

Fig. 1.4 The International Space Stationphotographed by an STS-132 crew member on board the Space Shuttle *Atlantis* after the station and shuttle began their post-undocking relative separation (May 23, 2010) (https://images.nasa.gov/)

been added. The station serves as a microgravity and space environment research laboratory, observatory, and staging base for future spaceflight missions. Since the first inhabitants arrived in 2000, there has been a continuous human presence in space. Much of the early research work by ISS astronauts focused on long-term life-sciences and material-sciences investigations in the weightless environment.

History of Spaceflight Medicine

Human spaceflight has proven to be an exceptionally risky endeavor over the years. Between Soviet and American spacecrafts disasters, 18 people have lost their lives during spaceflight. Human beings have evolved in the Earth's environment, and understanding the effects of low gravity, wide temperature variations, high levels of ionizing radiation, and lack of atmosphere is crucial to safely participating in future long-duration flight.

Aerospace Medicine Organizations

Aerospace medicine was pioneered by Paul Bert of France in the nineteenth century. He has become known as the Father of Aviation Medicine due to his novel research into the effects of air pressure and oxygen toxicity on health. As early as World War I, flight surgeons aided pilots in unique atmospheric conditions and worked closely with design engineers to develop equipment for them to overcome adverse environments. Hubertus Strughold, a former Nazi physician and physiologist, was brought to the United States as part of Operation Paperclip to give the US military advantage over the Soviet Union in the Cold War Space race. Strughold first coined the term "space medicine" in 1948 and was the first and only Professor of Space Medicine at the School of Aviation Medicine at Randolph Brooks US Air Force Base. In 1949, the first Department of Space Medicine was created at Randolph Brooks [8]. The next year, the Aerospace Medicine Association formed the Space Medicine Branch. Soon after, in February 1953, the American Medical Associated authorized the establishment of aviation medicine as a specialty in the field of preventative medicine [6].

Initial Spaceflight Medical Problems

It was anticipated that the first problems astronauts would encounter in spaceflight were those of acceleration and weightlessness. By extrapolating animal experiments utilizing terrestrial rockets, water-immersion, and sensory deprivation, it was thought that the main difficulties would be in the central nervous system and organs of positional awareness. This could lead to disorientation, hallucinations, and psychological adjustment failures in the astronauts. Other immediate problems would be external stresses from noise, toxic hazards in the spacecraft, and ambient space radiations [9].

Physiological disturbance during spaceflight was reported as early as Vostok 2 by the Russian cosmonaut Gherman Titov [10]. Approximately 6 h into the flight, he experienced malaise, nausea, vomiting, and vertigo. This constellation of symptoms was first referred to as "space motion sickness" (SMS) [11] due to the similarity to motion sickness in the terrestrial environment. It is hypothesized that two physiologically distinct mechanisms converge to produce the symptoms of SMS [12, 13]: Cephalad fluid shifts are thought to alter the response properties of vestibular receptors while loss of tilt-related otolith signals in microgravity creates a conflict between the actual and the anticipated signals collected from the external environment. The breadth of symptoms that astronauts report is likely due to a complex interaction between the neurovestibular system and autonomic nervous system [14]. Similarly, the term "space adaptation syndrome" was used when motion sickness was accompanied by head congestion and headaches brought on by a cephalad fluid shift into facial structures [15].

US astronauts would not go on to report these symptoms until Apollo 8 when the crew left their seats during the first orbit to obtain in-flight measurements. It has been suggested that the small confines of the Mercury and Gemini spacecraft limited rapid head and body movement of astronauts within the cabin, thereby decreasing the chances of experiencing SMS during exposure to microgravity [16]. The small number astronauts in the early space program and readily available press access following mission completion made it impossible to anonymize medical data on specific astronauts. This likely prevented astronauts from fully disclosing subjective symptoms and required repeated convincing from flight surgeons that reported difficulties would not preclude them from returning to flight status [17].

Most astronauts require only 2–3 days to acclimate to motion sickness in space and few continue to have residual symptoms during short-term spaceflight [12]. As more time is spent in space, physiologically distinct yet overlapping symptoms seem to arise including headache and visual disturbance. These findings were noted to be similar to the cases of intracranial hypertension in the terrestrial environment which are caused by an elevation in intracranial pressure (ICP) [18].

Spaceflight-induced visual disturbance, first termed by NASA as VIIP, was identified as a serious risk to astronauts during future long-duration space travel, having already affected over 40% of ISS inhabitants [19]. Although VIIP was originally attributed to spaceflight-induced elevated ICP, further factors now seem to contribute. For that reason, it has more recently been referred to as space flight-associated neuro-ocular syndrome [20].

Long-Duration Spaceflight

The first documented neuroscience experiments performed in space were during the third manned mission of the Russian Vostok spacecraft [21]. The vast majority of life sciences experiments on crewmembers have been during short-duration missions, and therefore our knowledge of the effects of long-duration spaceflight is limited. The first 20 missions to the ISS were made up of three crew members living aboard for approximately 6 months. As of 2008, there were only 47 crewmembers with flight durations of 6 months or greater and only four with durations of 1 year or greater. With limited subjects and limited data from the mostly Russian crew, it was difficult to draw adequate conclusions about the effects of long-duration space flight [21]. Since then, the time each astronaut spends in space has dramatically increased. Russian cosmonaut Valery Polyakov spent nearly 438 consecutive days aboard the Mir space station, from January 1994 to March 1995. Cosmonaut Sergei Krikalev has accrued 803 days in outer space in total. Contemporary medicine has now made it easier to measure and track physiologic and genetic changes that occur in the human body. To study these long-term effects better, in 2015 US astronaut Scott Kelly spent 340 consecutive days on the ISS while his twin brother, Mark, remained on the ground.

With time, the cost and risks of human spaceflight have become better able to accommodate the business of space tourism. Although the space shuttle program ended in 2011, private companies such as Boeing and SpaceX have contracts to fly humans to the International Space Station. Other private enterprises with Virgin Galactic and Blue Origin hope to capitalize on a new industry of suborbital space tourism and perhaps help facilitate a permanent moon colony. Unlike the mostly symbolic Cold War moon race, several countries aspire to establish permanent lunar colonies and cultivating and commercializing the moon's yet untapped minerals and resources.

Conclusion

Although there are innumerable harms that face man's spaceflight attempts, little can stop the desire of our species for exploration of the unknown. Little is known as to how the spaceflight environment will alter the anatomical and physiological integrity of our nervous systems and related structures, but aerospace physicians and astronauts should be educated in the current understanding of how human physiology reacts to this extreme environment. It will be critical to develop countermeasures to these known obstacles so that astronauts and civilians can participate at their peak in these missions and return safely to earth. The goal of extending the duration of missions and sending individuals further into space than ever before will challenge the current capabilities of aerospace medicine.

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Cardiovascular Physiology and Fluid Shifts in Space

2

Aya Hesham Sayed and Alan R. Hargens

The Cardiovascular System on Earth and in Space

General Concepts of the Circulatory System on Earth and in Space

Supplying whole cells with essential nutrients such as oxygen to maintain the different cells and tissue compartments is an important role of the cardiovascular system (CVS). Oxygen diffuses from the lungs via the CVS to the brain and all tissues of the body. Hormones are also distributed in the body by blood flow. During rest, approximately 5 l/min of blood is pumped through the vascular system. Blood is pumped from the left ventricle into the arteries which feed the whole body. On average a person spends 70% of his or her day in an upright position. The pressure difference from the level of the heart to the feet is 100 mmHg during standing (Fig. 2.1). Consequently, the blood tissue fluid distributions are affected by gravity [1]. The body needs the heart's "pump" to push enough arterial blood upward to the head to overcome gravity. It also needs other mechanisms in the veins and arteries of the lower body to prevent pooling or retrograde flow of blood in the direction of the gravitational force. Moreover, any changes in the body position will affect the hydrostatic pressure gradient induced by gravity. For instance, if one changes position from a supine to an upright posture, temporal dizziness or pre-syncope may be produced. This is because of a sudden, temporal decrease in blood pressure in the head and upper parts which is rapidly compensated by the baroreceptor reflex and myogenic mechanisms. The baroreceptor reflex is an effective way to regulate heart activity and vascular peripheral resistance, keeping the arterial blood pressure within a normal range all the time [2].

The goal of this chapter is to understand CVS mechanisms of adaptation to space and the importance of these adaptations to the central nervous system. During human spaceflight, the force of gravity is lost [2] so the blood redistributes from the lower extremes to the thorax and brain, thus producing a puffy face and swollen jugular veins, unweighting of skin and internal organs [3], and increasing intracranial and vestibular pressures generated by the headward shift of body fluids [2]. Moreover, the heart is affected during spaceflight and may be prone to arrhythmias or alterations in the normal sequence of the electrical impulses responsible for atrial and ventricular contraction [4]. Common arrhythmias involve atrial or ventricular fibrillation (disorganized regional depolarization), bradycardia (slower than normal heart rate), tachycardia (faster than normal heart rate), premature contraction, and other conduction problems [5]. Arrhythmias make the heart pump less efficiently, increasing the risk of sudden cardiac arrest, stroke, cardiovascular diseases, and dementia [6].

Seventy-five arrhythmias and 23 conduction disorders were recorded by the Russian Federation to NASA, including a 14-beat episodes of ventricular tachycardia with a maximum frequency of 215 bpm [7]. Electrolyte disruptions, abnormalities in the autonomic nervous system, and alterations in the mass of the cardiac chambers may be causative factors for these cases, but the exact mechanism remains unknown. Moreover, these risks increase during long-term spaceflight [6].

Basic Concepts of Blood–Brain Barrier

The CNS is vascularized by capillaries which are highly impermeable, called the blood–brain barrier (BBB). These capillaries are essential for providing oxygen and nutrients and for the elimination of carbon dioxide and waste products from neural tissues. The BBB allows the CNS to manage the

A. H. Sayed (✉)
Department of Medicine, Ain Shams University, Cairo, Egypt
e-mail: 30012290102866@med.asu.edu.eg

A. R. Hargens
Department of Orthopaedic Surgery, University of California, San Diego, Altman Clinical and Translational Research Institute, La Jolla, CA, USA
e-mail: ahargens@ucsd.edu; ahargens@health.ucsd.edu

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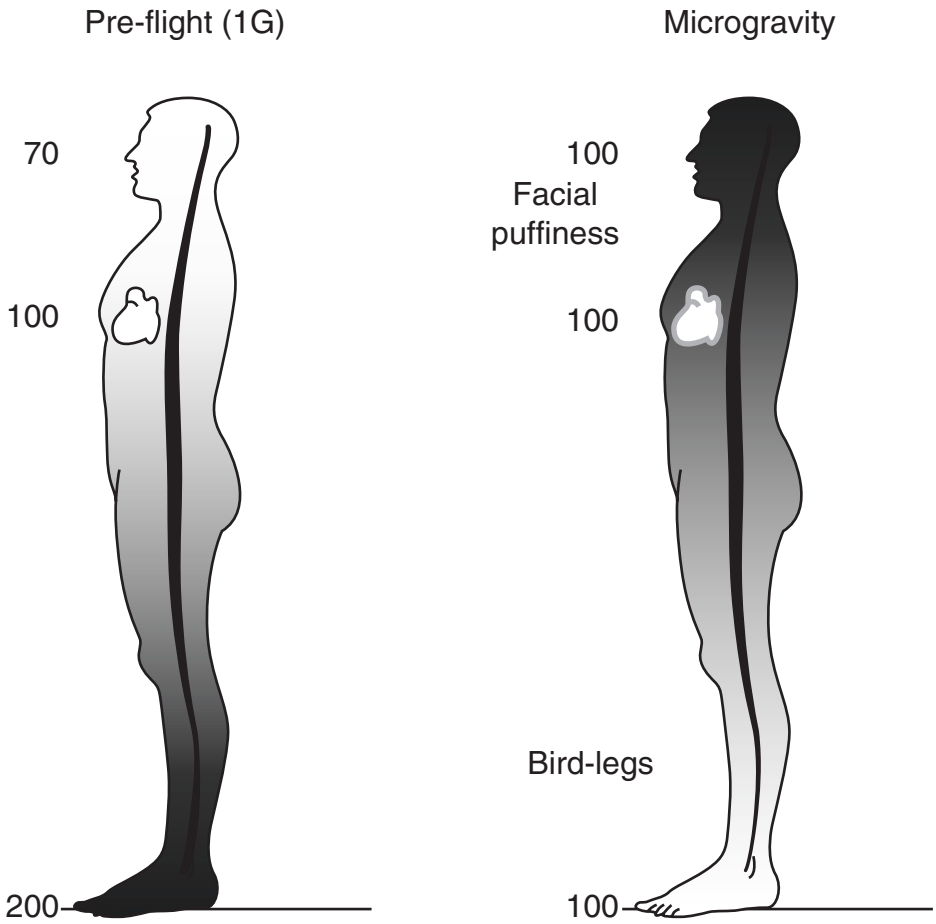

Fig. 2.1 Fluid shift; preflight (left) the lower extremities are easily supplied by blood due to the work of gravity. Early in-flight the blood begins to shift from the lower extremities to the upper body causing "puffy face" [Reproduced with permission from Hargens et al., 2009] [8]

movement of different ions, molecules, and cells between the blood and neural tissues. This barrier is essential to preserve brain homeostasis for normal neural activity in the CNS and also saves the tissue from diseases related to BBB dysfunction which may occur during space missions [9, 10].

The BBB exists in all brain regions except at circumventricular organs [10]. A physical paracellular barrier is formed by tight junctions (TJs) between brain endothelial cells (BECs) [11]. TJs consist of claudins, occludin, and zona occludens and seal the paracellular path between BECs creating a high trans-endothelial cell electrical resistance (TEER) barrier impeding the harmful substances from crossing the BBB [12, 13]. Those tight junctions are polarized into luminal (blood-facing) and abluminal (brain-facing) plasma membrane domains. The TJs are linked with adherens junctions (AJs), which sit abluminal to tight junctions and consist of VE-cadherin dimers that facilitate cell to cell membrane adhesion and bind to the actin cytoskeleton through catenins [14]. In addition, TJs induce a high TEER and reduce paracellular diffusion to a greater extent than AJs. Additionally, there are astrocytes which are highly branched cells with small bodies found in white matter (fibrous astrocytes) and gray matter (protoplasmic astrocytes), their podocytes not only encircle nerve fibers and neuronal somas (respectively) but also surround the abluminal surface of the capillaries. Then, the processes are called perivascular end-feet [10].

BECs lack fenestra and express low levels of transcytosis producing a transcellular barrier to the dissolved hydrophilic molecules [13]. These paracellular and transcellular barriers help to transfer molecules between the blood and the brain by special transporters. Commonly, these transporters fall into two groups. First, efflux transporters, such as Pgp and BCRP, are represented on the luminal membrane and use the energy (from ATP hydrolysis) to efflux small hydrophobic molecules toward their blood concentration gradients, thus providing a barrier to many small non-polar molecules that could passively diffuse via the cell membrane [15]. Second, BECs have nutrient transporter which pass substrates (such as Glut-1/glucose, Lat-1/amino acids) down their concentration gradients into the brain, supporting the neural tissue with important nutrients [9, 15]. BECs also represent low rates of leucocyte adhesion molecules (LAMs), thus reducing CNS immune surveillance by blocking the binding of immune cells to BECs and their movement to the CNS (Fig. 2.2) [16]. BECs also have unique metabolic properties such as "metabolizing molecules" that change their capacity to diffuse or be transported [17]. A high concentration of mitochondria is found in BECs relative to peripheral endo-

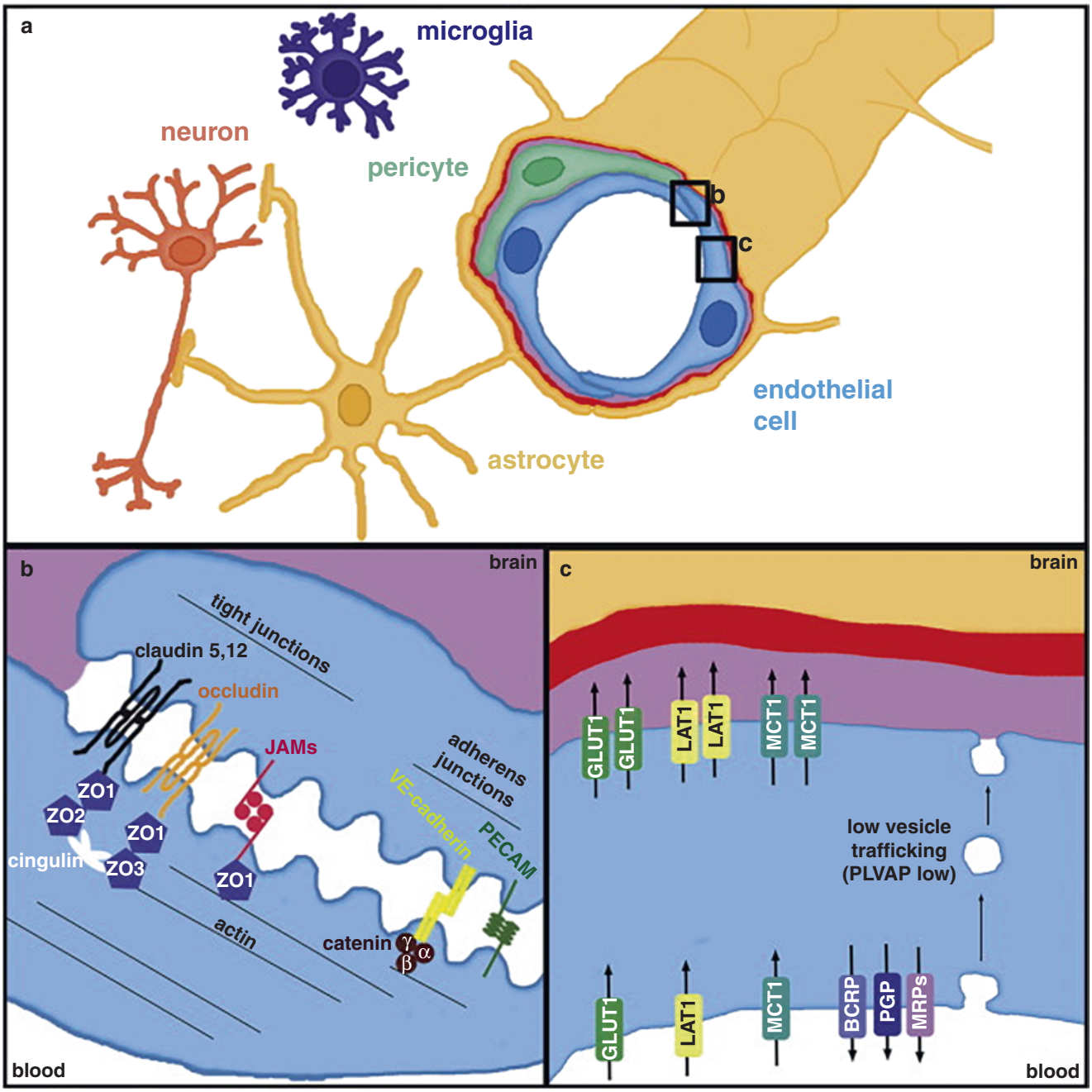

Fig. 2.2 The neurovascular unit (NVU). (**a**) The NVU defines all the components that communicate at the interface between the blood and the CNS. ECs (blue) create the blood vessel walls and interact with pericytes (green) in the vascular abluminal surface, together are ensheathed by astrocyte processes (orange). Neurons (light red) and microglia (purple) interact with the vasculature to form the NVU. (**b**) The TJs consist of transmembrane proteins such as claudins [5, 12], occludin, and junction adhesion molecules (JAMs). Adherens junctions and TJs are attached to the actin cytoskeleton by ZO-1, -2, and -3. (**c**) Low rates of vesicular transport limit transcellular movement of non-specific molecules from the blood to the brain. ECs express a variety of transporters, both to efflux potential toxins (Pgp, BCRP, MRPs) and to deliver specific nutrients to the brain (glut-1/glucose; lat-1/amino acids; Mct-1/lactate) [Reproduced with permission from Elsevier] [9]

thelial cells (PECs) in order to satisfy the energetic demand for BBB.

There is a similar membrane barrier that serves as an interface between blood and cerebrospinal fluid, called the blood–cerebrospinal fluid barrier. It is similar to the blood–brain barrier in the following: endothelial cells in the capillary beds, circumferential basement membrane across the abluminal domain, and astrocytes on the abluminal surface (perivascular end-feet) in the capillaries [18]. But, unlike the BBB, it has fenestrated endothelial cells(ECs) which is

relatively leaky and more permeable to water, gases, and lipophilic substances from the blood to the CSF [19]. In addition, there are choroidal epithelial cells which produce cerebrospinal fluid. So if the brain is dehydrated, the CSF becomes a source of fluid to rehydrate it [20].

Adaptations to Microgravity

The differentiation between the fluid transition itself and the response to this shift provides two timeframes for physiological alteration. First, the immediate changes produced by the absence of the gravitational force are indicated as acute adaptations in the following section. Second, the consequent adaptations to these changes will be defined as long-term adaptations below [1].

Acute Adaptations and Microgravity-Induced Fluid Shift

The impact of spaceflight begins several hours before the liftoff when the astronauts are in their position in the shuttle, lying on their backs with a 90-degree hip and knee flexion (see Fig. 2.3). This supine position stopped the blood from pooling into the legs during the ascent, which may lead to syncope in serious situations, and also indicate what will happen in microgravity of moving the blood from the lower parts to the head and upper parts of the body. About two-thirds of space crew members report headache, malaise, lethargy, anorexia, nausea, vomiting, and gastric pain within the first few hours or days of spaceflight [21]. In addition, loss of hydrostatic pressures increases intraocular pressure (IOP) and induces facial edema "puffy face" and distension of temporal, forehead, and neck veins, resulting in cephalad fluid shift [8].

After entering weightlessness, astronauts suddenly feel the fluid pooling within seconds without depending on visual or physiological indicators. All the symptoms are noticed visually without physical measurements and are complete within the first 6–10 h of flight [1, 22]. The higher concentrations of fluid in the upper body are experienced through a feeling of fullness in the head and discomfort in the sinuses and eyeballs, the same as felt in nasal congestion during a cold. Smell and taste diminished as they used to during flu, and non-verbal contact between subjects may happen as facial expression is impaired [1]. The change in the thickness of superficial tissues can be assessed to determine the appar-

Fig. 2.3 The supine legs up posture is very common for launches (courtesy of NASA)

ent fluid change [23]. Consequently, the thickness in the forehead increased by 7%, reflecting an increase in fluid volume of around 2 L in the upper body [11]. In the first 4 days in space, the leg circumference falls by up to 30% to the degree that remains quite low for the rest of the mission and may include "chicken-leg syndrome" 1.5 years later [10, 12].

Interestingly, heat transmission is also affected by fluid shifts. As convective and evaporative heat loss reduces in weightlessness, radiative heat loss in space becomes much more significant than on earth. In space, more than 30% of the heat exchange between the body and the atmosphere happens at the head and neck because of increasing the blood volume in this part of the body [24].

Long-Term Adaptations

Upon the sudden decrease of gravity in space [2], the cardiovascular system develops primary reactions to deal with the short-term rise in thoracic length or spinal curvature. This rapid response involves a reduction in the heart rate, as well as a dilation of the lower limb arterioles to reduce peripheral resistance, hence decreasing mean blood pressure [1].

After that, arranging a new set-point is a way for the cardiovascular system to adapt to the long-term stimuli. Due to the high blood filling of the thorax, the body become overloaded with fluid, inducing a reduction in the blood volume. This is an acceptable way to adapt to microgravity, but results in a fluid volume that is considered hypovolemic condition on Earth [25]. It is indicated by the reduction in stroke volume and plasma-atrial natriuretic peptide (ANP) levels [26]. The mechanism of volume reduction involves stretch receptors in the intrathoracic vessels and heart [27]. Higher amounts of fluid in the thorax cause greater filling of blood vessels, which activates the stretch receptors that activates baroreflexes, resulting in suppression of the renin–angiotensin–aldosterone pathway, and produces ANP [28]. Together, these processes decrease the blood plasma volume of approximately 10%–15% [29]. In addition, the reduction in plasma volume does not arise from elevated diuresis or natriuresis, but rather likely from decreased interstitial pressure in lower body and increased vascular pressure in the upper body, both which facilitate transcapillary fluid flow through the interstitial upper body [30] (Fig. 2.4). In addition, reduced plasma volume increases the concentration of circulating red blood cells (RBCs), which in turn allows the body to destroy newly released RBCs to preserve the homeostatic equilibrium [31]. Moreover, long-duration spaceflight probably decreases both systolic and mean arterial pressures, giving rise to a 10% rise in carotid diameter and cardiac output [6].

Long-term adaptations include the challenges facing the body upon return to Earth [32]. The effects of sustained exposure to microgravity and adaptation of the cardiovascular system to loss of gravitational stimulus are starting to appear [33]. The issues include dizziness, sweating, presyncope, decreasing blood flow to central nervous system, and, above all, orthostatic intolerance. This condition is characterized by elevated heart rate and decreased systolic pressure and may lead to faint due to hypovolemia [34]. Hypovolemia of the cardiovascular system significantly decreases exercise capacity experienced by returning astronauts and decreases VO2max (maximum amount of oxygen that can be used—the standard indicator for exercise capacity) which is a consequence of decreased intravascular

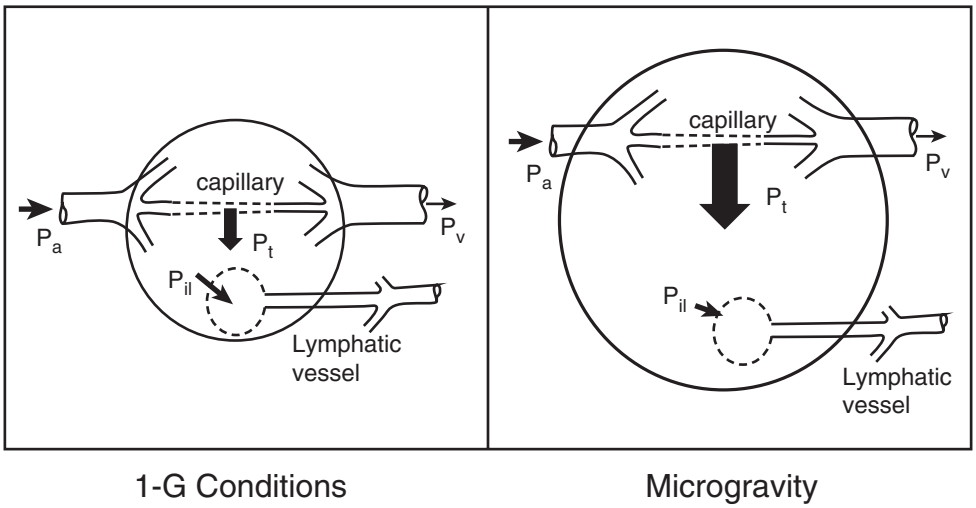

Fig. 2.4 Changed capillary transmural pressure (blood to tissue) due to weightlessness. The arterial pressure (Pa), venous pressure (Pv), transmural pressure (Pt), and interstitial fluid to lymph pressure gradient (Pil) are shown, with larger arrows indicating greater pressure gradients. 1-G conditions represent relative values on Earth. In microgravity, the loss of tissue weight reduces tissue hydrostatic pressure, therefore inducing higher transmural pressure which can cause edema. Lymph flow depends mainly on tissue deformation and local hydrostatic gradients but may be reduced in space. Arterial flow depends on the input arterial pressure Pa. Capillary hydrostatic pressures are regulated by pre-capillary sphincter activity and myogenic responses [Reproduced with permission from Hargens et al., 2009] [8]

blood volume and reduced stroke volume and cardiac output [35]. Of note, long-term spaceflight has led to cardiac remodeling, in other words, atrophy. Moreover, decreasing mass and size of the left ventricle have also been confirmed post-flight [36].

Circulation and the Central Nervous System

Endothelial Dysfunction

Endothelial cells are a major factor maintaining vascular integrity, angiogenesis, and many homeostatic functions in the body. Moreover, ECs improve secretive, synthetic, metabolic, and immunological activity. The endothelium of the CNS vasculature plays a vital role in the maintenance of normal CNS function. In the brain, spinal cord, and peripheral nerves, the blood vessels are distinguished by endothelial tight junctions that maintain a restrictive blood–brain barrier. This advanced adaptation ensures the adequate ion and water balance required for normal neuronal transmission inside the CNS [37]. In addition, the endothelium releases antithrombotic and fibrinolytic factors to prevent the blood from the formation of thrombi and emboli. ECs also help form new blood vessels (angiogenesis) as protagonists molecules, leading to functional capillaries. Finally, ECs efficiently regulate vasomotor reactions through the synthesis and metabolism of vasoactive molecules acting on smooth muscle cells such as endothelin-1 (ET-1), nitric oxide (NO), and angiotensin II (AngII). They also regulate the proliferation of smooth muscle cells [38–40].

Arterial vessels differ from venous vessels in terms of the structure and function of their ECs in micro- and macro-blood vessels. Moreover, the endothelium of the cerebral circulation, the major component of the BBB to protect the brain from harmful substances, deserves special emphasis. The BBB has uniformly tight junctions and differs from both fenestrated endothelium as cells have pores and discontinuous endothelium where cells have intracellular and transcellular discontinuities [38].

Endothelial dysfunction is sometimes caused by altered activity of the endothelium by decreased vasodilation, pro-inflammatory state, and prothrombic processes. It is associated with many causes of cardiovascular diseases, such as hypertension, coronary artery disease, chronic heart failure, peripheral vascular disease, diabetes, and chronic kidney failure. Mechanisms that engage in decreased vasodilatory responses involve reduced production of nitric oxide, oxidative overload, and reduced development of hyperpolarizing agents [41].

Endothelial dysfunction sometimes occurs from disturbances in the balance of pro-oxidant and anti-oxidant amounts due to lack of physical activity such as with spaceflight [42]. Reduced daily exercise in space is also associated with the incidence of insulin resistance, which is closely associated with endothelial dysfunction in individuals with diabetes [43]. Endothelial dysfunction is evident in animals exposed to high-energy ionizing radiation. Dysfunction of ECs is sustained for 2 weeks to 6 months after radiation exposure [44]. Whether endothelial dysfunction associates with radiation exposure in spaceflight is not well understood, but there appears some evidence that radiation and microgravity exposures may elicit more damage to ECs [45].

As mentioned above, proper brain activity relies on an intact BBB. For example, despite its small mass, the brain consumes about 20% of the oxygen intake through the body [46]. There is evidence that the brain vasculature is destroyed by high-dose low-LET radiation during space missions [47]: vascular lesions are common in areas of radiation necrosis in irradiated humans and non-human primates [48, 49]. Rodent studies also demonstrate strong consequences of low LET radiation. For example, a cranial X-ray dose of 9 Gy contributed to a decrease in hippocampal micro-vessel volumes at 2 days, which lasted to 1 month after exposure to 8-month-old male mice. Similar results were also recorded in rats 1 month after 10 Gy of cranial irradiation [50–52].

Previous ground-based research has shown that simulated microgravity and ionizing radiation triggered chronic endothelial dysfunction and BBB disturbance leading to maladaptive tissue remodeling [9]. Ionizing radiation is an important endogenous factor in inducing neuroinflammation, by causing a cellular damage in the brain [53]. This figure illustrates the role of inflammatory and immune reactions in the presence of radiation-induced cognitive deficits (see Fig. 2.5). In vitro models also showed that changes in BBB integrity were observed after much lower doses (4 Gy). These changes were long-lasting and followed by increased permeability for low- and high-molecular-weight proteins [53]. Morphologically, an endothelial layer rarefaction was seen, which could open the endothelial tight junctions, despite the reality that no gross changes were detected in the immuno-labeling of the tight junction protein panel (ZO-1, claudin-5, and occludin) [54]. Thus, all these processes induce endothelial dysfunction and BBB disturbances.

Despite these data, there is a relative lack of research on low-dose or high-LET radiation on brain vascular effects [49]. Interestingly, using a 3D human brain microvascular endothelial cell culture model, 1 Gy Fe and protons (both at 1000 MeV/n) affect vascular synthesis and proliferation, suggesting that regeneration of injured vessels may be impeded after radiation exposure [55].

Total peripheral vascular resistance decreased during spaceflight [26], although there is evidence of increased sympathetic nervous activity by increased catecholamine

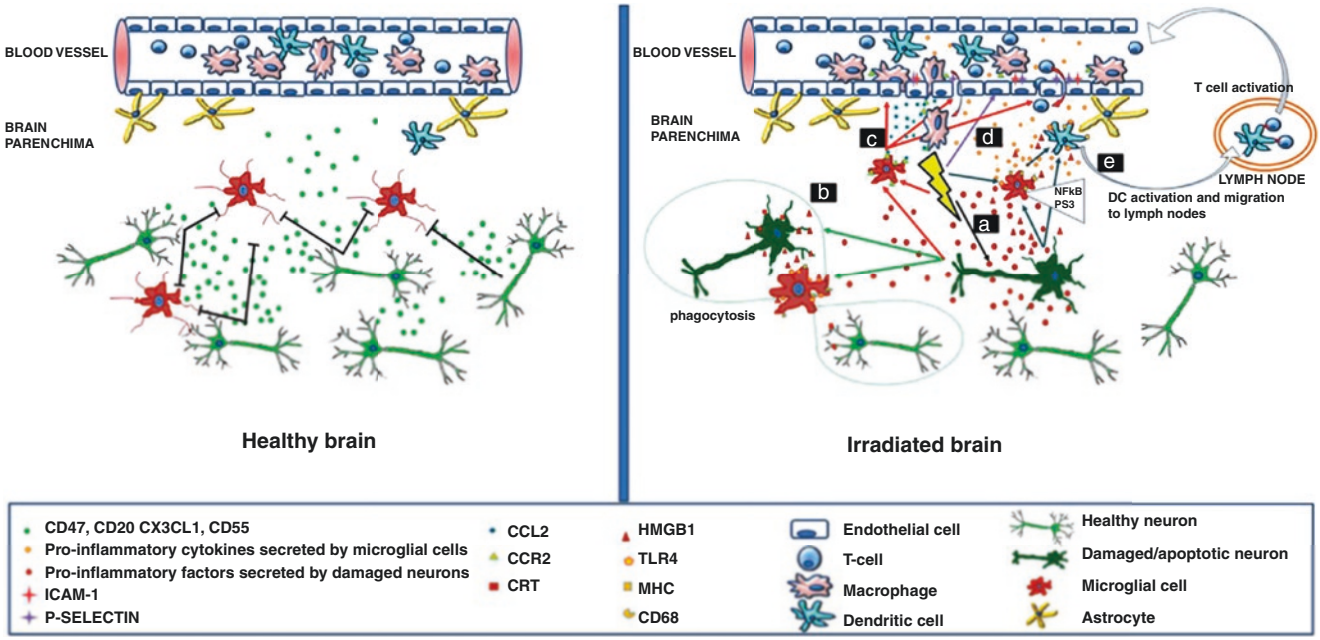

Fig. 2.5 In the healthy brain (left part), neurons secrete CD47, CD55, CD20, and CX3CL1, which maintain adjacent microglial cells. In the irradiated brain (right part), neurons secrete pro-inflammatory cytokines, which activate microglia (**a**). In microglia, radiation-induced DNA damage through the NFKB pathway activates microglia (MHC, CD68 upregulation) and secretes pro-inflammatory cytokines (**a**). Damaged neurons secrete high-mobility group protein 1 (HMGB1) extracellular, which is a ligand for TLR4. Damaged neurons also express calreticulin, sensed by activated microglia and induces phagocytosis of damaged and healthy neurons (**b**). Irradiation increases the secretion of CCL2 that is a chemoattractant for CCR2-expressing peripheral macrophages, which penetrate the BBB (**c**). Radiation increases intercellular adhesion molecule 1 (ICAM-1) and P-selectin on brain microvascular ECs. Peripheral lymphocytes and monocytes adhere to these ECs and transmigrate through the micro-vessel wall (**d**). Pro-inflammatory signals and HMGB1 activate brain-residing dendritic cells, which migrate to regional lymph nodes and induce immune reactions (**e**) [licensed under CC BY 4.0] [54]

levels, which could trigger arterial stiffness [56]. As noted above, amounts of the renin–angiotensin–aldosterone hormones increase during spaceflight [43]. Angiotensin II and aldosterone are strongly involved in mechanisms that increase arterial stiffness by endothelial dysfunction, activation of collagen production, remodeling and hypertrophy of matrixes, and proliferation of smooth muscle vascular endothelial cells [57]. In addition, higher insulin resistance may increase glycation end products, including cross-bridge formation in the extracellular vascular matrix, adversely affecting arterial structure and function [58].

Importantly, endothelial gap junctions are kept locked by the combined pressure of the interstitial fluid in the brain and intracranial capillary pressure. A study has suggested that during 1-G the hydrostatic pressure is transferred from the brain to the capillaries, leading to raise the pressure required to close endothelial cell junctions. Thus the brain cannot contribute its weight to keep the balance of the pressure during spaceflight, causing capillary filtration into the interstitial fluid [59]. The brain is surrounded by a cranial vault, so its compliance is very low. As a result of the inability of these tissues to quickly extend their interstitial volume, comparatively minor increases of transcapillary fluid filtration cause large increases in interstitial fluid pressure. This, in particular, decreases the gradient of transmural vascular pressure and physically compresses capillaries, therefore limiting the perfusion of nutrient tissue due to cerebral edema [60].

CSF Hydrodynamics and Brain and Neck Venous Congestion

CSF Hydrodynamics Circulation on Earth and in Space

Cerebrospinal fluid (CSF) is secreted from choroid plexuses of ventricles (90% by lateral ventricle), a little amount is formed around cerebral vessels and from ependyma cells lining the ventricles [61]. The CSF circulates around the brain and spinal cord [62]. Its main role is to protect the brain against trauma acting as "water jacket" around it; it also keeps the volume of fluid inside skull constant and therefore maintains a constant intracranial pressure [63] (Fig. 2.6).

During long-term spaceflight, the volume of CSF spaces increase, including the subarachnoid space, causing visual impairment and eye-structural changes [64]. Van Ombergen et al. indicated in an MRI study that there is loss of brain white and gray matter volumes and changed volumes of CSF spaces. Cosmonauts' MRI data was collected preflight, post-

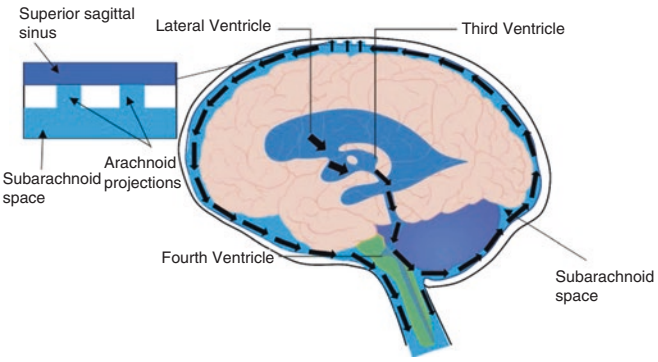

Fig. 2.6 The traditional circulation of CSF begins from lateral ventricles and flows toward third ventricle >> fourth ventricle >> subarachnoid space. From here it flows around brain or around spinal cord. Then it drains into the arachnoid projections, especially into the superior sagitta sinus [63] [licensed under CC BY 4.0]

flight, and at follow-up for 7 months after returning to Earth. The results showed a significant difference between preflight and postflight values for all supratentorial ventricular spaces, ventricular CSF volume was increased after spaceflight in supratentorial ventricular structures (i.e., lateral and the third ventricles), while the infratentorial fourth ventricle was not significantly enlarged. The superior sagittal sinus and Pachioni's granulations (responsible for the most of CSF resorption) were compressed due to the upward fluid shifting [11], leading to a generally reduced CSF resorption [65]. Interestingly, these changes are sustained as long as 7 months after spaceflight [65].

Another study proved that changes in thoracic and abdominal cavity pressures are dominant regulators of CSF dynamics [66]. During Forced inspiration, the CSF is shifted toward head and brain ventricles against the hydrostatic pressure, while the venous outflow is shifted from the brain and cranial cavity toward the heart and therefore counterbalance the CSF upward. Both the fluid systems are in balance to keep the intracranial volume constant [67]. In contrast, during deep expiration CSF moves toward the spinal lumbar region, facilitated by hydrostatic forces [66]. Microgravity and hydrostatic pressures are affecting these downward systems, so the net result is shifting the CSF upward and widening the intracerebral CSF spaces. Forced deep expiration can be a way to mitigate the changes made by microgravity [68].

Increased ICP and ventricular volumes leads to a compression of cerebral blood vessels and enhances vascular resistance, causing a reduction of cerebral blood flow [69]. The fluid shift may cause a clinical syndrome called visual impairment intracranial pressure (VIIP) syndrome or spaceflight-associated neuro-ocular syndrome (SANS) [70]. It was indicated that VIIP or SANS is associated with choroidal folds, optic disk edema, hyperopic visual shift, and a risk of permanent visual acuity changes (discussed in section "CSF Hydrodynamics and Brain and Neck Venous Congestion") [21].

Brain and Neck Venous Congestion

There are many factors that contribute to the elevation of intracranial pressure, including microgravity and changes in intrathoracic and abdominal cavity pressures (as mentioned in Section "Adaptations to Microgravity"). Inhibiting venous drainage from the skull is also a leading cause for ICP elevation. This may be a result of cephalad fluid shift in microgravity or increasing central venous pressure (CVP) [71], which may reduce the CSF and lymphatic drainage from the cranial cavity [72].

IJV cross-sectional area and flow are influenced by both cardiac and respiratory cycles and are affected by posture, anatomical differences, jugular valve incompetence, and changes in central venous pressure. On Earth, during standing position, venous pressure is affected by venous hydrostatic pressure and the IJVs act as a protective system that stops extreme negative ICP during collapsing (Starling resistors). Previous study showed that normal IJV blood flow changes during spaceflight. Pressure in the IJV increased during brief periods of weightlessness in parabolic flight [72]. It was observed that the IJV pressure remained elevated in the ISS during long-term spaceflight. This finding was supported by previously measured increases in ICP and central venous pressure during exposure to microgravity and cephalic fluid shifts [73].

During microgravity, astronauts are exposed to constant cerebral venous congestion with the ability to develop stagnant venous blood flow. Virchow triad identifies three main factors that lead to thrombosis: flow stasis, hypercoagulability, and endothelial injury or dysfunction. Blood flow stasis induces many thrombotic factors such as local hemostasis-activation factors and blood cell–endothelium interaction and creates local hypoxia-induced endothelial activation [74]. So the constant stagnation of blood flow in the IJV increases risk for thrombosis during weightlessness. Although during astronaut selection process, extensive medical screenings are performed to ensure they are healthy individuals. Notably, oral contraceptives are considered a risk for thrombosis during space missions. Estrogen-containing contraceptives are commonly used in human spaceflight for menstrual suppression [75]. The combination of oral contraceptives and weightlessness-induced blood flow stasis in the IJV during spaceflight leads to increased risk thrombosis formation [76].

Space Adaptation Syndrome (SMS)

Space motion sickness (SMS) occurs in 67% of the astronauts. Two hypotheses can explain SMS: the sensory conflict hypothesis and the most potential, fluid shift hypothesis [77]. The symptoms of SMS include headache, pallor, malaise, loss of appetite, nausea, vomiting, and loss of peripheral vision. The fluid shifting also causes cerebral and visible facial edema due to the filtration of fluid into tissues [71, 78] and may increase the ICP, the cerebrospinal fluid pressure, or

the inner ear fluid pressures, affecting the functional properties of the vestibular receptors [77]. SMS leads to reduced astronaut performance, reduces situational awareness, and threatens the safety of the crew members [79].

Visual Impairment Intracranial Pressure Syndrome

Spaceflight affects the visual acuity negatively especially during long-term missions. It has been reported by Mader et al. [80] that the crew members after 6 months on the ISS had anatomical ophthalmic alterations such as optic disk edema, posterior globe flattening, choroidal folds, cotton wool spots, thickening of retinal nerve fiber layer (RNFL), and reduced near vision and hyperopic shifts. Unfortunately, some vision alterations persist for years after the space flights, although the relation between severity and duration mission remains unclear [21]. To date, 15 long-term male astronauts have been diagnosed with inflight and postflight visual acuity alterations and vision anatomical disorders [81].

Many hypotheses explain the VIIP pathogenesis. For instance, if subarachnoid pressure moves from the intracranial to the intraocular compartment through the peri optic subarachnoid space, it can lead to optic nerve sheath distension and disk edema [80, 81]. The chronic and mild increase in ICP leads to elevated pressure gradient across the lamina cribrosa, that may cause posterior-globe flattening, disk edema, choroid folds, and a hyperopic shift [80, 82]. In addition, elevated cabin CO_2, high-salt diet, and resistive exercise are considered potential secondary contributing factors [83]. But the exact reason and pathogenesis for VIIP is still unclear. Kramer et al. [84] observed that the upward fluid shifting in microgravity which led to intracranial and intra-orbital hypertension is similar to idiopathic intracranial hypertension (IIH) (also called pseudotumor cerebri). However, some authors suggest that elevated ICP is not the only cause of VIIP, because the astronauts had not experienced many clinical symptoms of IIH such as chronic hypertension [84].

Integrated Physiologic Countermeasures

Artificial Gravity

Artificial gravity (AG) is an effective countermeasure for the effects associated with weightlessness, either by using centrifugation with a rotating spacecraft, a short-arm centrifuge within the spacecraft, or exercise via lower body negative pressure [21]. A study indicated that orthostatic intolerance caused by bed rest can be mitigated by AG [85]. However, centrifuge-induced artificial gravity of the space stations is still a theory due to the excessive amount of energy needed to keep the station spinning, and it is very expensive as well [1]. So, in order to maintain the same effective results of centrifugation, we should use an early, low power, low-cost countermeasure such as exercise within LBNP. It is an integrated, non-expensive and well-tested countermeasure for long-term spaceflights [86]. It was indicated that combining AG with aerobic exercise has been noted effective on muscle sympathetic nerve activity and fluid shifts, it also restores cardiac and muscular functions as noted with centrifugation alone [87].

Lower Body Negative Pressure With and Without Exercise

Lower body negative pressure (LBNP) is a potential countermeasure to reverse the cranial fluid shift associated with weightlessness [88]. A previous study showed that during spaceflight LBNP was associated with reducing IJV area, but the reduction did not reach seated baseline IJV values. In addition, the left IJV blood flow improved in 59% of LBNP sessions during spaceflight [89]. Furthermore, a possibility of syncope during application is a risk; thus, medical monitoring is warranted [90]. Notably, LBNP was associated with improved blood flow patterns in most LBNP sessions during spaceflight and thus may be a promising countermeasure to blood flow stasis and thrombosis associated with spaceflight [89]. Recently, Marshall-Goebel et al. established a head-down-tilt (HDT) bed rest study on nine healthy males, indicating that the LBNP-induced reactions such as improving cerebral drainage and reducing CVP, CBF, and IOP make LBNP a candidate for the study of mechanisms for the development of VIIP [91]. LBNP alone is an effective method to prevent some of the head-ward fluid shifts in microgravity [92]. During exposure to LBNP, interstitial fluid pressure decreases in parallel with LBNP chamber pressure leads to increase in leg circumference significantly by shifting plasma to interstitial fluids, thus reducing cerebral and facial edema [93]. These changes affect the area around the optic nerve, where chronic increase in intracranial, intraocular, venous, and retinal pressures may cause visual impairment. Early development of a simple LBNP chamber with mild negative pressures in about 30 mmHg moves the fluids to the lower extremes for 6–8 h/day on ISS [86]. Such a system is useful while crew members are busy at work stations so that crew operations are not interrupted [86].

Since LBNP alone offers little protection against cardiovascular deconditioning, combinations with treadmill exercise have been suggested to be more efficient. This combined technique mitigate the microgravity-induced effects on human body [8]. Many studies were developed using a treadmill exercise protocol within LBNP during prolonged (30- and 60-day) bed rest [94–96], they had significant effects on

different muscles and bones such as the endurance of knee extensor, in the non-exercise control group, decreased significantly but was maintained in the LBNP exercise group. A bone resorption detector was increased in the control group (urinary n-telopeptide excretion), but was not changed in the countermeasure group [97, 98]. Notably, cardiac mass increased significantly in the countermeasure group, but decreased in the control one [99]. Therefore, the treadmill exercise within LBNP maintained plasma volume, orthostatic tolerance within a degree (orthostatic tolerance time decreased in women-exercise group), upright exercise capacity, muscle strength, and sprint speed [100]. Applying lower body negative pressure during HDT position provide effective results on baroreflex sensitivity and distensibility of lower limb vessels [96]. These significant mitigations of body fluid shifting (blood, lymph, and CSF) protect against brain congestion and visual impairment during spaceflight.

Coagulation and LBNP

A study was conducted on 3 astronauts using LBNP, showed that their venous blood flow changed from stagnant or reverse (grade 3 or 4) to nominal flow (grade 1 or 2), indicating that LBNP can acutely improve IJV flow and potentially reduce thrombosis risk [89]. However, from another prospective, using LBNP may activate the coagulation process and increases risk for thrombosis. The pressure gradient produced by LBNP moves intravascular fluid to the lower body's extravascular compartments and hence increases hemoconcentration level. This increases blood viscosity and plasma protein concentrations and enhances interactions between procoagulant factors and coagulation factors, thus activating procoagulant pathway [101]. Zaar et al. observed that exposure of healthy subjects to 10 min of 30 mmHg LBNP activates thrombin-generating part of the coagulation system such as thrombin anti-thrombin (TAT) complex levels. They reported that increases in TAT level associated with LBNP is also seen in the deep venous thrombosis patients and that the fluid shifts toward the legs is similar to those associated with prolonged sitting during bus or aircraft travels [102]. It was suggested that the increased sympathetic activity seen in both LBNP and bleeding may induce coagulation by activating endothelial beta-2 adrenergic receptors [103]. Cvirn et al. noted that the presyncope state (associated with LBNP) can also activate coagulation. At presyncope, plasma volume decreases and the hemoconcentration increases leading to increased blood viscosity. Presyncope also activates thrombin generation parameters (e.g., prothrombin fragments 1 and 2 and thrombin-antithrombin complexes) and increases endothelial activation markers such as tissue plasminogen activator and tissue factor, as well as thrombin generation parameters (e.g., prothrombin 1 and 2 and thrombin-antithrombin complexes) [104]. And all these factors generated by LBNP can lead to thrombosis.

Sodium Intake

It is important to mention the role of sodium in diet in altering visual acuity in some degree. Astronauts eat a low-sodium diet in attempt to avoid long-term visual damage. The daily sodium amount in diet of astronauts is about less than 3 g/day, because high sodium levels result in an osmotic shift of body fluid from the interstitial to the intravascular spaces leading to increased venous volume, congestion, and jugular venous outflow obstruction [105].

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Effects of Microgravity and Space Radiation on the Nervous System

3

Vivek Mann, Alamelu Sundaresan,
Marie-Francoise J. Doursout, and Sundar Devakottai

Introduction

As early as 1609, Galileo became the first human to see Mars through a telescope. With the advancement in technology and human's curiosity for interplanetary travel, NASA recently sent the largest and most advanced rover to Mars, after a 203-day journey covering approximately 293 million miles. The mission itself personifies the human ideal of persevering toward the future and will help us prepare for human exploration of the Red Planet. This will set the stage for future robotic and crewed missions. The Mars 2020 mission is part of a larger program that includes missions to the Moon to prepare for human exploration of the Red Planet. This has renewed interest of international community in space exploration, with planned man missions to asteroids, Moon, Mars, and beyond in the future. Nonetheless, the effects of long-term spaceflight on human health remains a significant perturbation. One crucial challenge to astronauts on future space missions is extended exposure to environments of microgravity (μg) and radiations [1–3]. Past studies have shown adverse effects of μg and radiations on several physiological systems, including notable deleterious effects on the nervous system. Because planning and management and cost are vital limitations to spaceflight studies of nervous tissue, it is important to use alternate models that simulate μg to test hypotheses, design experimental parameters, and augment spaceflight experiments.

V. Mann (✉) · A. Sundaresan
Department of Biology, Texas Southern University, Houston, TX, USA
e-mail: Vivek.mann@tsu.edu; Alamelu.sundaresan@tsu.edu

M.-F. J. Doursout
Department of Anesthesiology, McGovern Medical School at UTHealth, Houston, TX, USA
e-mail: Marie-Francoise.Doursout@uth.tmc.edu

S. Devakottai
Department of Internal Medicine, Mc Govern Medical School at UT Health, Houston, TX, USA
e-mail: sundar.Devakottai@uth.tmc.edu

During both short- and long-duration spaceflight, astronauts are exposed to cosmic radiation and microgravity, resulting in changes across multiple neurological domains including alterations in sensation, movement, cognition, and coordination [4]. Spaceflight-associated changes to the brain are complex as microgravity itself affects brain by different mechanisms such as cephalic fluid shift, vestibular dysfunction, and weightlessness [5]. In addition, they also endure some common stressors including but not limited to social separation, confinement, sleep deprivation, circadian rhythm disruption, and anxiety. Maintaining the probity of the central nervous system during long duration space flights is a high priority, since proper cognition and somatosensory function are important for many mission critical tasks.

Experiments in real microgravity conditions are rather rare, which is why simulation devices such as Rotary Cell Culture System (RCCS) and Random Positioning Machine (RPM) are used (Fig. 3.1a, b). These devices make use of the principle of microgravity, which is a continuous free-fall. Cells are cultivated in a chamber, which rotates around the horizontal axis, thus counteracting the sedimentation process and keeping the cells in a constant state of free-fall. The Random Positioning Machine (Fig. 3.1a) or, by some referred to as the 3-D clinostat, is a micro weight ('microgravity') simulator that is based on the principle of 'gravity-vector-averaging' [6]. The system may be compared with a classic 2D clinostat although such a clinostat has only a two-dimensional averaging of the **g** vector while the RPM provides a functional volume, which is 'exposed' to simulated micro weight. Gravity is a vector, i.e., it has a magnitude and a direction. During an experiment run in this two axis RPM the sample's position about the Earth's gravity vector direction is constantly changing. The sample may experience this as a zero-gravity environment. The principle of an RPM is to randomly rotate. As with other rotating systems this will generate acceleration. Since we want to simulate microgravity, we are to avoid any additional **g** forces. The level of simulation within this RPM depends very much on the speed of rotation and the distance of the sample to the center of rota-

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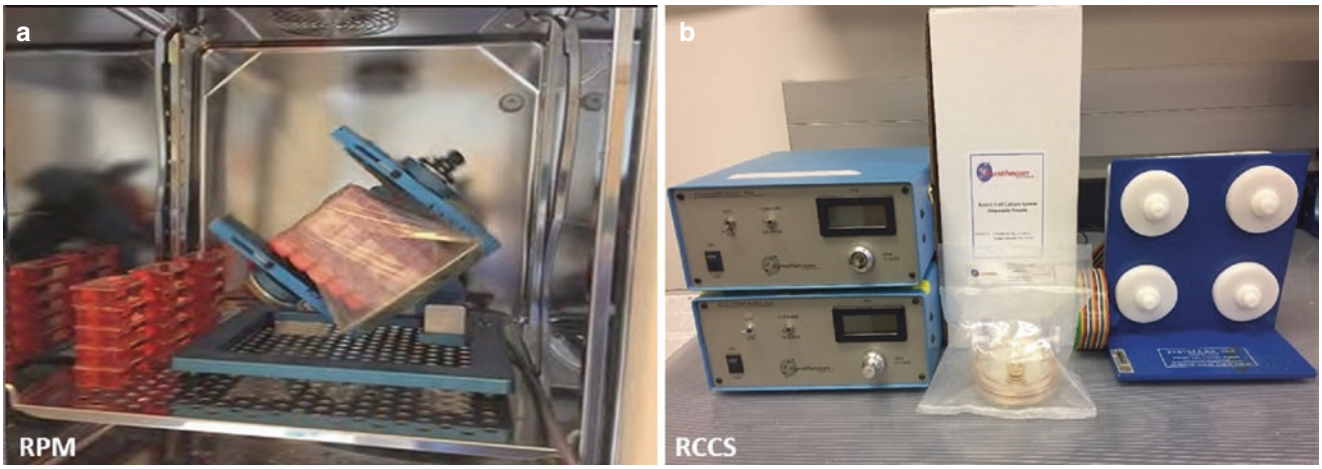

Fig. 3.1 Simulated microgravity analogue systems. Two of the most frequently used ground analogue systems the Random Positioning Machine (**a**) and Rotary Cell Culture System (**b**) are illustrated here. Courtesy: OIPL Lab, Texas Southern University, Houston Texas. (Open Source: Reprinted with Permission)

tion. In principle only the exact center of the RPM i.e., the center of rotation provides you the ultimate microgravity simulation.

The Rotary Cell Culture System (Fig. 3.1b) is a bioreactor technology that produces3D cultures. It is a dynamic system which suspends cells in a low-shear stress, microgravity-like environment allowing anchorage dependent cells to readily aggregate into 3D spheroids while simultaneously producing high mass transport of nutrients and oxygen. Unlike spinner flasks, the RCCS suspends cells without cell damaging mechanical force. The RCCS can also be used with a variety of scaffolds. The RCCS was originally developed at NASA, Johnson Space Center to simulate the microgravity conditions in space [7]. It was based on the principle of clinorotation, defined as the nullification of the force of gravity by slow rotation around one or two axes. The clinostat developed at NASA is a single axis device known as the Rotating Wall Vessel (RWV). The RCCS is the commercial version of this device.

Effects of Microgravity on Neurobiology

Microgravity has been implicated as a major initiator in space-related neurologic dysfunction. Microgravity in addition with hypobaric exposure during space travel can cause various neurophysiological changes. These encompass decompression sickness, altered central nervous system, and peripheral nervous system symptoms such as memory loss, visual changes, headache, seizures, vertigo, unconsciousness, dysesthesias, paresthesia's, bowel, and bladder incontinence, fasciculations and paresthesias. Microgravity has been observed to affect cells cytoskeleton [8–10]. The delicate interconnection of the intracellular organelles and cytoskeletal structures is maintained by gravity which when altered can affect biochemical and biosynthetic pathways, ultimately negatively effecting DNA replication, microgravity on RNA transcription, and protein transport [11].

Experiments performed by He et al. analyzed the cytoskeletal effects of simulated microgravity in the slime mold *Physarum polycephalum.* Actin cytoskeletal changes were observed after 40 h of simulated microgravity exposure. Actin fibers appeared to be shortened, disordered, and depolymerized [9]. Another study performed by Mann et al. examined changes in cell morphology due to alterations in cytological architecture in human fetal osteoblasts (hFOB). Following simulated microgravity RPM exposure, a decrease in F-actin filaments was observed. A shift in the microfilament distribution toward F-actin accumulation at the cell boundaries was clearly noticeable in both the 7 days and 14 days RPM samples [12].

As reported by Sarkar et al., microgravity can cause oxidative stress within the hippocampus. Their study in mice hippocampi subjected to microgravity environments showed decreased presence of pyruvate dehydrogenase (PDK-1) and Synuclein β. The decreased presence of Synuclein β could be due to the increased incidence of abnormal protein aggregations seen in microgravitational states [11]. Another study conducted by Demertzi et al. has reported the instance of cortical restructuring in an astronaut's brain post long-duration spaceflight. The authors reported decreased intrinsic connectivity in right insula and ventral posterior cingulate cortex and diminished integration between right motor cortex and left cerebellum. These outcomes underline the cardinal neural basis for the noted physiological deconditioning due to the spaceflight [13]. Kohn et al. have described struc-

tural loss of muscle and bone mass due to continuous adjustments in the sensory and motor systems [14]. According to Fujii et al., a better knowledge of mechanisms of microgravity-induced adverse effects on the nervous system will lead to more effective treatments [15].

Spaceflight-Induced Intracranial Hypertension

Astronauts participating in spaceflight missions are exposed to microgravity which has adverse effects on various organs including eyes. The risk of visual impairment/intracranial pressure (VIIP syndrome) is therefore one of the leading health concerns for NASA. It has been more recently renamed as Spaceflight Associated Neuro-ocular Syndrome (SANS). Intracranial hypertension post spaceflight is now received as a recognizable clinical phenomenon. Although, the key physiological mechanisms causing an increase in intracranial pressure are not well known yet [16]. The most plausible mechanisms of increased intracranial pressure due to microgravity involve a cephalic shift of body fluids, venous outflow blockage, blood–brain barrier malfunction, and disturbance to the cerebrospinal fluid flow. Wostyn and Devyn concur that the response of optic nerve sheath to changes in intracranial pressure may be a potential predictive biomarker for optic disc edema in astronauts [17].

The postflight study of 300 astronauts found that approximately 29% and 60% of astronauts on short-duration and long-duration missions, respectively, reported paucity in distant and near-visual acuity [18].

A retrospective review of data in astronauts post long-duration spaceflight revealed that after 6 months of spaceflight, seven astronauts had ophthalmic findings consisting of optic disc edema in five, globe flattening in five, choroidal folds in five, cotton-wool spots in three, nerve fiber layer thickening detected by optical coherence tomography in six and decreased near vision in six. Five of seven astronauts with near-vision complaints had a hyperopic shift [19].

In another study, Corydon et al. investigated the influence of simulated microgravity using a Random Positioning Machine (Fig. 3.2) on human adult retinal pigment epithelium (ARPE-19) cells. The finding of this study revealed that simulated microgravity causes significant changes in the cytoskeletal (F-actin) and cytoskeletal-related proteins ARPE-19, along with cell development behavior and gene expression patterns involved in cell morphology, migration, adhesion, and angiogenesis [20].

According to Kramer et al. there is enlargement of total brain and cerebrospinal fluid volumes after long distance spaceflight which can be attributed to microgravity-induced intracranial hypertension [21]. The authors reported from a study conducted on 14 astronaut subjects that the increased postflight CSF production rate. This concludes a decrease in CSF production in a microgravity environment, which is upregulated upon return to conventional gravity [22].

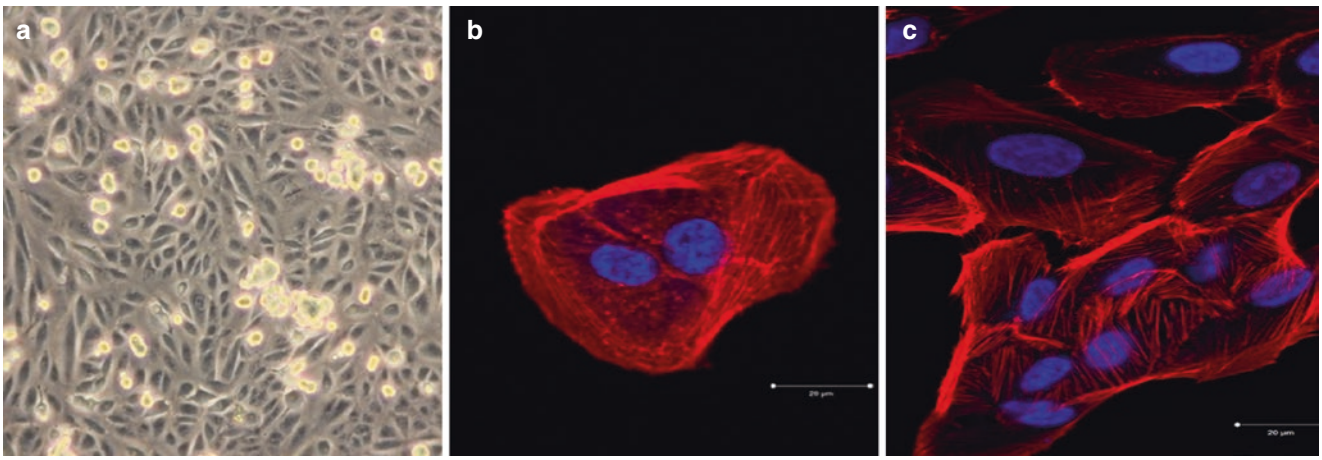

Fig. 3.2 Astronauts participating in spaceflight missions are exposed to microgravity which has adverse effects on various organs including eyes. The risk of visual impairment/intracranial pressure (VIIP syndrome) is therefore one of the leading health concerns for NASA. Here the influence of simulated microgravity using a Random Positioning Machine on human adult retinal pigment epithelium (ARPE-19) cells is represented. Following exposure to simulated microgravity for 5 and 10 days a subset of ARPE-19 cells formed multicellular spheroids (MCS), whereas most of the cells remained adherent (AD) as shown by phase contrast microscopy (**a**) and confocal laser scanning microscopy (**b**, **c**). (Open Source: Reprinted with permission)

Space Motion Sickness

Motion sickness occurs when brain gets mixed signals from various sensory organs including eyes, ears, and body. Motion sickness can begin quickly, and the person might break out in cold sweat and feel nauseated. Space motion sickness symptoms are like those in other forms of motion sickness; they include cold sweating, malaise, loss of appetite, nausea, fatigue, vomiting, and anorexia. Within first 2–3 days in microgravity up to 60%–80% astronauts experience space motion sickness which can affect their operational performance. Spaceflight appears to precipitate headaches without other space motion sickness symptoms in otherwise excellent health status male subjects. Space motion sickness can be due to cranial shifting of body fluids resulting from the loss of hydrostatic pressure gradients in the lower body when entering microgravity. Also, loss of tilt-related otolith signals upon entry into microgravity can cause a conflict between actual and anticipated signals from sense organs discharging spatial orientation inducing space motion sickness.

According to the point of view of Vein et al., headaches are a common, but rarely expressed, complaint during space travel [23]. International Classification of Headache Disorders, second edition (ICHD-II) criteria questionnaire has been used to classify secondary headaches. In a study conducted on 17 astronaut subjects, 12 reported to have experienced at least one headache event while in space. A total of 21 space headache incidents of moderate to severe intensity in 71% of sample subjects was also reported. Majority of headache experiences (76%) were not related with symptoms of space motion sickness. In another post spaceflight study, Penchenkova et al. have reported a diminished association between the vestibular nuclei and sensory/motor regions due to central adaptation which downregulates vestibular input during space flight lessening sensory discord, mitigating space motion sickness [24, 25].

Radiological Changes (Magnetic Resonance Imaging) in Brain Tissue After Microgravity Exposure

Using MRI scans, doctors, scientists, and researchers are now able to examine the inside of the human body in high details. MRI uses a strong magnetic field and radio waves to create detailed images of the organs and tissues within the body (e.g., anomalies of the brain and spinal cord). Nervous system works because information flows from neuron to neuron. The structural characteristics of central nervous system chambers have been examined by Hasan et al. in a retrospective study of 10 healthy astronauts, using multimodal quantitative magnetic resonance imaging (qMRI) [26]. The study reported definitive attributes, indicative of structural neuroplasticity, and adjusting neurogenesis. The brain is made up of gray and white matter. Gray matter consists of short, nonmyelinated neurons and cell bodies, whereas white matter consists of myelinated neurons. The basic pattern of distribution of white and gray matter found in CNS includes a central cavity surrounded by gray matter, with white matter external to the gray matter. The spinal cord exhibits this basic pattern; however, pattern changes with ascent into the brain stem. Brain stem has additional gray matter nuclei scattered within the white matter. Cerebrum and cerebellum contain outer layer of gray matter called the cortex, and they also have scattered areas of gray matter nuclei amid white matter. Several studies have been conducted utilizing MRI to see changes of brain structure following spaceflights, including brains of astronauts before and after long/short-duration missions on the international space station (ISS) and from the Space Shuttle Program [27]. Multiple studies have shown no notable changes in total volume of gray and white matter in astronauts after spaceflights. However, a recent study conducted by Kramer et al. has reported noteworthy augmentation of white matter volume in astronauts (5.5%) post long-duration spaceflight. Pre- and postflight MRI scans after long-duration flights and short-duration flights showed constriction of the central sulcus occurred in 17 of 18 astronauts after long-duration flights (mean flight time, 164.8 days) and in three of 16 astronauts after short-duration flights (mean flight time, 13.6 days) [28]. In another study, Koppelmans et al. have reported increase in gray matter volume in sensorimotor and motor areas of the brain in astronauts post spaceflight [29]. According to study conducted by Jillings et al. MRI scans in cosmonauts post spaceflight showed chiefly changes in gray matter due to volume shifts and white matter volume expansion in the motor and coordination regions of the brain [30]. Also, post flight studies done by Lee et al. have demonstrated focal changes in white matter microstructure within multiple sensory regions including vestibular and proprioceptive processing [31].

Effects of Microgravity on the Vestibular System

The vestibular system is a highly physics-dependent system which exists to aid with proprioception and the ability to adapt the body to optimal position during movement. This process revolves around small movements of endolymph within the semicircular canals for rotatory acceleration adjustments and calcium oxalate crystals on the saccule and utricle for vertical and horizontal acceleration adjustments. These movements are translated and transmitted via the ves-

tibular nerves and associated nerve tracts/nuclei which helps not only the brain send impulses on position but also fires various reflexes to adjust multiple body positioning such as the eyes, head, and torso. Gravity plays a big role in this as it is a major physical force contributing to the speed and acceleration at which the fluid and crystals mentioned move. What happens if gravity is removed from the equation such as with microgravity in outer space? This is an important question to ask as the possibility of space tourism requires a better understanding of space travel and return to gravity as a whole.

Normally the vestibular system works in congruence with the cerebellum and eyes to maintain spatial awareness. In microgravity, these facets are increasingly challenged when compared to the rest of the central nervous system [32]. Specifically, for the vestibular system, the functionality of the otolith organs are more affected than the semicircular canals due to their specialized role in detecting linear accelerations [33] such as gravity, which in turn creates a mismatch in vestibular input as the semicircular canals now provide the majority of signaling [34]. This creates a sort of space sickness, as the body now thinks there is much more angular acceleration than linear, which can cause nausea, vomit, etc. just as motion sickness would. Therefore, when microgravity is introduced, the human vestibular system undergoes a variable adaptation [35]. Functional connectivity of sensorimotor and special working memory has been shown to be increased in microgravity simulations indicating a potential increase in neuroplasticity with a particular focus on spatial adaptation [33, 35]. The contributors to the speed at which adaptation occur likely remains multifactorial and are difficult to quantify [32]. Currently there is no reliable data on countermeasures to take during the adaptation period to minimize space sickness [36].

Research on this subject has been rather generalized with advancements being made every day. Originally, much of the research on the effects of microgravity on vestibular system were done on Earth utilizing microgravity-like methods such as dry immersion, head-down bed rest, and parabolic flights [32]. Now there are more studies being conducted in space, and this is likely to yield more accurate results. Many data-gathering methods such as functional MRI and EEG studies have been utilized, but a combination is likely to provide more accurate results than any one method alone [32]. There is also difficulty in assessing how quickly the vestibular system readapts or potentially maladapts to gravity upon return to Earth as this seems to happen variably and might hold another key into understanding more on this topic. With the increasing prevalence of humans in space, it is also important to look at microgravity effects on human development. Studies currently being done with animal models on this show mixed results and require further exploration [37]. As more studies are being done in space and as technology develops further, it is likely the data will change, and there will be more insight into the exact effects of microgravity on the vestibular system as well as into possible maneuvers to help improve adaptation.

Effects of Space Radiation on the Nervous System

Examination of the health risks associated with long-term deep space missions necessitates an understanding of possible tissue damage resulting from prolonged exposure to HZE radiation. Whereas any type of tissue damage from this radiation is undesirable, CNS injury would be especially devastating to the individual and would be expected to be relatively permanent.

It is known that an astronaut on a 6-month journey to Mars—the time required with conventional propulsion—would be exposed to about 0.3 Sieverts (1 Sievert = 1 Gray = 1 Joule/kg = 100 rad = 100 rems for X-rays, but = Qx1 Gray = 100 rems = Qx100 rads for high-LET radiation, where Q > 1 is the biological quality of radiation), or even to 0.6 on a round-trip. Eighteen months on the surface (if it takes so long to get there, you might as well stay awhile!) would bring another 0.4 Sieverts, for a total exposure of 1 Sievert. Limits set by NASA vary with age and gender but range from 1 to 3 Sieverts. Among the least well-understood health risks for long-term deep space flights is neurological damage induced by HZE particles and secondary nuclei. Exposure to GCR's will be chronic, ≈1% neurons hit per month. During a 3-year mission to Mars at solar minimum (worst case for GCR exposure), 46% of brain neurons might be hit by a HZE particle (with the electric charge $Z > 15$), with 13% hit by an iron particle ($Z = 26$). Therefore, there is a low probability of two hits by iron particles on the same neuron, but a significant likelihood of a hit by an iron particle and another high-LET particle. For nuclei only, hit frequencies are 4–8 times lower. Every cell nucleus in the brain would also be traversed by a proton twice a week, and an alpha particle once a month [38]. Particle fluences may be more relevant than radiation-absorbed doses from GCR to the brain, which will be a few tens of cGy. For low-LET radiation, this would not have severe consequences, but HZE radiation-induced neurological damage could jeopardize mission success and/or induce early onset of neurodegenerative diseases such as Parkinsonism. The existing neurochemical, histological, and behavioral literature on HZE radiation is not comprehensive. First, effects measured at short times after single doses of 100 cGy or higher, which correspond to several hits per cell, may overestimate astronaut's risk because of DNA repair and/or compensation for lost func-

tion by other neurons. Repair and adaptation mechanisms that can counteract effects of particles delivered chronically may be overwhelmed by delivery of radiation in a single dose. Second, other conditions during spaceflight may modify responses to HZE radiation. We believe this is particularly likely for oxidative stress. A major source of indirect damage to the CNS will be oxidative stress caused by free radicals generated during radiation of brain tissue. Spaceflight is known to downregulate antioxidant defense systems [39] which could amplify the impact of free radical generation. Additionally, inflammatory cytokines and other mediators of inflammation are released in response to oxidative stress and amplify the effects of oxidative stress. Oxidative stress and inflammation both activate the hypothalamic–pituitary–adrenal axis, increasing brain exposure to glucocorticoids. Glucocorticoids are known to impair hippocampus-mediated cognitive functions and to suppress hippocampal neurogenesis and reduce hippocampal synaptic density.

Energy deposition from GCRs is largely vconfined to a thin cylinder of tissue which receives a high local dose, especially at the end of the particle range, within a few nanoseconds [40]. One can calculate that for a 1 GeV/n iron particle, the average dose to a cell in the irradiated cylinder will be <40 cGy or that the dose to a nucleus that would be traversed would be about 200 cGy. These doses would be of little consequence for low-LET irradiation of post mitotic cells. However, recent studies have demonstrated active neurogenesis in the hippocampus, a brain structure critically involved in memory, so that effects on mitotic cells have to be considered. Furthermore, effects of ionizing radiation on tissues stem primarily from damage to DNA, and the precise ways in which particular types of radiation interact with matter and break and/or otherwise alter DNA structures govern the potential consequences of irradiation, modulated by the ability of cells to repair damage. A passage of a HZE particle through the nucleus of a cell should cause multiple, intense, and essentially instantaneous ionization events, which induce complex patterns of DNA damage that cannot be fully repaired. Little is known about the effects of charged particles at the cellular and molecular level in mitotic cells and even less about the situation in neurons. Mitochondrial as well as nuclear DNA may be a radiobiological target. Since the mitochondrial electron transport chain is the main endogenous source of reactive oxygen species that cause oxidative stress, damage to mitochondrial DNA may be particularly relevant during spaceflight. Mitochondria have multiple copies of their genome and even possess DNA repair enzymes. However, studies of the effects of HZE radiation in this area are lacking.

The likely nature and extent of brain damage is likely to include necrosis, apoptotic loss of neurons and functionally impaired surviving neurons, as well as impaired neurogenesis. Neuronal apoptosis is an important component of brain ontogeny [41] and is important in the progression of neuropathological conditions such as stroke and neurodegenerative disease [42]. Previous work by both us and other researchers demonstrated that DNA damage activates the apoptotic process in neurons. For example, irradiation [43], cytosine arabinoside [44], cisplatin [45], topoisomerase-II inhibitors [46], and the topoisomerase-I inhibitor camptothecin [47] all induce apoptotic neuronal cell death. A number of these agents cause peripheral neuropathies and neurodegeneration [48]. DNA damage may also participate in initiating cell death in neuropathological conditions such as stroke [49]. Given these observations, it has become increasingly important to understand the downstream signaling events that control DNA damage-evoked neuronal cell death. Several molecular events that mediate death in some neuronal apoptosis paradigms have been described. For example, it has been suggested previously that proteins that normally function to control cell-cycle progression in actively dividing cells may play required roles in the death of terminally differentiated postmitotic neurons [50]. Specific to DNA damage, CDK inhibition, by both pharmacological and molecular means, prevents the death of sympathetic and/or cortical neurons evoked by UV irradiation, AraC, and/or camptothecin [47]. Furthermore, studies that use of camptothecin has demonstrated an increase in cyclin D1-associated kinase activity and protection by the expression of dominant-negative CDK4/6 [47]. These studies indicate that CDK4/6 activity plays a required role in DNA damage-evoked neuronal apoptosis. At least three other molecular events have been suggested to be required for the neuronal death that follows DNA damage. These include the tumor suppressor p53 [43], the proapoptotic Bcl2-related Bax [51], and the various death effector protease enzymes, caspases [51]. The obligate nature of p53 in some neuronal death paradigms is evidenced by significant neuroprotection in p53-deficient neurons exposed to excitotoxic injury [52], ischemia [53], and DNA damage [54].

Studies of retinal cells as surrogates for CNS neurons have suggested a loss of several percent of neurons per 100 cG of iron particles [55]. Older studies demonstrated changes in histological appearance and size of areas of the rabbit brain at doses as low as 100 cGy at times up to 5 years post irradiation [56, 57]. Effects were in the following order: Fe > Ar > Ne > gamma. Dose- and particle-dependent effects were also documented in mouse olfactory tubercle [56]. In other CNS models, HZE radiation induces acute and chronic neuroanatomic changes with lower doses. Philpott et al. (1985) claimed a decrease in the synaptic density in the CA1 area of hippocampus at both 6 and 12 months after exposure to ^{40}Ar particle radiation (0.5–50 cGy). As noted above, effects at the lower dose are very hard to credit. CA1 plays an

important role in working memory. Other neuroanatomic effects of high-LET neon particle radiation include neuronal necrosis and altered glial morphology. The neuronal and glial alterations were maintained for at least 35 days after exposure to 4 cGy 84 Kr particle radiation. Some in vivo studies suggest that chronic low-dose exposure to HZE particles might produce effects like aging and neurodegeneration [58]. The retina is part of the central nervous system, and Krebs et al. (1990) [55] found that densities of rat photoreceptors cells or bipolar cells were unaffected by 100 cGy at times up to 185 days. After 250 cGy, photoreceptors and bipolar cells densities were decreased by 20%–50% at 15 days, and this decrease persisted at 185 days. Vazquez and colleagues (1994, 2000) studied effects of 1 GeV/a iron particles in retinal explant cultures and observed dose-dependent reduction of neurite outgrowth 3 days after exposure to varying doses of iron particles (LET 148 keV/μm), with a maximal effect achieved with a dose of 100 cGy. Doses as low as 10 cGy were able to reduce neurite outgrowth by 20% as compared to the control group. In the past, several reports claimed the existence of microlesions expressed as morphological detectable "holes" in the cell surface, as well as tracks in tissues resulting from the passage of high-energy heavy particles with a charge of 20 or more, and with an LET of 200 keV/μm or greater [59, 60]. This purported lesion was considered one of the most harmful for the CNS. The neural retina, as an extension of the CNS, has been used in several studies to first corroborate and later reject the microlesion concept [61]. While the evidence for tunnel lesions has been shown to be inconclusive [55], the data does not exclude the possibility of functional expressions of discrete particle traverses or "microlesions." A "microlesion"is now generally envisioned as a discrete injury, which need not be reflected by morphological evidence of damage. It could simply represent transient or chronic molecular changes that may alter the cellular/tissue integrity. In the case of neurons, this may in turn impair the neural functions at the integrative level [62]. HZE irradiation on the brain has also been addressed in behavioral and biochemical studies, where alterations in, e.g., conditioned taste avoidance, conditioned place preference, and drug self-administration have been reported [58, 63–71]. The data suggest that neurological functions may be impaired in rats at doses of 100–200 cGy. An advantage of mice over rats for these studies is that it allows use of transgenic models to investigate the role of particular enzymes in facilitating or ameliorating effects of toxic insults. A drawback of animal experiments is that subtle aspects of human behavior (e.g., reasoning) could be more sensitive to HZE radiation than easily quantified rodent behaviors. Effects on neurochemistry that underlie behavior and cognition could be more sensitive than behavior itself and may lead to realistic models of human vulnerability.

Conclusion

In conclusion, various studies and data recommend that multiple central nervous system regions are affected during spaceflight, and these alterations probably result from the combinatorial effects of numerous spaceflight associated stressors. The expansion of tedious and lengthy manned space missions as well as future planned travel to Moon, Mars, and beyond will affect human health especially nervous system, and its knowledge has become a relevant subject of study. The vocational risks for astronauts are great, but research into the causes and mechanics of nervous system disorders will not only benefit the astronauts but also the general patient population. Eventually, the knowledge gathered from these space studies will structure the way we prepare for and design exploration class missions, beyond the moon and mars, where nervous system disorders could result in increased risk of wide ranging adverse medical events. Countermeasures to safeguard the astronauts from microgravity and space radiations will require further research and these are essential components in making certain safe and reliable journey to outer deep space.

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Cognitive Performance and Neuromapping

4

Stijn Thoolen and Gary Strangman

Overview

In human space exploration, crew members are exposed to a variety of environmental and psychological stressors that can seriously impact brain function and cognitive performance. Alterations in gravity and the related physiological adaptation, a closed and potentially hostile living environment, space radiation, high CO_2 levels, dietary changes, fluctuating workloads, sleep deprivation, altered lighting and shifting day–night cycles, sensory deprivation, isolation and confinement, working in a small multicultural team, and a long distance from Earth that further causes communication delays and limited social support are *all* recognized risks of adverse cognitive or behavioral conditions [1]. Anecdotal reports from spacefarers have repeatedly described cognitive deficits during flight, and terms like "space fog" or "space stupids" have been coined to describe experiences such as difficulty paying attention or concentrating, memory impairments, confusion when performing dual-tasks, and psychomotor problems [2–4]. In addition, Russian space psychologists and flight surgeons have emphasized the psychological condition "neurasthenia" to describe a process of psychological de-adaptation to the rigors of long-duration spaceflight, including symptoms of fatigue, decreased work capacity, memory deficits, attention and concentration difficulties, anxiety and internal stress, sleep and appetite problems, irritability, and heightened perceptual sensitivities [5, 6]. These anecdotal reports—and the limited empirical evidence available to support them [7]—highlight the need for further investigation into the underlying cognitive processes affected by these conditions.

While nearly all spaceflight missions to date have been performed in low Earth orbit, upcoming exploration class campaigns will extend greater distances into our solar system and for longer durations. The shift from 2-week shuttle missions to the 6-month ISS missions has anecdotally already shown the importance of the psychological stressors in space, where astronauts require a larger, more robust set of coping skills and more psychological support [1]. These demands will increase further when traveling to and operating on the Moon or Mars, where crew members will be exposed to new or elevated threats, for more extended periods of time, and with reduced "rescue" opportunities. They will also be required to perform complex operational tasks with unprecedented autonomy, given Mars communication delays of up to 22 min one-way, along with increased human-technology interactions. Despite this, the majority of the psychological support mechanisms reported by astronauts on the ISS will not be applicable in deep space, including live connections with Earth, resupply packages with favorite foods or presents from loved ones, and Earth viewing and photography [3]. As error margins are small in the extreme environment of space, the success and safety of these expeditions will thus greatly depend on the crew's mental composure and ability to maintain high levels of operational performance. Given the current knowledge gaps and high impact on mission success, the detection and mitigation of cognitive decline during long-duration exploration class missions has become one of the highest priorities in human space exploration [8].

The first experiments that directly addressed some aspect of cognitive alterations during spaceflight were performed as part of the Skylab medical program, using film and task schedules to investigate operator efficiency [9, 10]. At that time, most of the neuroscientific experiments in space focused on the acute neurovestibular disturbances encountered with gravity transitions early inflight and postflight, including space motion sickness, locomotion disturbances and spatial disorientation [11]. With the advent of the Space Shuttle, the focus of research shifted to the impact of sensorimotor disturbances on manual control and landing tasks, although these missions were typically of short duration (17 days or less) [12–16]. As longer missions and more advanced

S. Thoolen · G. Strangman (✉)
Department of Psychiatry, Harvard Medical School, Boston, MA, USA
e-mail: sthoolen@mgh.harvard.edu; strang@mgh.harvard.edu

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research equipment became available aboard Mir and ISS, the literature has become substantially larger, and long-duration space studies have since been performed on various cognitive domains [7, 17–19]. More recently, using electroencephalography (EEG) inflight or magnetic resonance imaging (MRI) of the brain pre- and postflight, researchers have started to investigate functional and structural brain changes in association with cognitive performance: neuromapping. These studies can elucidate the underlying mechanisms of cognitive decrements in space and provide further insight into affected brain regions that are relevant to mission success [20–23].

In addition to spaceflight itself, analog settings on Earth are being utilized to help assess the likelihood and consequences of cognitive impairment during deep space exploration missions and to investigate the effectiveness of potential countermeasures [24]. Each analog mimics a subset of the unique aspects of space missions, such as isolation and confinement, social and sensory deprivation, prolonged immobilization, or dangerous environmental conditions with limited possibility of rescue. Among the most relevant platforms where cognitive assessments and brain imaging studies have been performed are (1) controlled mission simulations in small volume isolation chambers (ICC environments) [25–30]; (2) overwintering expeditions at polar stations (ICE environments) [31–36]; (3) long-duration bed rest studies [37–39]. Each of these platforms has the potential to provide additional insight into the cognitive consequences of spaceflight (Fig. 4.1). In addition, preclinical animal radiation studies are another important analog model to better under-

Fig. 4.1 The effects of spaceflight-relevant stressors on the brain and cognitive functioning are not only investigated in space, but also on Earth. (**a**) The International Space Station has been the primary platform for testing the effects of long-duration spaceflight on cognition. Credit: NASA/ESA—T. Pesquet. (**b**) Isolated, Confined and Controlled (ICC) environments such as the NEK complex at the Institute of Biomedical Problems (IBMP) in Moscow or the NASA Human Exploration Research Analog (HERA) at the Johnson Space Center in Houston (pictured here) are dedicated laboratory facilities for prolonged spaceflight mission simulations. Small heterogenous crews are typically bound to a small volume habitat and exposed to mission dynamics, including operational tasks, altered lighting, sleep deprivation, and food restrictions. Credit: NASA. (**c**) Isolated and Confined Extreme (ICE) environments such as polar stations and submarines can provide excellent opportunities to study prolonged isolation and confinement in a real, natural setting that cannot be realized in typical laboratory studies. Suitable stations, like the French-Italian Concordia Station pictured here, are characterized by small crew sizes and extended mission duration (one year or longer), and include complex logistical operations with lack of opportunities to quit the expedition and limited or no rescue capabilities during the polar winter. Credit: ESA/IPEV/PNRA—S. Thoolen. (**d**) Head-down tilt bed rest studies like the international campaigns at the German Aerospace Center (pictured here) provide conditions of microgravity-related prolonged immobilization and headward fluid shifts, sometimes in combination with high levels of CO_2, and with strict control of physical activity, sleep schedules, and dietary intake. Credit: German Aerospace Center (DLR)

stand the impact of space radiation exposure, even though knowledge on extrapolation of such data to humans is still limited [40, 41]. The effects of radiation exposure are further discussed in Chap. 11.

Despite all efforts, measuring cognitive status in the operational environment of space has been a challenging endeavor, and significant gaps still remain in understanding cognitive functioning and its underlying neural pathways in space [7]. In this chapter, we will discuss the methodology of spaceflight-relevant cognitive assessment in humans, and describe findings of cognitive alterations both in spaceflight and in analog environments, including sensory and motor systems, spatial cognition, memory and learning, attention, executive and higher cognitive functions, emotional processing, social processing, and complex performance on operationally relevant tasks. We will examine the potential implications of such changes for long duration exploration missions, and what countermeasures can be implemented to mitigate the risk of cognitive impairment and maintain operational performance in space.

Cognitive Assessment Approaches

A particularly wide variety of tasks and measures have been utilized for spaceflight-related cognition experiments. These measures can be broken down into two broad categories: (1) elemental cognitive tasks, and (2) complex operationally relevant tasks.

Elemental Cognitive Tasks

Elemental tasks represent a reductionist scientific approach and are intended to identify alterations in specific cognitive abilities. Examples include perceptual discrimination, simple or choice response time, verbal working memory, grammatical reasoning, cognitive set switching, dual-task performance, or facial emotion identification. In general, such tasks are designed to be sensitive to specific cognitive alterations and can help identify the mechanisms underlying any observed cognitive or performance changes in spaceflight by more narrowly identifying the source deficit. For example, impaired operational performance on the robotic arm could result from basic problems with perception, difficulties with motor control, deficits in working memory, complex reasoning difficulties, or any combination of these. Identifying one or two specific deficit(s) can accelerate the development of targeted countermeasures. Since the precise elemental processes affected by spaceflight are still in the process of being identified, a common approach has been to select a battery of tasks that spans a reasonably large portion of cognitive capabilities.

Numerous attempts have been made in the past, and multiple test batteries have been used in space and analog environments [13, 42–44]. To this day only one of these batteries has been used operationally, namely the Spaceflight Cognitive Assessment Tool for Windows (WinSCAT). This five-task battery has been implemented by NASA as a clinical tool in flight operations to monitor neurocognitive status on Shuttle and ISS, focusing on processing efficiency, working-memory, memory, arithmetic, and sustained attention [43]. WinSCAT however has limited sensitivity (i.e., tests are too easy to detect subclinical cognitive changes) in the high-performing astronaut population, and fails to assess cognitive domains like spatial orientation, abstract reasoning, sensorimotor speed, emotion processing, stability of sustained attention, and risk decision-making that are also important for mission success [44]. An improved neurocognitive assessment battery has therefore more recently been developed by Basner et al. and adopted by NASA for future exploration missions, specifically designed to assess cognitive functions in astronauts, including these domains, and based on tests known to engage specific brain systems during functional neuroimaging (Table 4.1) [45, 46]. This battery, named Cognition, is currently used on the Columbus module

Table 4.1 Overview of the cognition test battery

Test	Cognitive domains assessed	Brain regions primarily recruited	Administration time (minutes)[a] median (range)
Motor Praxis (MP)	Sensorimotor speed	Sensorimotor cortex	0.4 (0.3–2.3)
Visual Object Learning (VOLT)	Spatial learning and memory	Medial temporal cortex, hippocampus	1.7 (1.4–8.2)
Fractal 2-Back (F2B)	Working memory	Dorsolateral prefrontal cortex, cingulate, hippocampus	2.0 (1.7–16.5)
Abstract Matching (AM)	Abstraction, concept formation	Prefrontal cortex	1.8 (1.3–7.9)
Line Orientation (LOT)	Spatial orientation	Right temporo-parietal cortex, visual cortex	1.2 (0.8–2.4)
Emotion Recognition (ERT)	Emotion identification	Cingulate, amygdala, hippocampus, fusiform face area	1.7 (1.2–3.1)
Matrix Reasoning (MRT)	Abstract reasoning	Prefrontal cortex, parietal cortex, temporal cortex	2.1 (0.6–3.9)

(continued)

Table 4.1 (continued)

Test	Cognitive domains assessed	Brain regions primarily recruited	Administration time (minutes)[a] median (range)
Digit Symbol Substitution (DSST)	Complex scanning and visual tracking	Temporal cortex, prefrontal cortex, motor cortex	1.6 (1.6–2.6)
Balloon Analog Risk (BART)	Risk decision-making	Orbital frontal and ventromedial prefrontal cortex, amygdala, hippocampus, anterior cingulate cortex, ventral striatum	2.1 (1.7–4.1)
Psychomotor Vigilance (PVT)	Vigilant attention	Prefrontal cortex, motor cortex, inferior parietal, and some visual cortex	3.2 (3.1–4.5)

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[a]Administration times based on $N = 15$ administrations of the *cognition* battery in each of $N = 19$ astronauts, astronaut candidates, and mission controllers ($N = 285$ total administrations; see text for details). Administration times include the time needed to input comments and any pause taken by the subject before proceeding to the next test

on the ISS, and has already been implemented in multiple ICC, ICE, and bedrest analog studies [18, 30, 39, 44, 47].

While clearly of benefit, there are two main challenges of using elemental tasks. First, when it is unknown at the outset what cognitive functions might be affected and to what degree, it can be difficult to select tests that span the full range of cognitive abilities to be investigated, in a sensitive way, and within the operational constraints of spaceflight missions—hence the variety of test batteries used in spaceflight research to date. Besides selecting the right tasks, a second drawback is that the results of these tests are not easily translated to a metric of complex operational performance [48]. To help assess whether a cognitive change has any meaningful operational consequences, as well as to develop operational decision rules, operationally relevant tasks may make a more appropriate measure.

Complex Operationally Relevant Tasks

Operationally relevant tasks that have been used to investigate cognitive performance in spaceflight research include simulated docking [49, 50], robotic arm manipulation [51], driving [17], cabin air management [52], and management of the chemical environment of the spacecraft [53, 54]. Such tasks require a complex combination of perception, executive functioning and planning, 3D mental manipulation, and motor multitasking, affording multiple potential compensation strategies. While this complexity tends to obscure the core source of a deficit—making them considerably less effective for targeted countermeasures—they are presumed to transfer more accurately to real operational performance. As such, an assessment on such tasks can help to inform operational decisions, like selecting crew members that are most capable for a specific operation, or postponing a mission-critical procedure.

To establish such a link with actual operational performance, researchers have developed tasks and criteria for operational assessment using regular crew training platforms, such as the Russian spacecraft docking program [29, 49], or the Robotic On-Board Trainer that is used for Canadarm2 training onboard the ISS [51]. A more reliable alternative would be to develop an evaluation system embedded in actual operational processes, considering that the current tasks are still simulator-based. While this would be of tremendous value from a compliance point of view, such systems have been exceptionally difficult to design without interference with the primary operational activity, and are equally difficult to norm given the small amount of assessments that would be available in space. Hence, no major inroads have been made on this front.

Considerations for Cognitive Assessment in Space

Accurate cognitive testing generally requires tasks that have (1) no ceiling or floor effects, (2) high test-retest reliability, (3) high construct validity (i.e., the test measures the intended cognitive capability), (4) high responsiveness (i.e., sensitivity to the variables relevant to spaceflight), and (5) minimal sensitivity to learning effects, or an exceptionally well-understood learning curve. In addition, tasks need to be (6) feasible for implementation within the operational constraints of the spaceflight environment, including being designed for self-administration, with flexible and repeated administration possibilities, and minimal administration time.

Meeting these requirements in spaceflight research has been challenging. The tests used in individual studies may lack sensitivity because they have been designed for clinical populations and fail to detect subclinical but mission-relevant deficits in high functioning individuals. Operational-style tests in particular have not been fully evaluated on many of the above key considerations as they are too specific to receive any scientific support from clinical or military appli-

cations on Earth. Small sample sizes resulting from operational constraints, in combination with the large variety of tasks and cognitive domains they assess, have complicated task characterization and comparison among studies. Finally, even optimal tests need to be coupled with proper experimental design and include appropriate control groups, and numerous spaceflight and analog studies have been plagued by learning confounds and inadequate controls due to practical restrictions. The above limitations may account for most of the equivocal results found in spaceflight-relevant cognition research and should be kept in mind when evaluating such studies [7].

Adaptation to the Spaceflight Environment and Early Cognitive Effects

When astronauts fly to space, the transition to microgravity is associated with numerous adaptive processes affecting the brain, including redistribution of fluid toward the head and sensorimotor disturbances. Altered physical forces on the body and altered input to the vestibular and proprioceptive systems result in postural changes, new movement strategies and sensory conflict that subsequently causes spatial disorientation, space motion sickness, and modifications in eye–head coordination [55, 56]. These adaptation effects tend to be most prominent in the first 3–4 days upon entering weightlessness, with inter-individual variation depending on rates of adaptation and previous spaceflight experience [56]. Space motion sickness is generally viewed as the most operationally disruptive of these effects, producing symptoms of nausea, loss of appetite, vomiting, lack of initiative, and drowsiness [55]. Eventually, after 1–3 weeks in space, it appears that information coming from the vestibular and proprioceptive organs is gradually reinterpreted. As astronauts adapt to their new environment and develop new ways of relating to the external world, these symptoms tend to abate [55, 56].

The suddenly altered gravitational input and the resulting vestibular and sensorimotor adaptation are especially important to consider as it may cause a direct interaction with cognitive performance both inflight as well as upon return to Earth. Short-duration spaceflight studies of 21 days or less have shown reasonably consistent evidence for reductions in motor speed in the first days of spaceflight, at least when complex motor performance is required [12]. When speed is forced to be constant, for example with a manual tracking task, reductions in motor accuracy are seen instead [14, 57, 58]. Also, there are clear alterations in perception that are particularly prominent during the first days of spaceflight adaptation, including time estimation, body orientation, and mass discrimination [15, 59–61]. Interestingly, research on terrestrial patients with vestibular dysfunction has demonstrated cognitive impairments similar to what astronauts have described when they are "in the space fog" [62]. However, so far the scientific support for early alterations of memory [16, 63, 64] as well as attentional and executive functions [13, 57, 65–67] in spaceflight has been variable. Additionally, and still under investigation, the sensorimotor disruptions may have important implications for higher-order spatial navigation [23, 68, 69].

Whether these observations are indeed a direct effect of gravity-induced vestibular and sensorimotor adaptation, or rather result from the cumulative effect of a multitude of spaceflight-associated stressors is not entirely clear, however. Separating these effects has not been easy, in particular due to the lack of experimental control on spaceflight missions. In support of the multistressor theory, dual-tasking has been observed to be impaired while single-task performance remained unaffected. Performance decrements concomitant with subjective ratings of high mental load also support the hypothesis that the perceptuomotor decrements seen in early flight may be the result of a more general cognitive or emotional overload—or reduction in cognitive reserve—arising from the physiological stress of adaptation, sleep deprivation, workload, and irregular schedules [57, 67, 70, 71]. One recent study (n = 5 astronauts) found decreases in performance on highly taxing visuospatial tasks with simultaneous reductions in attention-related event-related potential (ERP) components on EEG, suggesting reduced attentional resources after about 1.5 weeks in flight [23]. In further support, another short-duration spaceflight study investigated the processing of stimuli that were emotionally related to personal or flight conditions [72]. Such stimuli were found to be more difficult to process, not only in microgravity, but also in the days immediately before and after flight. These results suggest that microgravity alone may not be able to explain the early cognitive performance decrements observed in space, and the latter is especially intriguing given the common reports of affective changes during spaceflight [4].

Understanding to what extent the alterations in cognitive functioning are specific to the vestibular and sensorimotor adaptation to microgravity or related to a broader set of spaceflight-relevant stressors has important implications for countermeasure development and mission design. This is particularly true for long-duration spaceflight, where long-lasting sensory reintegration as well as additional stressors of isolation and confinement, circadian disruption, chronic hypercapnia and radiation may provide multiple pathways toward performance degradation [69]. So far however, given the small number of subjects and the considerable inter-individual variability in existing short-duration spaceflight cognitive studies, it would appear particularly unwise to extrapolate or generalize the findings of these studies on long-duration missions.

Cognition During Long-Duration Spaceflight

More relevant for future exploration missions, the findings of cognitive studies performed on long-duration spaceflights—generally lasting 30 days or longer—are summarized below for each of the major cognitive domains. Because a substantial body of evidence originates from long-duration ICE, ICC, and bed rest studies, these are included as well, where appropriate.

Perceptual and Motor Systems

Basic perceptual and motor functioning related to long-term adaptation to space, including changes in the vestibular system, oculomotor control, postural control, and space motion sickness, is discussed in Chap. 8. Here, we focus on more complex capabilities and cognitive processing. In brief, both sensory and motor systems largely but perhaps not completely adapt to the spaceflight environment over time, and that adaptation may be more rapid with previous microgravity experience [56]. Importantly, not all functions adapt in all individuals, nor is adaptation necessarily complete within any specific time period. Certain cognitive effects, such as distortions of perceived size and shape of objects [73, 74], impaired line orientation [23], lengthening of time perception [75], motor slowing [76], and increased motor variability [77] were all in evidence beyond 30 days, and hence may represent capabilities that do not completely adapt (or are maladaptive) in spaceflight. These sustained impairments are important to consider as task performance in general may depend on such basic perceptual input or motor outputs.

Bock and colleagues examined unstable manual tracking in three subjects on the ISS and found a sustained tracking error that lasted 5–6 months postlaunch [77]. Improvements were observed over time, suggesting a learning effect, but there were no ground-based controls for comparison. In contrast, on the 438-day flight of Russian cosmonaut Dr. Polyakov, manual tracking was impaired only during the first 2 weeks following launch, then returned to pre-flight levels for the remaining 13 months of spaceflight [70]. The discrepancy between these studies is probably best explained by variations in task difficulty (i.e., one- vs. two-dimensional tracking movements) and thus sensitivity and/or individual variability.

Visuospatial processing was examined by Clement et al. in eight astronauts during their 6-month mission on the ISS. Their results showed that the heights and depths of objects were perceived as smaller and larger, respectively, and that distances were generally underestimated following several months in orbit compared to Earth [74]. These findings suggest that the perception of the three-dimensional world changes in space. Spatial perception was further examined in three long-duration spaceflight studies [18, 23, 78]. In five astronauts performing a line orientation task after 2 months on the ISS, Tacaks and colleagues found increases in response times and reduced accuracy, thereby providing the first evidence for impaired visuospatial cognitive performance during long-duration spaceflight [23]. In contrast, two cosmonauts performed another line orientation task over the course of their 6-month stay in orbit without alterations in accuracy or speed [78], and in the NASA Twin Study, performing the cognition test battery once a month during his 12-month stay on board the ISS, astronaut Scott Kelly did not show decreases in line orientation [18]. In comparison, the task used by Tacaks et al. seemed to require additional working memory and attentional functions, but the researchers also pointed out that the inflight sessions were performed in quasi free-floating position, potentially affecting the task results [23].

The perceptual and motor changes that have been observed in long-duration spaceflight, including decrements in unstable tracking and spatial orientation, have not been reported in ICE [79–81] and ICC studies [82–85]. One study at the Argentinian Belgrano II Antarctic station found evidence that time intervals were overestimated by overwintering crew members toward the end of the expedition, but it remains unknown how changes in other cognitive domains may have acted as cofactors [86]. More importantly, almost none of these studies implemented a control group, limiting the interpretation of these results.

Performance on the cognition test battery in recent 30- to 60-day head-down tilt bed rest studies has shown a modest slowing across a range of cognitive domains, and most consistently for sensorimotor speed [39, 87]. The observed slowing may have been masked in earlier bed rest studies due to practice effects and missing controls [37, 88, 89] and has been hypothesized to results from an upward shift of the brain with increased brain tissue density at the vertex and somatosensory cortex, which in seen in both space and bed rest [22, 90, 91]. Such sensorimotor slowing was not observed in Scott Kelly's 1-year mission, where—at least for this individual—speed and accuracy on the motor praxis task and other domains of the cognition battery actually increased during the first 6 months in space compared to preflight levels [18].

Spatial Cognition

More complex spatial cognition has been addressed by two long-duration spaceflight studies using a mental rotation task [19, 92]. In a study of eight cosmonauts, of which four on long-duration flights lasting up to up to 199 days, Leone et al. found evidence of a learning effect, such that mental rotation became faster during the mission [92]. A similar learning effect was seen in a control group of four backup crew members and an additional student, although the heterogeneity of the control group and their pooled timelines

limited the interpretation of this comparison. In the second study, mental rotation was assessed in 15 astronauts, with no performance changes after 1, 3, and 5 months in flight compared to preflight levels [19]. This study did not include controls.

Analog studies have not reported evidence of decrements in higher spatial cognition either [35, 93]. Mental rotation improved in various long-duration bed rest studies [88, 89, 94], presumably as a result of practice effects. Mild decrements were originally reported in a study in Antarctic winter-over personnel for mental paper folding [31], although serious problems were found in study design and data analysis [95], and the authors were not able to reproduce the results in later winters [96, 97]. After 105 days of a controlled spaceflight simulation study in the NEK facility in Moscow, no cognitive alterations were detected on visuospatial working memory and spatial reasoning [93].

Whether exposure to spaceflight (or altered gravity) environments have any effect on spatial navigation requires further investigation. Encoding representations about self-to-object relations and integrating this information into a spatial map of the environment will be critical for many future space exploration activities, including piloting a spacecraft, operating a robotic arm, extravehicular activities, and navigating through new territory. Spatial updating has shown to be sensitive to exposure to weightlessness or hypergravity in parabolic flights [68], and considering that the hippocampus, a highly plastic brain region key to complex spatial cognition, is vulnerable to various stressors associated with spaceflight [69], it is important to address the current knowledge gaps around spatial processing during long-duration spaceflight. A specific battery of tasks called "Spatial Cognition" was recently developed to assess visuospatial memory formation, topographic mapping, path integration, and spatial updating [69]. The battery will be implemented during long-term ISS missions, and combined with multi-modal neuroimaging that are expected to provide new knowledge on the relationships between the length of spaceflight missions, brain changes, and their implications for spatial orientation and navigation.

Memory and Learning

Intact memory function, particularly for remembering preflight training and procedures, is crucial for mission success. Anecdotal reports have included memory dysfunction as an explicit concern in astronauts [3, 56], in individuals wintering over in the Antarctic [98, 99], and in those in confined or restricted sensory environments [4, 83]. Currently however, there is little direct evidence to support these anecdotal reports, either in spaceflight or in analog studies. Although subjective, Kanas et al. administered the POMS questionnaire each week to five astronauts and eight cosmonauts during flights lasting 119–203 days, and they rated the cognitive item "forgetful" close to the "not at all" end of the rating scale [6]. Working memory was indirectly assessed via line orientation and cube rotation tasks in a total of 22 subjects, where performance has shown to remain largely intact [19, 23, 78]. A more direct objective assessment of working memory was done in Scott Kelly's 1-year mission, using Cognition's fractal 2-back (F2B) task [18]. Overall, his performance was relatively stable throughout the flight and similar to his twin brother, who performed the same measurements on the ground. Performance decrements that may have involved working memory were only seen in an oriented lines task used by Tacaks et al., but the exact contribution of different cognitive domains in this task remains unclear [23]. With regard to short-term memory, only two tasks have been studied in long-duration spaceflight, and only in two subjects. Kelly showed a reduced accuracy throughout his 1-year flight in comparison to his brother on Cognition's visual object learning test (VOLT) [18]. Polyakov's performance on the Sternberg memory task remained stable throughout his 438-day flight and was impaired only in the days around launch and again after landing, coinciding with periods of high workload, high stress, and re-adaptation [70].

Of the analogs investigated, most studies have not reported memory deficits. Results from the European ISEMSI and EXEMSI studies [84, 100], the 105-day pilot study for MARS500 [93], and the Human Exploration Research Analog (HERA) at NASA [101] have all supported relatively stable working memory with isolation and confinement lasting 30 days or longer. Decreases of working memory were only reported from older Russian isolation and confinement studies that lasted from 7 to 365 days, but these results were not further specified [83]. Similarly, no evidence of major decrements on working- or short-term memory was found after long-duration bed rest lasting 28–70 days [37, 39, 87, 89, 102] nor most studies in Antarctic winter-over personnel [79, 97, 103–105]. Some of the Antarctic studies have even shown steady improvements over time [33, 35, 80, 106, 107]. Unfortunately most of these studies lacked controls, and the often observed inter-individual variability may have masked within-subject effects [81, 103]. Premkumar and colleagues for example found that individuals with higher depression symptoms showed lower scores on a visual memory task in the mid-winter period [103], highlighting the importance of adaptation differences between individuals in these environments and the underlying emotion-cognition interactions [108].

In one well-controlled randomized trial at McMurdo station, 12 subjects periodically performed a match-to-sample working memory task and became impaired (up to 11%) over the first 4 months of Antarctic residence [32]. Participants subsequently received levothyroxine or a placebo. Those receiving the placebo showed continued impair-

ments on the memory task, whereas the intervention group returned to baseline performance. This suggested evidence of significant memory decrements in Antarctic analogs, a mechanism (hypothyroidism), and a countermeasure (levothyroxine replacement). Follow-up studies involving 85 crew members overwintering at McMurdo and the South Pole however were unable to reproduce the result. No cognitive decrements were found over time and between the stations on the ANAM-ICE battery, which includes both working- and short-term memory tasks [106, 109].

Summarized, while the majority of studies did not find any decrements, there have been hints of potential memory deficit in at least some individuals in extreme environments, although it remains unknown to what extent these are related to spaceflight-specific factors. The lack of evidence for memory dysfunction in spaceflight and analog studies may be accurate. However, it is difficult to conclude that given the various confounds in many studies on the topic. In addition, different processes and mechanisms exist for working versus long-term memory, implicit versus declarative or explicit memory, and storage versus retrieval, whereas most experiments to date have focused on working memory. Longer-term memory has only been assessed in one short-duration flight, and only for faces [63]. Thus, memory function—and particularly short- and long-term memory—remains as a largely untested capability in spaceflight.

Regarding learning, various adaptation-based learning mechanisms appear to function during spaceflight, including those mentioned earlier for sensory and motor systems during the first few weeks of flight [56]. Multiple studies have also posited learning confounds to explain performance improvements during longitudinal inflight studies [75, 77, 92]. This strongly suggests that learning is effective during spaceflight, although it is still unknown whether learning is altered relative to non-spaceflight conditions.

In Antarctica and other analogs, some tests revealed a lack of learning where learning was expected [110, 111]. This rare convergence suggests that there may be a reduced capacity to learn new strategies in unusual or stressful environments. In addition, key brain structures for memory formation and retrieval—the hippocampus and basal ganglia—have proven to be highly sensitive to radiation [112, 113] and stress [114] and have shown to be affected after Antarctic overwintering [35] and head-down tilt bed rest [115]. These structures may therefore be uniquely at risk during long-duration spaceflight. In fact, a controlled study of eight individuals overwintering at the Antarctic Neumayer Station by Stahn et al. found a strong linear relationship between individual differences in specific cognitive functions (spatial processing and selective attention) and changes in volume of the hippocampal dentate gyrus, so that greater volume reductions were related to smaller improvements in cognitive performance [35]. The researchers also found lower concentrations of brain-derived neurotrophic factor compared to pre- and post-mission, which is an important regulator of synaptogenesis and synaptic plasticity underlying learning and memory in the brain [116]. Further evidence from rodents flown on biosatellites, shuttle, and ISS missions indicates that long-term spaceflight affects the principle genetic regulators of brain neuroplasticity and dopamine pathways that may be crucial for learning [117]. As such, both memory function and learning require further investigation.

Attention

Like memory, difficulty concentrating or focusing attention is another anecdotal concern for long-duration spaceflight [3, 56, 83, 99]. The evidence available from long-duration studies is limited and has mostly examined dual-task cost: the performance decline between single- to dual-task conditions that mark the limitation of available resources or "cognitive reserve" needed to perform the task. The observations of impaired dual-tasking during short-term spaceflights suggest that higher attentional functions may be particularly prone to the demanding effects of adaptation to space [57, 66, 118] and may at least in part account for the observed manual tracking deficits [67, 71, 77]. On Dr. Poyakov's 438-day flight, an increased cost of dual-tasking occurred primarily during the first weeks in space, and correlated with ratings of physical demand and effort [70]. Others did not find increases in dual-task costs during later flight either [19], except when additional complex motor processing was required [77]. Based on these findings, it has been suggested that general stress and/or spaceflight-specific adaptation processes contribute to high mental load and a reduction of attentional resources as a basis for the observed tracking and dual-task deficits [77].

Other long-duration spaceflight studies did not support inflight attention deficits. The POMS study by Kanas et al. found subjective scores of "unable to concentrate" close to zero in 13 flyers [6], and no performance decrements on the psychomotor vigilance test (PVT) were found in Kelly's 1-year flight [18]. Importantly, attention is a multifaceted cognitive capability [119], and spaceflight studies to date have mostly excluded sustained attention as well as selective and alternating attention paradigms. It may be that certain aspects of attention are altered while others are not or that individual variability plays a key role.

The mainly anecdotal findings of attention deficits in space have modest support from analog studies. Increased performance variability on distributed attention (dual-tasking), changes in allocation strategy, and decreased response time to rare events were reported in the ISEMSI and EXEMSI spaceflight simulation studies [26, 120, 121]. Older isolation studies also reported attention impairments [83, 122, 123]. Over the course of 1 year Antarctic isolation, Terelak et al. found that performance on a demanding 1-hour

continuous math addition test increased only during the initial segments of the task, but decreased in the final segments, suggesting a decline in sustained attention [124]. Mairesse and colleagues showed that at Concordia station, where sleep quality is typically reduced as a combined effect of isolation, confinement, and high-altitude hypoxia, performance on a psychomotor vigilance task was comparable to middle-aged sleep disorder patients [125]. In another Antarctic winter-over study, LeScanff et al. showed that dual-task performance declined mainly during the midwinter period, during which stressors are highest, but not at the end of the year [81]. Other ICE studies, including Antarctic stations [103, 107, 126], stations in Greenland [127], and a study at the Flashline Mars Arctic Research Station (FMARS) in northern Canada [128], have reported stable or even improved performance on attention tasks, but again, all of these studies lacked controls.

Like memory, attention deficits may manifest only in those individuals who are less resistant to the stressful environmental conditions in space. In the Mars500 isolation study, no deterioration of psychomotor vigilance was observed except for the one crew member with the highest ratings of stress and sleep loss [28]. Similarly, in Antarctica, subjects with higher depression symptoms showed poorer attention shifting capabilities in midwinter [103], and crew members with more variable work regimes and higher self-reported fatigue showed a gradual decrease in psychomotor vigilance in contrast to their colleagues with imposed sleep/wake schedules [125].

Finally, while no evidence of major attention decrements were found in most bed rest studies [37], dual-tasking was more recently found to be impaired in a 70-day head-down tilt bed rest campaign in 18 subjects in comparison to controls [38]. In this study, simultaneous functional MRI measurements further revealed that dual-task decrements were associated with increased activation in frontal, parietal, cingulate, and temporal regions of the brain [38]. In line with the cognitive load or cognitive reserve theory and suggested reduction of attentional resources in space [71, 77], these findings imply that more neurocognitive control is needed during head-down tilt bed rest and that such findings could be predictive of changes in dual-task processing or even other cognitive functions during spaceflight.

Executive and Higher Cognitive Functions

Isolating impairments in executive and higher order cognitive function during spaceflight is difficult, as it requires intact perceptual and motor processing, memory function, and attention processing, all of which have shown at least some potential to be altered in spaceflight. Classic executive function tasks have been reported for only two short-duration studies, both using Stroop tasks. One found no performance differences in a 6-day flight [65], while the other found deficits only with personally relevant stimuli during an 11-day flight [72]. For long-duration spaceflight, a looming concern is the effects of the multi-stressor environment on the brain. Radiation [129] and chronic stress [130] appear to affect not only memory structures but also the basal ganglia and prefrontal cortical structures critical for higher cognitive functioning. Several studies have demonstrated alterations in this region after Antarctic overwintering [35], head-down tilt bed rest [115, 131], and after spaceflight itself [132]. These observations underscore the importance of paying careful attention to even mild executive function deficits during long-duration missions.

So far, only grammatical reasoning, digit symbol substitution, abstract matching, abstract reasoning, and risk-taking behavior have been reported as tests of higher cognitive functioning, and each of these tests only in one subject, on missions lasting up to about one year [18, 70]. For both Kelly and Polyakov, performance remained relatively stable throughout their missions. Kelly showed a decrease in abstract matching relative to his Earth-bound twin (control), but the latter had a major strategical insight mid-mission. Interestingly, Kelly also took more risk on the balloon analog risk test (BART) inflight compared to pre- and postflight [18]. Other aspects of executive function remain uninvestigated in space, including inhibitory control, set alternation, error monitoring, or problem solving.

There is very limited evidence of executive and higher order cognitive impairments from analogs. In ICC studies, prior reviews [82, 133] summarized the early literature as supporting no intellectual impairment even up to 60 days. Only a report of older Russian isolation and confinement studies reported unspecified effects in decision-making [83]. Later work in hypoxic chambers, the Mars Desert Research Station (MDRS), the NEK facility and HERA also showed relatively stable performance on tasks including symbol coding, grammatical reasoning, temporal reasoning, abstract reasoning, and Stroop task performance after multiple weeks of isolation and confinement [30, 85, 93, 101, 134, 135]. Only one of these studies included controls [101].

Four Stroop studies have been conducted in Antarctica, with no observed changes [35, 80, 97, 103]. Antarctic winter-over studies have further investigated a large variety of tasks that have involved logical reasoning, abstract reasoning, arithmetical problem solving, decision-making, and processing efficiency [33, 35, 79, 104, 106, 107, 109]. None showed evidence for cognitive decline, although it is important to keep the experimental limitations in many of these studies into account. Out of ten ICE studies for instance, only three implemented controls [35, 97, 106].

Finally, executive functioning was examined in a 60-day head-down tilt bed rest study, including the Iowa Gambling task, 2-back working memory, and a flanker task. Significant impairments were found in the gambling task (in line with

the higher levels of risk-taking on BART mentioned above), although learning confounds were deemed likely in the other tasks [136]. Further analysis on the gambling task revealed that controls exhibited a typical change in strategy across task trials, whereas bed rest participants did not [111]. This provided limited evidence supporting executive function deficits (perseveration) in head-down tilt bed rest. Other bed rest studies found considerable inter-individual variability but no major decrements on mental arithmetic performance, grammatical reasoning, code substitution, and pattern comparison [37, 88, 89].

Overall, the status of executive and higher cognitive functioning during long duration spaceflight basically remains an open question. Analog studies have provided only limited support, with some suggestions that further research—particularly into risk-taking behavior—is warranted.

Cognitive Processing of Emotional Stimuli

Emotional states, including depression, anxiety, asthenia, and euphoria, have been described extensively both in spaceflight [137] and in analog ICE settings [4]. The prefrontal cortical structures that have shown to be at risk during spaceflight [35, 129, 130] are pivotal for the generation and regulation of emotion [138], and in turn, it is a well-known effect that emotional alterations can interfere with cognitive performance [108]. Nevertheless, studies in space or analogs have been mostly devoid of tests addressing emotional processing.

One short-duration spaceflight study in three astronauts found reductions in executive control of cognitive functions with respect to emotionally charged stimuli using an emotional Stroop task [72]. In this study, spaceflight participants exhibited impaired decision-making when the presented words were generically related to personal concerns ("death"), and larger impairments were seen when the emotional words were mission-related ("depressurization"). That is, processing of the spaceflight relevant emotional words was more impaired than processing more generic words. During long-duration spaceflight, emotional processing has to date only been examined in the Twin Study [18]. Kelly was asked to label emotional facial expressions of varying intensities in Cognition's emotion recognition test (ERT) and showed a significant decline in performance from early to late flight compared to this brother. In a 60-day head-down tilt bed rest study, 24 participants also performed the Cognition battery. They required longer time to decide which facial emotion was expressed with increasing time in bed rest and were more likely to select categories with negative valence over categories with neutral or positive valance [87]. However, in another 30-day bed rest study by the same study team in the same research facility, the results were not reproduced [39]. Still, the spaceflight relevance of a deterioration of emotional processing with increasing time in mission cannot be overstated, especially for exploration missions, where astronauts will be confined to a small space with a small group of peers for a period of up to 3 years. Based on these relatively consistent initial findings—and the known interactions between emotion, social functioning, and cognitive functioning—it would appear particularly important to examine in more detail how emotional stimuli affect cognitive processing, and to what extent, in the context of spaceflight or ICE environments.

Cognitive Processing of Social Stimuli

Similar to emotion, there are numerous reports of degradations in social functioning in ICE environments, despite participant pre-screening [4, 139]. These reports range from altered interpersonal relationships and conflict, to clique formation, to self- or group-imposed isolation as with the Spacelab 4 "mutiny" [4, 140, 141]. While studies have been conducted to examine variables such as team cohesion and team performance, there have been no examinations—apart from the Cognition test battery [18]—of cognitive processing of social stimuli during spaceflight or in analog studies. Examples of research include the processing of social cues [142] or social decision making [143, 144]. The absence of this work may be historical: such tasks were not incorporated in early standardized task batteries [145] from which the ANAM [146], AGARD-STRES [42], WinSCAT [43], and other batteries were derived. Given the high priority placed on the psychosocial aspects of spaceflight, and because of the importance of emotion identification abilities to long-term social interactions, the ERT test was included in the cognition battery for future cognitive assessments in space [44].

Operationally Relevant Performance

The relevance of testing operational performance for long-duration missions has been highlighted by the collision of the unmanned progress supply vehicle with the Mir station in 1997, which was teleoperated by the station's commander after 136 days in orbit [141]. Five more significant incidents happened when teleoperating the Canadarm2 or Mobile Transporter on the ISS, including a collision with a Shuttle payload bay door, and several close calls [147]. An opera-

tionally relevant test is an important and often overlooked component of cognitive assessment that can provide further insight in complex skill acquisition and maintenance during long-duration spaceflight missions. So far, however, the experimental evidence of operationally relevant performance in space has been even more limited than that from elemental cognitive tasks.

The first assessments of operational performance were made during the Skylab 2, 3, and 4 missions, with flight periods of 28, 59, and 84 days, respectively. Calculating operational efficiency on a large number of operational tasks from schedules and video material, the investigators found that performance improved as the missions progressed [9, 10]. While attributed to the waning of initial motor and physiological adaptation processes, these measures were almost certainly influenced by task-specific learning effects (e.g., learning how to manipulate objects in 0g, how to efficiently use the stowage facilities, where to find the handles, how to operate the fasteners, etc.).

So far, the only operational performance assessment platform that has been both tested in spaceflight and integrated in training flows is the PILOT Soyuz docking simulator, which has been implemented on Mir and ISS to investigate the performance of manual docking during different stages of long-duration spaceflights [49, 50]. This research has demonstrated that performance levels were sufficiently high on Mir according to safety standards, although preliminary findings showed that the reliability of manual docking on Mir was decreased even in well-trained astronauts after a period of 3 months without training [148]. This highlights the importance of a training program that facilitates the retention of complex skills in space. Further analysis in 17 cosmonauts on 6-month missions did not show changes in docking performance comparing pooled inflight data to preflight [49], but further analysis of changes throughout the flight was not explicitly reported. Due to the investigators' emphasis on developing a prediction model to facilitate the assessment of docking performance in general—thus including training—their analysis did not correct for practice effects and did not include controls.

Based on PILOT, the 6df system has more recently been developed as a self-sufficient training program for manual docking that allows for the assessment of the training process as well as performance maintenance. 6df has been implemented during the Mars500 project, during head-down tilt bed rest, and has been used on board the ISS since 2015 [29] (Fig. 4.2). While individual learning curves have recently been characterized [149] and direct links with performance on the cognition test battery have been demonstrated [48], no results from spaceflight or analogs have been reported thus far. Such findings will provide interesting insights into the evolution of operationally relevant performance inflight.

Docking performance on different Soyuz flight simulator was also assessed in 44 overwinterers on the Antarctic stations Halley VI and Concordia [36]. Subjects were divided in two groups preforming the task at either 1- or 3-month intervals. In all campaigns, a trend of improved performance was seen over time as a result of practice, with the frequent flyer group (10 sessions throughout the campaign) showing much better performance compared to the infrequent flyers (four sessions throughout the campaign). Comparison of steering errors showed that in the infrequent flyer group, errors were higher in Concordia (where stressors are highest), still existed in Halley VI, and were unchanged in a control group. In line with the observations from the PILOT study, this suggests that ICE environments may affect complex skill retention especially if not regularly practiced.

For assessment of performance on the Robotic On-Board Trainer, which is used for astronaut training on Canadarm2 track-and-capture activities, a research version of the system, ROBoT-r, has been developed as well [51]. In a total of 36 crewmembers in 45-day isolation studies at NASA's HERA facility, subjects exhibited significant learning. Interestingly, after adjusting for learning effects, significantly poorer performance was found on all performance metrics when crew members were inside the facility, versus before and after isolation [150]. Further testing in astronauts during 6-month spaceflight aboard the ISS is currently ongoing, but no results have been reported yet.

Other operational performance assessment has been done using the Cabin Air Management System (CAMS), which simulates a spacecraft's life support system that requires the management of multiple task goals. Relatively stable performance was found in three cosmonauts during the "Human Behaviour in Extended Spaceflight" (HUBES) ICC study, simulating a 135-day Mir spaceflight [27]. In an Antarctic winter-over crew, a number of subtle indications of hidden decrements were reported [110].

The prolonged learning curves for complex tasks, in combination with the operational constraints and small number of available subjects in spaceflight studies, challenge the assessments of operationally relevant performance in space. While operationally relevant testing may perhaps not be able to detect specific cognitive decrements, this approach greatly simplifies the definition of safety margins and implementation of Go-No Go decision rules based on the performance on such tasks. This is especially valuable in the face of increased autonomy during future exploration missions and the potentially degraded ability of astronauts to critically assess their own performance [151].

Fig. 4.2 Astronaut Scott Kelly using the 6df docking assessment platform during the joint US–Russian 1-year mission on board the ISS. Credit: NASA/RKA

Cognition upon Return to Earth

Most of the acute physiological effects associated with spaceflight occur around launch and landing, when astronauts are exposed to gravitational transitions. Upon re-entering Earth's gravity field, crew members experience sensorimotor disturbances that are similar to the adaptation effects seen during the first days in space, including motion sickness, postural and gait dysfunctions, and proprioceptive and visual illusions [56]. These effects are likely the result of inflight deconditioning of otolith-mediated reflexes, requiring readaptation to the gravitational input experienced on Earth. The time constant of recovery after flight is generally related to the duration of the stay in space, with longer duration flights generally associated with longer recovery periods [56].

With regard to cognition, most spaceflight studies of up to 21 days have not shown evidence of postflight cognitive alterations [12, 14, 57, 64, 65, 67, 152]. There have been some suggestions of decreased aiming and tracking performance [118, 153] and attention deficits [16, 71] in the days after flight, quite similar to what is found during the initial days in space, but the evidence from these studies remains inadequate to draw any conclusions, mostly due to low statistical power and lack of controls. Nevertheless, results from the shuttle era demonstrate that even short-duration missions can affect pilot performance, where 20% of orbiter landings were outside of acceptable speed limits, and the hardest touchdown on record occurred following the commander's momentary loss of orientation [154].

These findings are particularly important in light of upcoming exploration-class missions, where longer-term exposure to spaceflight stressors and the reintroduction to (partial) gravity have the potential to impact operator proficiency during critical landing and post-landing operations on the moon or Mars—with no support-personnel available on the ground. Using both elemental cognitive tasks and a driving simulator, Moore et al. found that after six months in space, astronauts exhibited significant deficits in manual dexterity, dual-tasking and motion perception, and a striking degradation in the ability to operate a vehicle on the day of return to Earth [17]. In this study, performance recovered to baseline levels by the second postflight measurement at 3–5 days after landing. Tacaks et al. however observed decrements after 6-month flights on visuospatial tasks that recovered only 2 or 3 weeks after landing [23], and Dr. Polyakov did not show recovery after his 438-day flight up to 2 weeks [70]. Most strikingly, Scott Kelly's cognitive data, which remained relatively stable during his 1-year flight, showed a postflight decline on almost all domains of the cognition battery that was still present 6 months after his flight [18]. These findings suggest that extended mission durations that allow for a complete adaptation to space conditions may require a more demanding re-adaptation process.

On the other hand, not all studies have found cognitive impairments after long-duration flight. In 15 ISS astronauts, Tays et al. found declines in balance, mobility, and bimanual coordination after 6 months in space, but no changes in cognitive-motor dual-tasking, visual field dependence for spatial orientation, spatial working memory, and cognitive processing speed [19]. In another 12 ISS astronauts, Roberts et al. observed faster reaction times on almost all WinSCAT subtests with sustained accuracy at approximately 1 month postflight and found no significant association between mission length and performance on any of the subtests (code substitution, delayed code substitution, delayed matching to sample, mathematical processing, and continuous performance) [22].

In analogs, post-mission decrements have not always been assessed or have been assessed at different post-mission time intervals. In the ICC and ICE studies, no alterations were found [27, 35, 80, 84, 93, 96, 106, 109, 110, 155]. After 30–60-day bed rest, cognitive slowing was observed across multiple domains on the cognition battery, which gradually returned to baseline levels within 1 or 2 weeks [39, 87]. Others did not find cognitive deficits after bed rest [156].

Again, multiple explanations can account for these ambiguities. Many studies are methodologically limited by operational constraints, such as reduced testing capabilities in these environments, and limited availability of crew members immediately postflight due to schedule conflicts or travel requirements. In addition, the complex interactions of (post) spaceflight stressors and the varying mission and crew dynamics make it hard to disentangle the relative contributions of re-exposure to gravity, other spaceflight-specific stressors, and demanding elements that characterize the postflight period. For example, besides vestibular deconditioning, returning astronauts may also have accumulated stress

from isolation, confinement, and high workloads depending on mission duration. They must then transition from an environment somewhat insulated from outside happenings and with a single primary focus (i.e., mission success) back to a world with multiple pulls on their time and attention, including participation in research studies, media attention, and reintegration into everyday life. All these factors may affect postflight cognitive functioning [1]. Unfortunately, it is not known how to extrapolate from our current datasets to the postflight effects of exceptionally long duration missions such as a two-and-a-half-year mission to Mars or to the effects of landing on a planetary surface far away from home versus Earth. A better understanding of which cognitive functions are particularly vulnerable to postflight readaptation and how they are affected by these different factors is seriously needed.

Neuromapping

Neuro-structural responses to spaceflight have been discussed in Chap. 5. Here, we will primarily focus on findings of structural and/or functional changes in the brain in relation to performance on cognitive tasks. So far, several MRI studies after short- and long-duration spaceflight have found widespread structural changes in white and gray matter, including regions involved with motor and coordination, visual, vestibular and proprioceptive processing, but also higher-order visuomotor control, visual recognition (object, facial, emotional), spatial representation, and visually guided decision-making, and language comprehension [157]. These reorganizations also seem to be more pronounced with increasing mission duration [22, 91, 158–160]. Decreases in functional brain connectivity have also been found within the right insula, which is involved in vestibular processing and cognitive control, and between the cerebellum and regions with proprioception, visual, motor, and somatosensory functions [21, 161]. The cerebellum is important for coordination and fine-motor control as well as cognitive performance and is believed to play a significant role in sensorimotor adaptation to microgravity [157, 162]. However, there have been only two MRI studies to date that have directly investigated the associations between such postflight changes and performance on cognitive and motor tasks. In 12 ISS astronauts who performed the WinSCAT battery as part of the NASA Lifetime Surveillance of Astronaut Health protocol, Roberts et al. found that volume changes in three white matter regions within 3 weeks after flight—the left and right optic radiations and the splenium of the corpus callosum—correlated with altered reaction times on the sustained attention test [22]. Those astronauts with the least reduction in reaction time postflight showed the greatest change in local volume in these regions. Although there were no correlations found with any of the other WinSCAT subtests in this relatively small sample, these findings suggest that the spaceflight-related brain changes may have measurable behavioral consequences. In the second study by Hupfeld and colleagues, pre- and postflight functional imaging was done during vestibular stimulation in 15 astronauts [163]. Reductions in visual and cortical deactivation were linked to postflight balance changes, but no associations were seen with postflight performance on a visuospatial processing task. Besides vestibular stimulation, functional imaging was also done for spatial working memory and dual-tasking, but these results are still to be reported.

Structural brain changes have also been associated with cognitive performance in analog studies. After an Antarctic winter-over, Stahn et al. found that reductions in dentate gyrus volume were associated with lower cognitive performance in tests of spatial processing and the resolution of performance conflicts [35]. In addition, decreases in gray matter volume were found in frontal areas that are pivotal for executive control such as response inhibition, working memory, and cognitive flexibility [164], but also the generation of emotion [138]. Data from the MARS500 study showed decreases in white matter integrity of the right temporoparietal junction, which may play a critical role in responding to unexpected events and social processes [165, 166]. Finally, MRI during and after long-duration bed rest studies have shown to mimic some of the changes found in spaceflight, including decreases in fronto-orbital and temporal gray matter [90, 115, 167], and functional connectivity changes in motor, visual, somatosensory, and vestibular areas of the brain [158, 168, 169]. Decreases in functional connectivity between these areas have been related to increased response consistency on a visuospatial processing task, suggesting that the functional decoupling—a potential reflection of sensory re-weighting to facilitate adaptation to the microgravity analog environment—may ultimately result in improved visual orientation perception [169]. In line with the alterations found in decision-making under risk during bed rest [111], others found evidence that the ventromedial prefrontal cortex—a principal component of risky decision-making—showed less deactivation after 45-day bed rest when performing the balloon analog risk task [131]. This reduction was hypothesized to be related to a decreased level of value calculation after bed rest. Functional imaging during head-down tilt bed rest have further shown an increased activation in frontal, parietal, cingulate, and temporal regions during dual-tasking, suggesting a reduction in cognitive reserve [38].

EEG studies have also been performed in space [170, 171]. It has been the only capability to date to measure in-flight brain activity changes, due to its portability. Measurements of electrocortical activity have mostly been

performed in rest or with simple visuomotor tasks to measure different attentional states, and findings of altered alpha and mu rhythms suggest an increased processing demand to integrate incongruent vestibular information and stabilize posture in microgravity [171–174]. EEG changes in relation to cognitive task performance have only been measured by Tacaks et al. [23]. They found clear decrements in event-related potential (ERP) components suggesting that participants had reduced capacity to perceive unexpected, novel stimuli. The reductions were mostly seen at the frontal electrode sites and were associated with impaired performance on a spatial orientation task. Similar results were found during the 60-day EXEMSI isolation study using an auditory classification task [175], but not on a flanker-type paradigm in Antarctic winter-over personnel, probably because of the predictable nature of this task [126].

In summary, several studies have noted brain alterations after spaceflight and analogs and more pronounced alterations with increasing mission duration. However, there is not enough evidence to understand to what extent these changes affect cognition, and if they represent compensatory phenomena or maladaptive dysregulation [157]. Moreover, these studies have been performed in missions lasting no longer than 6 months. If and how brain alterations progress during longer periods of spaceflight exposure, such as during a multi-year interplanetary expedition, has not been investigated. The literature to date highlights the need for further studies on human brain adaptation to space in correlation to cognitive functioning, and multiple efforts are currently underway to examine these effects in long-duration spaceflight. Future modalities, including magnetoencephalography in combination with EEG for more accurate measurements of ionic motion in the brain, and inflight near-infrared spectroscopy (NIRS) to map hemodynamic responses at high temporal resolution inflight [176, 177], may assist in the goal of developing comprehensive cognition monitoring and countermeasures strategies for future long-duration space exploration (Fig. 4.3).

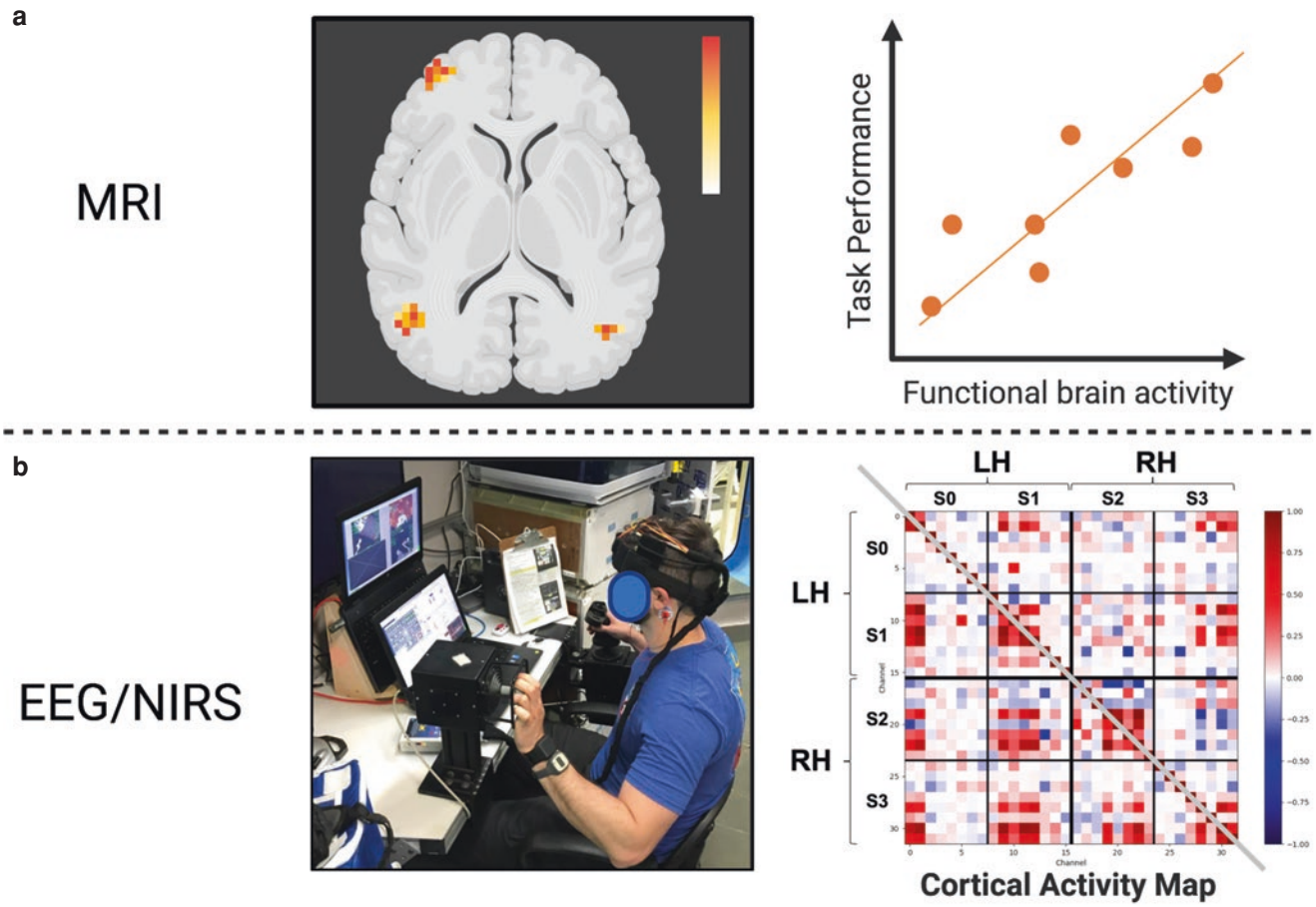

Fig. 4.3 Neuromapping. (**a**) Pre- and postflight functional MRI data may identify specific regional changes associated with spaceflight exposure that can help guide countermeasure development and monitor training and rehabilitation status. (**b**) Since MRI is not available in space, inflight use of event-related potentials (ERPs) and/or NIRS could provide images of task-related regional cortical activity and functional connectivity to help gauge cognitive capabilities and operator status during long-duration spaceflight. This figure is a conceptual illustration. Credit for photo: NASA—V. Ivkovic; Created with BioRender.com

Summary

The current evidence from spaceflight-relevant cognition studies is inadequate to strongly support or refute the existence of any generalized deficits, despite the steady stream of anecdotes about cognitive challenges. Experimental data remains particularly lacking for executive, emotional, and social processing. Findings so far indicate that cognitive changes may occur mostly around launch and landing—periods that include gravity alterations and high adaptational demands. These changes seem mostly limited to sensorimotor adaptation, and there are some suggestions that attentional functions are particularly prone to an increased cognitive load and stress in space-like environments. The possibility of developing cognitive decrements during long-duration spaceflight—particularly memory and attention—has been suggested by some analog and brain imaging studies, even though promising results from Polyakov and Kelly demonstrate intact inflight cognitive functioning for a year or more in low Earth orbit.

Basically all findings are based on an extremely small number of subjects, and a variety of different methods for any given cognitive function. Moreover, due to learning or other confounding variables, many study results have been difficult to interpret. Perhaps the most consistent finding recurring across all studies and environments is that novel environments (spaceflight or other) induce variable alterations in cognitive performance across individuals. This highlights the potential risks of generalizing from small groups or case studies, and the need for research into underlying individual factors that pose a risk of cognitive decline.

While our focus on potential cognitive impairment in space is crucial for safe and successful space exploration, it must be noted that most studies to date, both in space and analog environments, have not identified any major impairments. A substantial number even showed improvements over time. We have discussed the various methodological limitations of these studies, but it remains important to acknowledge that overall astronauts have been highly successful in space missions. They have been performing extremely demanding cognitive and physical tasks with positive outcome, including in numerous off-nominal situations. They have accomplished to venture beyond their Earth-imposed limits, going further and longer into the extremes of space than ever before—all with minimal impact on behavior and health. Yet, the lack of adequately powered studies to date, the infrequent use of controls, and the especially high consequences of cognitive or behavioral failure for mission success call for perseverance in our efforts to fully understand how spaceflight may affect cognition.

Potential Positive Effects

A particularly important and often overlooked explanation for the lack of evidence of cognitive decline in space may come from the positive psychological effects often reported by astronauts [3, 178], which is mirrored in other ICE environments [24, 179]. The beauty and grandeur of the environment, the camaraderie and mutual support of the team, and the thrill of facing and overcoming the challenges of the environment may all contribute to psychological benefits such as heightened strength, depth of insight, improved relations with others, increased self-confidence and humane values, and many other favorable psychological changes [180]. Such effects have been described under the term "salutogenesis," or "health-generating" [181]. In Antarctic crews, positive experiences have been reported much more frequently than negative ones, and like astronauts [180, 182], many volunteer to return for repeated assignments [179, 183, 184]. Responses of astronauts on measures of postflight personality changes have shown general increases in various aspects of positive psychological development [182, 185], and a follow-up study on Antarctic overwinterers of the American Operation Deep Freeze Program even showed that they had better health records after their return and more successful careers than a control group [186]. Although from the available evidence it has not been possible to separate the observed cognitive improvements in some spaceflight and analog studies from practice effects, the positive psychological effects of such undertakings may act as separate important mitigating factor in the face of multiple space hazards, both in- and postflight.

Risk Mitigation Strategies

In order to mitigate a potential cognitive decline in space, the goal is generally threefold, namely (1) prevention through reducing environmental stressors or increasing the crew's capacity to cope with the challenges, (2) providing the means for early detection and countermeasure application, followed by (3) treatment methods as needed [1]. A wide variety of strategies is currently used for long-duration missions to the ISS, including the selection of crew members that are resilient to the various stressors of spaceflight, preflight behavioral health and performance training such as conflict and stress management, pre- and inflight psychological monitoring and support interviews, regular inflight cognitive assessments on WinSCAT, inflight social interaction support and crew care packages that bring familiarity in the novel environment, inflight training on operational tasks, and inflight medical kits to cope with a variety of medical emergencies—including psychiatric conditions [1].

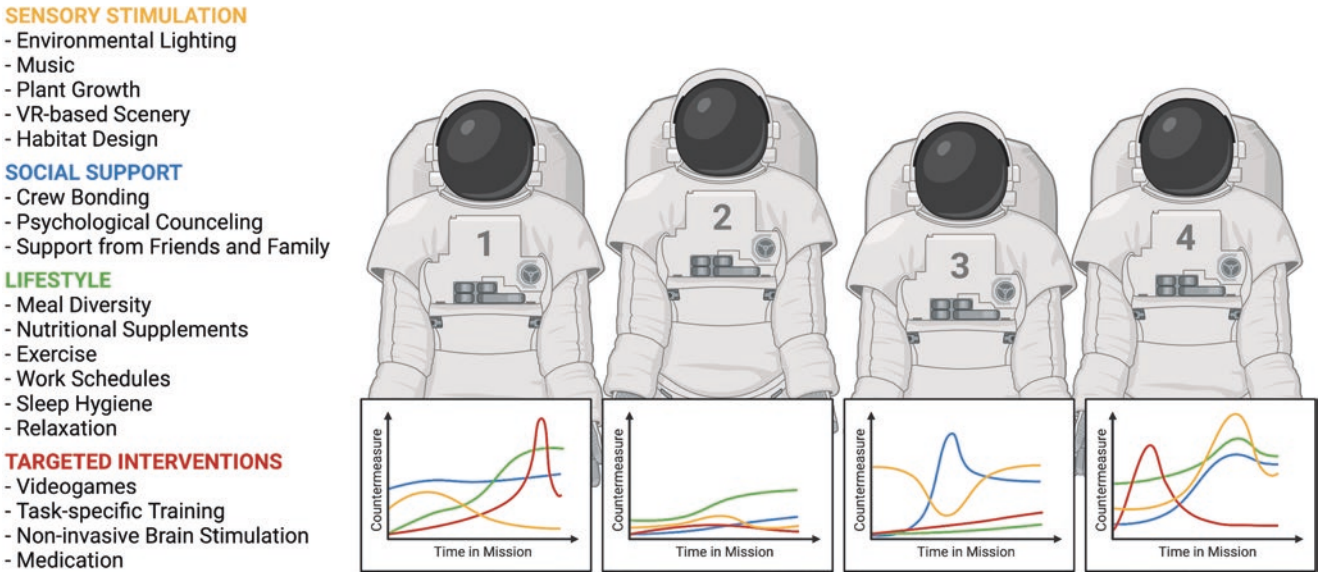

Fig. 4.4 Examples of individualized countermeasures to mitigate adverse cognitive and behavioral effects during long-duration expeditions. The use of countermeasures will vary between and within individuals, and the relative importance of specific strategies will vary over the course of the mission, requiring a constant evaluation of and tailoring to individual needs. Created with BioRender.com

While current practices allow for direct communication with psychological support specialists on Earth, crew members will be required to monitor their behavioral and cognitive status and autonomously implement countermeasures when on exploration missions. Comprehensive and objective methods will be needed that can assist in self-assessment and operational decision-making, such as regular performance on the cognition battery and operationally relevant tasks while using predefined cut-off rules. In addition, wearable inflight neuromapping capabilities such as EEG and functional NIRS may assist in predicting cognitive decrements before they manifest in behavioral changes, through measures of cognitive load and psychophysiological activation [176, 177, 187]. Neuromonitoring may also facilitate the identification and monitoring of brain networks and functional changes that could be targeted by specific countermeasures.

For future countermeasure design, it is important to take the substantial interindividual variability of the cognitive effects of spaceflight into account. Countermeasures will need to be both personalized and dynamic, in response to individual needs as a function of mission duration. Besides, it is expected that there is no single countermeasure that will serve as a universal remedy, and it is likely that the response to countermeasures will also vary between individuals. As such, combining multiple methodologies and approaches may be needed (Fig. 4.4) [69].

A variety of countermeasures for future exploration missions have been investigated and proposed, including lifestyle interventions such as exercise [188], nutritional supplementation [189], and altered lighting [190]. Other preventative measures could include mindfulness and relaxation techniques, which may provide the psychological resources needed in extreme environments to reduce stress and increase performance [191]. Recent findings from the MARS500 study and ISS missions of gut microbiome changes [18, 192–194]—which may have direct effects on cognition, emotion, and social behavior [195]—suggest potential intervention strategies based on probiotics. In addition to these more general solutions, countermeasures can also target specific cognitive domains. Specific types of video gaming have the potential to enhance brain plasticity [69, 196, 197], and specialized training programs may help improve operational performance skills [29]. The adaptation of such training systems to reshape specific brain networks would be greatly enhanced by the identification of brain plasticity mechanisms and functional brain changes underlying cognitive alterations [198]. Besides training regimes, exposure to sensory stimulation paradigms via virtual environments [199] and noninvasive brain stimulation methods, including transcranial magnetic and electrical stimulation, could also target specific regions to enhance inflight performance, or postflight rehabilitation strategies [200].

Future Directions

Plans are currently made to send expeditions to Mars within two decades. Given the current deficiency of cognition data in space, space agencies should do all they can to better understand—and potentially mitigate—the risks to the brain

and cognitive functioning so that they can safely support exploration class missions. The most obvious requirement will be an ongoing, standardized, occupational monitoring program that is feasible and sensitive enough to assess cognitive performance and underlying brain changes during long-duration flights. By using standardized measures on the ISS and in analogs, results can be pooled across experiments to obtain sufficient statistical power, as well as being compared between different environmental conditions. NASA is making progress in this direction with the cognition test battery [47, 201, 202], which will be tremendously helpful in this endeavor. The establishment of normative data and learning curves for operationally relevant assessment methods is also underway [51, 149, 203], and associations between performance on these different methods are being evaluated [48].

Further assessments will be needed across multiple cognitive domains, including spatial cognition, various aspects of attention, short- and long-term memory, various aspects of executive functioning, processing of emotional and social stimuli, and complex operationally relevant skills. Experiments are also needed into the effect sizes of individual factors that pose a risk to cognitive decline, as well as the effect sizes and potential interactions of different spaceflight stressors, ranging from drug-drug interactions to the residual effects of sleep medications plus microgravity, to radiation plus social stress. The incorporation of neuroimaging modalities, including novel inflight monitoring capabilities, will increase our knowledge of the effects of spaceflight on behavior-related brain plasticity changes, and help enable targeted countermeasures to assist crewmembers during these missions. These investigations will take time. Spaceflight studies are highly constrained by operational requirements and involve lengthy processes to design and implement. Plus, if serious concerns are identified, prevention methods and countermeasures need to be developed. Appropriate use of key Earth analogs will help greatly accelerate the knowledge gathering process.

In addition to the short-term plans of governmental space agencies, it is important to consider the recent accomplishments from private space companies as well, which have led to an increasing amount of flight opportunities for "space tourists." While all research to date has been done in highly selected astronauts, less strictly selected individuals are now engaging in suborbital flights, multi-day space station visits, and may soon follow government agencies into deep space. To what extent this population is able to endure the stressors of spaceflight and to what extent mitigation strategies will be needed to maintain brain and cognitive health is not well known and will require further—and perhaps even different—testing. Still, these recent developments in human spaceflight bring unprecedented opportunities to the research community to finally acquire a comprehensive understanding of how spaceflight affect human cognition and its underlying neural bases, and map the adaptational limitations of humans in space.

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Spine Biomechanics and Pathology

5

Lucas Brane and Jeannie F. Bailey

This chapter will discuss the effects that spaceflight has on spine biomechanics, the central nervous system, and resulting pathology as they apply to the astronaut both during spaceflight and postflight recovery. Both the biomechanical and pathological effects that spaceflight poses on spine health are important to understand not only as barriers to mission success, but with the right countermeasures in place, could also represent a preventable occupational hazard. As missions increase in duration and destinations become more remote from a source of outside assistance, the understanding of potential mission-threatening risks on spinal function and health will be paramount in anticipating and mitigating these decrements.

History of Back Pain and Spinal Injury Associated with Spaceflight

Spinal problems occurring from spaceflight were first reported dating back to 1977 [1, 2] (Fig. 5.1). Symptoms included inflight back pain during the initial phase of spaceflight "space adaptation back pain" [3], postflight low back pain, and disc herniation [4]. The prevalence of inflight space adaptation back pain (SABP) ranges from 52 to 68%, begins within the first 6 days of spaceflight, and is reported to be mild in severity in 86% of cases [3, 5]. During the shuttle era, back pain was the fifth most common reason given for medication use [6, 7]. The lower back is affected in 86% of SABP cases [3]. An existing history of low back pain (LBP) predicted risk for developing space adaptation back pain, leading to a significantly longer duration of low back pain experienced in space and often impacting additional spinal regions [5]. Space adaptation back pain often resolves within the first 12 days of spaceflight and is most commonly alleviated by assuming a "fetal tuck" stretching position where individuals bring their knees to their chest. Space adaptation back pain is often compared to adaptational back pain experienced during prolonged bedrest [5, 8], however with greater pain intensity, and experienced over a longer duration of time.

Following spaceflight, astronauts experience a heightened risk of intervertebral disc herniation or herniated nucleus pulposus (HNP). Disc herniation results from a bulging or extrusion of the nucleus pulposus due to compressive forces and/or weakened annulus fibrosus tissue [9]. The bulging or extruded disc often compresses or irritates the spinal nerves on the posterolateral side of the disc and compression on the spinal nerve roots can cause radicular pain and neurological deficits. The incidence of disc herniation (both cervical and lumbar) was 4.3 times higher in the US astronaut population compared to matched controls not involved in spaceflight [4]. Notably, astronauts incidence of cervical HNP was significantly elevated over the control group at 35.9 times higher in the first 12 months after spaceflight and a lifetime incidence that was 21.4 times higher than the control population [4]. Despite this increased risk of cervical HNP, the low back remains more affected overall with nearly 60% of postflight disc herniations in astronauts reported to occur in the lumbar spine [4]. The lower incidence of lumbar herniation compared to control group likely reflects the general population's propensity to manifest injury or wear and tear damage to their low back more often than their cervical spine region.

Importantly, compared with data on terrestrial backpain, there is a paucity of equivalent data as it relates directly to spaceflight. At the time of this publication, less than 600 people have flown into space, and of that number, less than 500 were for long-duration missions. Much of the early spaceflight program did not focus on collecting data on symptoms like back pain, instead, reasonably enough, focusing on hemodynamics, reaction times, and other acute physiologic considerations that could disrupt the mission. However, as missions have changed over time, the medical

L. Brane
Department of Physical Medicine and Rehabilitation, University of Pittsburgh, Pittsburgh, PA, USA

J. F. Bailey (✉)
Department of Orthopaedic Surgery, University of California, San Francisco, CA, USA
e-mail: Jeannie.Bailey@ucsf.edu

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Fig. 5.1 Roy Gagnon coinvestigator, conducting a training session on NASA's KC-135 microgravity simulator with subject Ken Money, Canadian astronaut. Reproduced with permission from(Wing et al. 1991)

considerations have broadened to include more chronic pathologies. To date, much of the data supporting the hypotheses behind spinal issues in spaceflight come from the terrestrial bed-rest literature, where analogous symptomology can often be found.

Comparing Epidemiology of Spaceflight-Related Low Back Pain to Terrestrial Low Back Pain

Back pain is a symptom, and not a disease, with many causal factors that are not always clearly associated with each presentation. LBP, in particular, is of concern as it is the leading cause of disability and economic burden due to work absence throughout much of the world [10, 11]. In terrestrial populations, low back pain is an extremely common phenomenon with a global point prevalence of 8% [12]. In astronauts, low back pain is one of the most common problems experienced in flight as well as postflight [3, 13].

There are some important distinctions in astronaut populations compared to terrestrial populations when considering the epidemiology of back pain. For terrestrial populations, both obesity and physical inactivity are significant predictors for low back pain [14]. Astronauts must maintain excellent physical conditioning as part of their training which obviates both obesity and sedentary behavior as factors for developing or exacerbating back pain. The pathology associated with obesity-mediated low back pain likely has to do with chronic hyper-loading of the spine and poor spine mechanics, as opposed to the chronic unloading associated with the microgravity environment of spaceflight. Additionally, there is a significant psychological and psychosocial component to chronic low back pain presentation in the general terrestrial population which often occurs concurrently and is possibly exacerbated by depression, anxiety, stress and economic uncertainty associated with lower-income socioeconomic groups [14, 15]. Among terrestrial populations, there is also a component of possible over-reporting in some cases as a means to gain compensation or time away from work, or in conjunction with the previously mentioned psychological components, as somatization of unaddressed psychological illness [16].

In terrestrial populations, the medical or musculoskeletal diagnosis associated with back pain is usually not predictive

of the degree of persistent disabling back pain [17]. Instead, it is the concurrent presence of psychiatric disease, poor physical function, low general health status. and maladaptive pain coping behaviors that predict the severity of impact from LBP. These difficult-to-quantify aspects of back pain presentation are largely not reflected in the astronaut population. It is not as though astronauts cannot experience anxiety, depression, or maladaptive pain coping behavior, but that if they have, it has not significantly hindered their performance. Astronauts are screened rigorously and selected from a pool of superbly resilient recruits who have already proven themselves to be so by coping well in other high-stress environments over time. Additionally, the astronaut population has been known to under-report symptoms to avoid the loss of flight status and are not typically experiencing socioeconomic hardship. As a result, studying causes of back pain in astronauts can be particularly revealing as they (as a population) lack many of the other confounding features known to influence back pain presentation. Therefore, the possibility of being able to better associate a particular identifiable pathology with the severity of symptoms seems more promising in the astronaut population, who are already so carefully monitored and assessed for optimal health over time.

Spinal Anatomy Affected by Gravitational Load

To better understand how prolonged exposure to microgravity can uniquely influence the incidence of back pain and spinal disorders in humans, we need to consider the effect of altered load on the diverse tissues of a spinal motion segment. An individual spinal motion segment includes two adjacent vertebrae connected by an intervertebral disc ("disc") and two facet joints. The human lumbar spine includes five motion segments spanning L1 through S1, stabilizing ligaments, and trunk musculature. The vertebral bodies are cylindrical and are built to absorb load without catastrophic fracture [18]. They are comprised mainly of trabecular bone and have a nutrient-rich interior with many blood vessels. The intervertebral disc is essentially a large ligament, serving as a viscoelastic joint between vertebral bodies, permitting intersegmental motion and absorbing axial load. The intervertebral disc is an avascular structure and is dependent on diurnal loading cycles to receive nutrients from adjacent vertebral bodies [19]. Nutrient transfer between the vertebral body and discs is dependent on load bearing, and this, in turn, maintains healthy discs. The well-being of the intervertebral disc can, therefore, be considered load dependent and is disrupted without diurnal gravitational loading. The effects of disuse and unloading are problematic for muscle health at large, and the human spine in particular is dependent on many specialized muscles supporting the mechanical demands of upright posture. Looking across several spinal tissues, including the intervertebral discs and paraspinal muscles, each of which are distinct stabilizing tissues of the spine and could contribute to risk for spaceflight related spinal injuries and pain.

Intervertebral Discs

Spaceflight-associated spinal problems were reported as far back as 1977 [1, 2], including inflight back pain [3] and postflight disc herniations [4, 20]. Originally, the pathophysiology of these inflight and postflight spinal problems was not reported/declared, but it was hypothesized to be a result of possible elevated disc swelling that could be associated with the apparent changes in spinal alignment and height during spaceflight and bed rest [1, 21–24]. This potential increased swelling during spaceflight could result in discs returning from space with greater hydration and presumably more vulnerability to herniation with compression from load bearing after returning to earth. Bedrest is considered to be an analog for spaceflight, and prolonged bedrest is shown to be associated with increased disc height long after upright posture is resumed [8, 25, 26]. However, there are only two studies that quantify changes in disc swelling following spaceflight, and neither find significant changes in disc size or water content [23, 27, 28]. Furthermore, animal studies on rodent disc properties following spaceflight do not show an increase in lumbar disc height or hydration [29].

Discs may still be swelling due to a supraphysiological state during spaceflight, but previous longitudinal astronaut data along with a previous bedrest study [22, 27] suggest that any effect from prolonged unloading on disc swelling is no longer present shortly after reintroduction of axial spinal loading under gravity.

Paraspinal Muscles

More recently, the effect of spaceflight on the paraspinal muscles has become a point of interest. The paraspinal muscles, particularly the multifidi, serve a key biomechanical role in stabilizing the lumbar spine segments in response to postural load and motion. As such, the paraspinal muscles are also linked to LBP, though the exact relationship between the paraspinal muscle changes and back pain is still under investigation.

Given the important role of the paraspinal muscles in stabilizing the spine and upper body in upright posture under gravitational load, then prolonged unloading would lead to decreased activity and atrophy of these muscles. Spaceflight-induced atrophy of these muscles could lead to postflight biomechanical instability, resulting in low back

pain and risk for disc herniation [27]. However, the extent by which the paraspinal muscles are affected by microgravity is unclear. Recent studies do show that the lumbar paraspinal muscles experience some degree of atrophy following spaceflight [27, 28, 30–32]. The inconsistency between study results may be, in part, due to variability in imaging methods and assessments. However, another factor that may influence inconsistency in results may be variability in exercises conducted in space by each crew member. These recent muscle studies follow crew that stay at the International Space Station, where there are exercise devices that can engage the spinal muscles by bearing the upper body during more aerobic and resistance exercise. The current version of the treadmill on the ISS, Combined Operational Load-Bearing External Resistance Treadmill, or COLBERT, utilizes a harness that loads the shoulders and, to a lesser degree, the hips. This harness is then connected to the treadmill frame by bungee cords that provide varying degrees of load, up to 60% of body weight. The Advanced Resistance Exercise Device (ARED) allows astronauts to perform up to 29 different free-weight-type resistance exercises with up to 270 kg of resistance force. The ARED uses a combination of lever arms and vacuum pistons to provide the force resistance and is connected to the structure of the ISS via vibration damping mechanism to protect the spacecraft during its use.

Changes in Spinal Biomechanics During and After Spaceflight

The human lumbar spine biomechanically supports upright posture and provides three functions: to protect the spinal cord, to facilitate motion between the upper body and pelvis, and to transfer load from the upper body to the pelvis [33]. During spaceflight, gravitational load is removed and astronauts often experience mild to moderate adaptational low back pain that develops within the first few days of orbit [3]. The cause of the SABP is unknown but thought to be a result of the assumed stretching and elongation of the spine in space [1, 24]. The spinal column is shown to elongate by 6% on average during the first few days of spaceflight which is thought to be attributed to a decrease in spinal curvature and increase in disc volume [24]. Bedrest studies are considered an analog to unloading from microgravity by removing vertical load from the spine and prompting adaptational spinal pain. Diurnal changes in spinal length have shown a 1% increase following bedrest from nightly sleep [34]. Adaptational pain associated with spaceflight and bedrest is thought to be a result of the sudden lengthening during the initial unloading phase [1, 35, 36].

Following spaceflight, astronauts often experience postflight spinal stiffness soon after return to earth and a heightened incidence of disc herniation and chronic low back pain well beyond the immediate reintroduction to gravitational load [4, 27]. Few studies have examined astronaut spine biomechanics following long-duration spaceflight. Recent work by Bailey et al. demonstrates an association between reduced spinal kinematics and reduced multifidus muscle quality following spaceflight [27, 37]. This work indicates that spaceflight-induced changes in paraspinal muscle leads to compromised post-spaceflight spinal biomechanics [27]. Additionally, disc hydration or height is not shown to significantly change with spaceflight and is therefore not supported as a factor influencing post-spaceflight spinal stiffness [27, 28]—running contrary to long held hypotheses that intervertebral disc swelling following spaceflight is a causal factor for disc herniations.

Spinal pain both during and after spaceflight appears to be due to changes in spinal mechanics, whether it be sudden lengthening inflight or stiffness and reduced stability following spaceflight. Localized pain in the spine is likely due to changes in forces on spinal tissues and not neurogenic. However, more work needs to be done on the effects of spaceflight on proprioception, balance, and how this may influence risk for spinal pain during and after spaceflight [38].

Backpain and Spaceflight

Pain Pathways for Low Back Pain

The perception of pain is not a unified single stimulus reflected in one conscious experience. Instead, it is the subjective experience resulting from the cortical processing of many different afferent nociceptive signals coming from a variety of sources.

Regarding low back in particular, the presentation and localization can be quite frustrating for both patient and clinician, as the innervation of many structures may produce a vague subjective location of pain. Many pathological origins that are quite distinct can have presenting symptoms of pain in similar locations. An example is that facet or zygapophyseal joint (z-joint)-mediated pain often refers to areas that appear to be remote from the facet but have other structures in that local area which could also be mistaken for the pain generator. Figure 5.2 shows a pain map of locations where pain is perceived when a certain z-joint is the cause of pain. The pain pathway that facilitates back pain is complex, but a simplified view of it is that a peripherally innervated structure receives a stimulus that triggers an afferent pain signal. This stimulus could be from a multitude of stimuli such as the stretch receptors in a muscle or joint capsule reaching a certain threshold of stretch, a noxious local environment facilitated by inflammation such as a tendinopathy at myotendinous insertion, a muscle overuse cramp, or mechanical

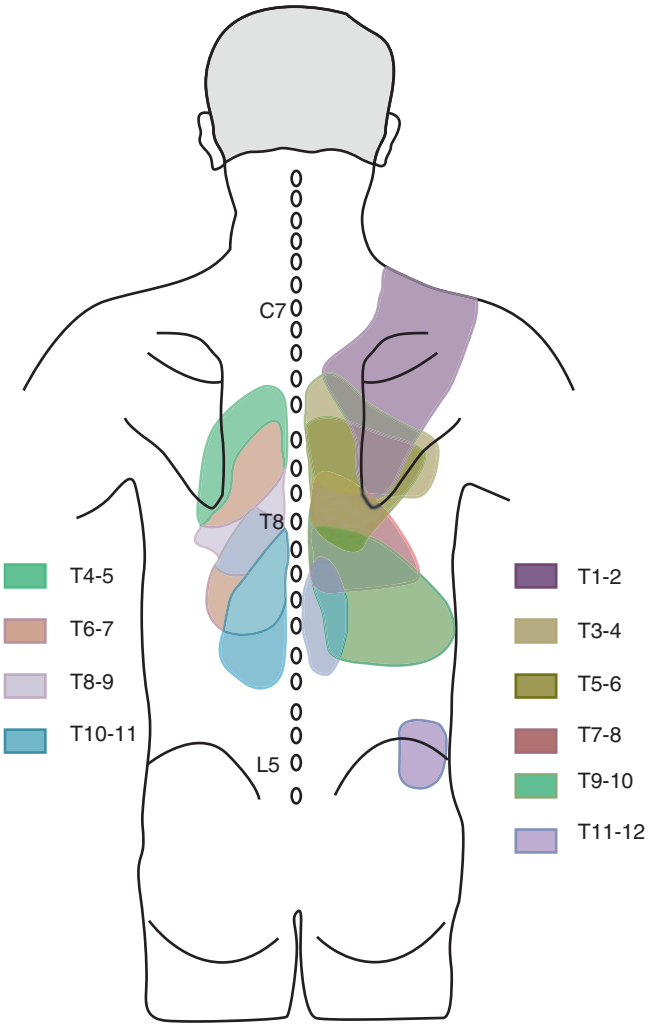

Fig. 5.2 Facet joint pain-referral map demonstrates regions where pain can be referred remote to the joint in question

disruption such as a tear in muscle or connective tissue. Each of these afferent peripheral signals then travels to the central nervous system and are integrated and further modulated in the spinal cord before being transmitted toward the brain. Habitual stimulation of these pathways can result, in some cases, in a consolidation of signal processing at the point where the peripheral nervous system meets the central nervous system, and the modulation can act to amplify the pain signal. Such centralization is a leading theory behind the development of chronic back pain.

The innervation of the structures in the back and known pain pathways can give some clues as to the cause of the pain, but often cannot account for the whole picture of the pathologic state. Muscle tightness in response to nearby zygapophyseal joint inflammation may generate the pain in the form of a cramping muscle. Alternatively, the pathological tightness of a muscle after a strain injury may place uneven forces across the joint complex, exacerbating any dysfunction already present there and causing pain to be generated (over and above the pain caused by the muscular strain) from the structures innervated at the joint complex. It is often impossible to tease one cause out entirely from another, as there can be overlapping and mutually reinforcing pain generators or pathologic states.

Potential Pain Pathways Associated with Back Pain During Spaceflight

There are several hypothesized pathologies in the production of back pain during spaceflight. At this point it is important to highlight the potential differences between possible etiologies for SABP and back pain from other sources during the flight. There is a predictable nature of SABP presentation in the majority of astronauts entering microgravity, and this might warrant a different approach to treatment or mitigation than other backpain causes. SABP tends to appear within the first day or so of exposure to microgravity and last as long as about 12 days, with the majority lasting around 6 days [1, 39]. The pain ranges from moderate to severe and is reported by the majority of astronauts [3]. Looking at the potential pain generators that could be consistent with the SABP presentation, it is important to consider the clinical presentation as well as the alleviating factors, most importantly that relief occurs in most cases with the astronaut assuming the fetal-tuck position, exercise, or spinal loading [3].

Upon reaching space, microgravity completely unloads the spinal column, allowing for a nearly total state of rest for all the muscles involved. Importantly, this includes the postural muscles like the deep multifidi and erector spinae that normally fire continuously at a low rate, controlled largely at a subconscious level, to resist gravity and prevent the trunk from falling over during upright posture in gravity. In microgravity, the body assumes what is known as the neutral body posture, where the hips and knees are slightly flexed, with a general loss of the normal spinal curvature. This unloaded state not only sets in motion the catabolic pathways within the muscle that begins the process of atrophy, but biomechanically it also starts to flatten out the natural spinal curvature. This unnatural flattening can have several possible effects which may act as pain generators. Traditionally, in a terrestrial population, a presentation of back pain that is relieved with forward flexion is suggestive of facet-mediated pain. Again, in the terrestrial population, disc-mediated pain is exacerbated by forward flexion and alleviated by back extension. In contrast, SABP is more commonly relieved with flexion [3] and extension has no effect [13]. Thus, we have to consider more closely the unique unloaded environment of microgravity and what physiologic features could contribute to this presentation. An explanation postulated by Sayson et al. is that the lower mechanical compres-

sion and subsequent over-hydration of discs for prolonged periods of time may contribute to SABP through the mechanism of excessive collagen deformation of the annuli with disc expansion and subsequent stimulation of type IV mechanoreceptors and nerve impulse propagation through the sinuvertebral nerves.

Another hypothesis for why this potential disc-mediated back pain is relieved with forward flexion is that it has metabolic origins. The traditional idea of disc-mediated back pain, such as an annular tear, should become more painful when a spine flexed posture is assumed and the load on the disc and subsequently the damaged tissue is increased. However, the disruption of the diurnal compression cycle on the disc could be causing a problem of microcirculation. The intervertebral disc (IVD) is the largest avascular structure in the human body and requires the slow influx of fluid containing nutrients via osmosis from the microvasculature of the vertebral body endplate [9, 13]. This process is facilitated through the diurnal compression and rehydration cycle produced with the normal human patterns of sleep (rehydration via proteoglycan-mediated osmosis during unloading) and compression (upright posture within a gravity environment causing increased hydrostatic pressure through compression and subsequent fluid efflux from the disc). This cycle is important because it is the only way that the chondrocytes and other metabolically active tissues that maintain the IVD can receive nutrients and remove waste (mostly lactic acid byproduct) [40]. The innervation of the outer third of the IVD is also provided by branches of the recurrent sinuvertebral nerve which is an unmyelinated mixed nerve with nociceptive fibers that may respond with pain signals to a metabolically deficient environment produced by the poor circulation of normal IVD nutrient and waste cycle caused by microgravity. If the astronauts are spending an unnatural amount of time unloaded without facilitating this nutrient and waste exchange, and subsequently developing a buildup of metabolic wastes in that local tissue, it may be enough to irritate the nociceptive fibers of the sinuvertebral nerves in the outer third of the annulus fibrosis of the IVD.

Alternatively, there could be facet-mediated pain unique to the microgravity environment caused by the change in biomechanical forces. An increase in disc height due to hydration without the normal diurnal compression may produce a new and unnatural form of mechanical strain on the zygapophyseal joints (z-joint). The increased disc size might act as a lever, which pushes the vertebral bodies away from one another using the z-joint as the fulcrum. Such non-physiologic pressure may provide enough noxious stimulus, when not relieved by diurnal compression, to produce back pain that has its local origin in the facet joint and is then relieved by the forward flexion (fetal tuck) that most astronauts have reported finding relief with. This forward flexion would preferentially reload the discs, potentially causing some fluid shift, but more immediately relieving the unnatural pressure placed on the z-joint.

Other Factors Contributing to Back Pain During Spaceflight

There are other aspects of spaceflight that might contribute to development of back pain in flight, starting with the actual launch from Earth itself. Astronauts spend a long time sitting in the seat of the spacecraft while launch preparations are being made. Hours in a cramped seat in a pressure suit could exacerbate any issues already present with respect to asymmetrically tight muscles, prior injuries that predispose the astronaut to recurrent pain, or other osseoligamentous deficiencies that may only produce pain when put in extreme circumstances. Another potential pathway for back pain generation in spaceflight is pain from an acute back injury. The COLBERT and ARED have been a huge improvement to inflight countermeasures for muscle atrophy and bone loss [41], but they also represent one of the largest generators of acute injury in space [42]. A strained muscle or inflamed disc from poor mechanics during a high-load exercise maneuver can cause significant impairment. While the injuries would be similar to terrestrial sports injuries, the recovery may follow a different trajectory, as the patient would otherwise be unloaded due to microgravity after the injury and remain so unless deliberately loading themselves using an exercise device. This complete unloading will change the muscle utilization across the spinal column as well as the diurnal loading pattern of the discs, resulting in a both poor spine biomechanics and a disc that is likely experiencing micro-circulation disruptions. Such changes may serve to predispose the tissue to injury over and above what might be seen with the same loads in a population that had not experienced microgravity. Additionally, and of paramount importance to inflight recovery from injury, many tissues, including the chondrocytes responsible for maintaining and repairing connective tissue, require load in order to be activated to repair a damaged area effectively [43]. Complete unloading acts as a net inhibitor of connective tissue repair over the long term [43].

Pain Pathways Associated with Back Pain Following Spaceflight

Following spaceflight, astronauts have a protracted period of recovery that is necessary, even with the current inflight countermeasures in place. Modern rehabilitation programs for astronauts returning from a standard 6 month stay

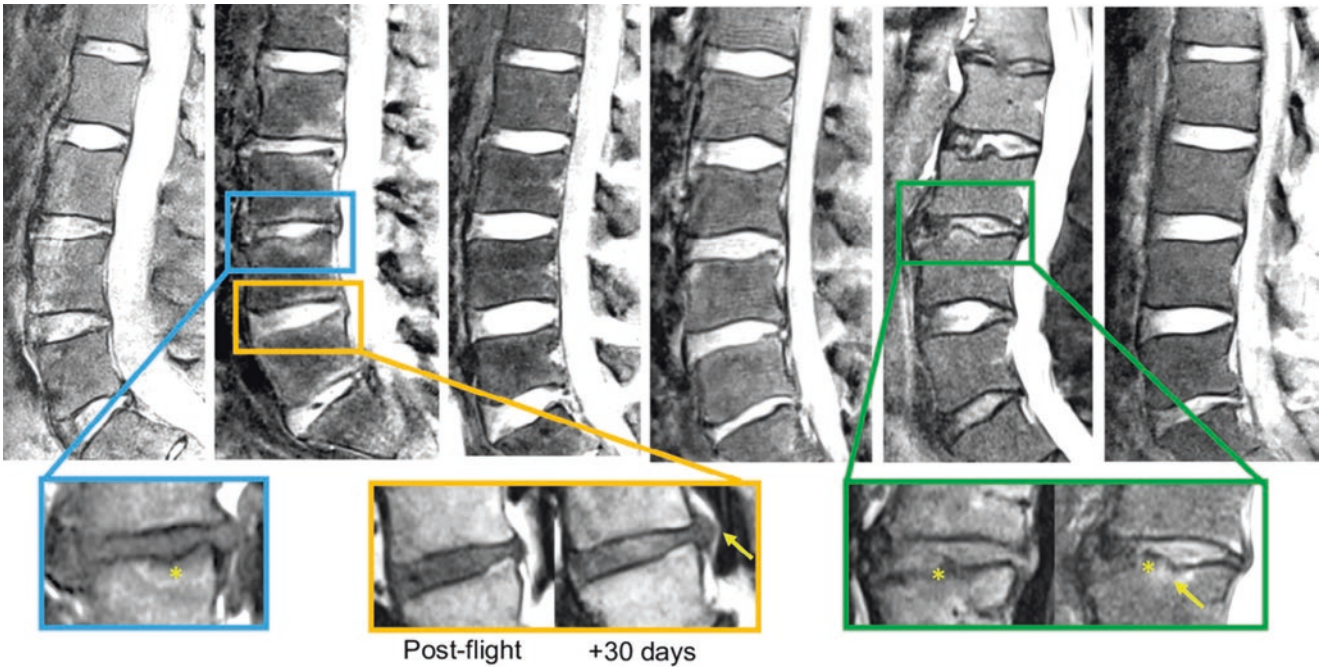

Fig. 5.3 Mid-sagittal views of T2-weighted 3 T lumbar spine MRIs for all six subjects (taken at preflight). Example sites for injury and potential sources of pain are pointed out in additional T1-weighted sagittal images (**a**–**c**) from two of the subjects who presented postflight symptoms: (**a**) indent end plate defect indicated with a yellow asterisk at the cranial L4 end plate, (**b**) images of postflight (left) and 30 days recovery following postflight (right), demonstrating a posterolateral disc herniation indicated with a yellow arrow, (**c**) T1- (left) and T2-weighted (right) images demonstrated a type 2 Modic change with severe end plate defect (Modic change indicated with a yellow arrow and end plate defect indicated with a yellow asterisk). Reproduced with permission from Bailey et al. 2018

onboard the ISS involves 2 h of rehab a day, for 45–60 days after landing. Even with this deliberate reconditioning, joint issues can persist for astronauts for many months after landing, often exceeding the amount of time spent in space [44]. It has been well established that many of the postural muscles of the back, especially those supporting the lumbar area, show significant atrophy during prolonged unloading [13, 27, 28, 39, 45]. This atrophy can lead to poor spine biomechanics and cause new pathology or exacerbate existing pathology within the spinal column when re-exposed to the 1G environment of Earth. This could trigger pain from a simple muscle strain, as weaker muscles and poor mechanics attempt to cope with the load that has been absent for many months. A strained muscle might begin with the immediate pain transmitted by the muscle nociceptors sensitive to noxious (tissue-threatening) stretch. Following the initial pain signals generated by stretch receptors, chemo-sensitive nociceptors pick up chemical changes in the local tissue milieu such as pH or molecular signals like ATP spilled from damaged tissue continuing the perceived sensation of pain [46]. In addition, poor spine mechanics and weakened muscular support could result in a disc injury. An annular tear would first be sensed through both mechanoreceptors and chemoreceptors from the sinuvertebral nerve, which innervate only the outer third of the annulus fibrosis in a typical healthy IVD [47, 48]. More dramatic pathology, like a herniated nucleus pulposus, might not only be sensed at the outer third of the IVD but also could manifest as pain from compression as the displaced nucleus pulposus presses against a nerve root or against the cauda equina (Fig. 5.3).

Risk Factors for Spine Injury or Pain

As mentioned by Pool-Goudzwaard et al., a history of back pain prior to prolonged unloading correlates highly with spaceflight adaptation back pain syndrome. This could be due to the previously mentioned changes in pain sense propagation that takes place in the chronic pain states, or as a result of prior pathology being exacerbated by the conditions of spaceflight. Additionally, there is likely a contribution of prior risk factors. As the person in question probably already had poor spine biomechanics (hence their previous injuries, or because of them) and these poor mechanics accompany them to space, including when they engage in exercise countermeasures which load the spine [41]. Of interest, there are still a substantial number of astronauts without a history of back pain that nevertheless experience SABP [5, 13]. This suggests that there is an independently developing pathology associated with the environment of spaceflight. In the setting of someone who has prior pathology, this may exacerbate it, or represent a separate pathology.

Inflight risk factors are less well understood, but certainly an acute injury while in flight, either during an exercise countermeasure or some other activity like a spacewalk, would likely predispose the astronaut to further back pain issues when coupled with the unloaded environment of microgravity. There is also the potentially tumultuous spacecraft landing to add to the picture, which can be rather violent and may exacerbate some existing or subclinical pathology.

Of note, the pathology that is associated with back pain and disc herniations upon return to Earth (or another gravitational environment) is likely different from the etiology of SABP. Regarding the increased risk of disc pathology, there is likely a component of disc dehydration and accelerated degeneration in microgravity as the regular diurnal pattern of loading the discs during the day and unloading at night that facilitates micro-circulation of nutrients is lost. In Fig. 5.4 we see that an astronaut's spine MRI showed an IVD herniation at L4–5 prior to flight, though notably not symptomatic at the time. Immediately postflight shows that the herniation had reduced, but clear endplate pathology here is detectable with modic changes in L2–3 and L3–4 endplates. One month into the astronaut's postflight recovery, they experienced symptoms consistent with lumbar radiculopathy and MRI imaging then showed a more dramatic herniation at the same site that had a prior asymptomatic herniation. While not enough data exists to make definitive predictions on risk factors like these, they can begin to inform decisions on not only countermeasures inflight, but also on directed rehabilitation programming upon return.

Associating Symptoms and Pathology Using Imaging

Spinal imaging is commonly used to assess any structural pathology underlying back pain symptoms. Imaging modalities used for spinal patients can include standard plain film X-rays and CT for evaluating the bony structures and ultrasound and MRI for evaluating soft tissue. More specialized nuclear imaging can give information about bone mineralization and density. Attaining high-quality imaging of the astronaut's spine is essential to improving our understanding of the pathologies responsible for their pain or dysfunction. However, this effort is limited by the fact that they are aboard a spacecraft while much of the relevant physiologic changes are occurring, as well as the difficulty in getting imaging in a timely fashion after the astronauts have landed. Additionally, interpretation of pathology seen on imaging like MRI is often unrelated to the pain a patient (astronaut) might be having. This is a key maxim in clinical practice—that pathology apparent on imaging does not necessarily mean that it is the pain generator, as imaging findings are only weakly associated with related back pain symptoms, and rarely statistically predictive. In one cross-sectional study of asymptomatic patients over 60, when evaluating an MRI, 36% had disc herniations, 21% showed evidence of spinal stenosis, and over 90% had a degenerated or bulging disc [15]. Therefore, caution must be exercised when interpreting pathology on imaging, and it should be carefully correlated

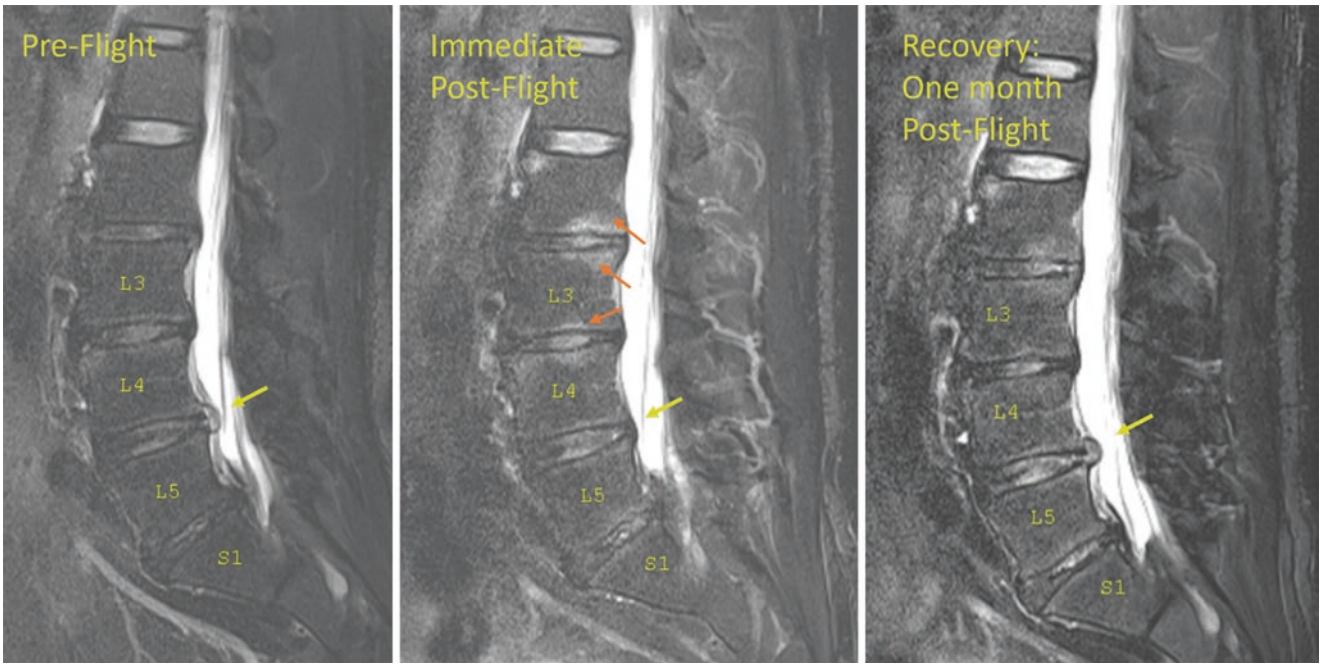

Fig. 5.4 This sequence of lumbar MRI images of an astronaut preflight (left), immediately post 6-month flight (middle) and 1 month post-flight (right), shows a relevant progression of disc pathology at L4/5 (yellow arrows) and accompanying modic changes (orange arrows) in the L2,3,4 vertebral bodies

with the clinical presentation. To date, inflight imaging has been limited, due to the constraints of spaceflight, though occasionally astronauts have been able to get MRI very shortly after landing, when such imagining is given priority during landing recovery operations. Other available forms of inflight imaging have included ultrasound (US), which has been used to assess muscle cross-sectional area as well as changes to the IVD during flight [45, 49]. US, unlike the other imaging modalities, adds in a factor of operator-dependence for the quality of imaging obtained, which can further limit data collection.

Treatment Possibilities

Preflight Surveillance

It has been noted that astronauts with a previous history of chronic back pain were much more likely to experience back pain in space [5]. There may also be a correlation to spine issues in space and injuries later, like herniated nucleus pulposus upon returning to Earth.

Astronaut-Specific Inflight Exercise and Postflight Rehab

Given an astronaut's experience with back pain, either prior history or inflight symptoms, an exercise program specifically tailored to address back pain would likely be beneficial. Taking the approach similar to terrestrial physical therapy, when a patient experiences back pain that affects their day-to-day activities, many benefit from a targeted exercise program to shorten the duration and severity of their symptoms. Likewise, if an astronaut is deemed to be higher risk for back injuries upon returning to gravity, a specific postflight rehab program could help to mitigate some of this risk is a more targeted fashion.

Inflight Spinal Assessment and Intervention

It has been noted, mostly anecdotally, that in addition to forward flexion (fetal tuck position) astronauts experience some relief from exercise or loading the spine [39]. It has also been noted that the cosmonauts of the Russian space program report a lower incidence of inflight backpain than their US counterparts. This may be due, in part, to the Russian space program's utilization of the Pingvin (Penguin) exercise suit, which has elastic bands that provide axial load and tension from the feet up through the shoulders. Such compression and/or proprioceptive cuing that the suit provides may act as a protective factor in certain pathologies related to inflight back pain. Though specific data to this effect has not been collected, there are other avenues of inquiry looking at employing similar compression suits to help mitigate some of these effects.

Clinical Impact of Spine Health in Spaceflight

The pathologies discussed in this chapter reflect important health and operational considerations for the current state of spaceflight. However, it is essential to make the distinction that these same issues represent critical factors for *future* planned spaceflight. While SABP on the ISS is inconvenient, there have been other occasional inflight issues associated with spine health, notably a delayed spacewalk in 2021 due to cervical radicular symptoms in the astronaut schedule to walk. Fortunately, these issues did not threaten to end the mission or place the astronauts in serious peril. Conversely, spinal health-related problems represent mission critical and life-threatening issues with upcoming planned Artemis missions. Even more profound would be those missions aiming to place humans on Mars. These mission profiles would require the astronauts to experience microgravity for many months and then reenter a gravity loaded environment before returning to the safety of Earth. In contrast to microgravity living, the human spine is the indispensable central nexus of locomotion and limb force generation required for setting up critical mission infrastructure and exploring new terrain on the gravity environments of the Moon and Mars. Such transitions between microgravity and gravitational re-loading currently represent the largest risk for spine-health-related mission failures, as a herniated disc on the surface of Mars could mean a crew member taken entirely out of operational status. Even a significant back spasm during surface operations, caused by weakened muscular support after many months in microgravity, could result in significant danger for the crew and their mission. Because of this added risk of gravitational transition in the settling of an extremely remote and austere support environment, careful consideration and planning must go into mitigating spine-related health issues in future crewed mission design.

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Vestibular System

6

Jamie M. Bogle and Ashley Zaleski-King

Introduction

Humans have evolved to function optimally in the presence of the Earth's gravity. The vestibular system provides sensory information utilizing the constant pull of gravity, allowing for the perception of verticality, appropriate motor function, and central nervous system integration. The impact of microgravity on the vestibular system significantly influences the ability of humans to maximally perform during spaceflight and may have complex consequences, especially for long-duration missions.

Vestibular System Anatomy and Physiology

The human vestibular system is comprised of peripheral sensory organs, central processing components, and mechanisms for motor output [1]. Information transmitted from the peripheral vestibular end organs leads to appropriate postural stability and stable gaze through numerous reflex pathways. Further integration of vestibular system information throughout the cortex influences other processes, including cognition, spatial awareness, as well as autonomic reflexes and bone maintenance.

The Vestibular Labyrinth

The peripheral vestibular sensory system lies within the inner ear, laterally adjacent to the air-filled middle ear, medially bordered by the temporal bone, posterior to the cochlea

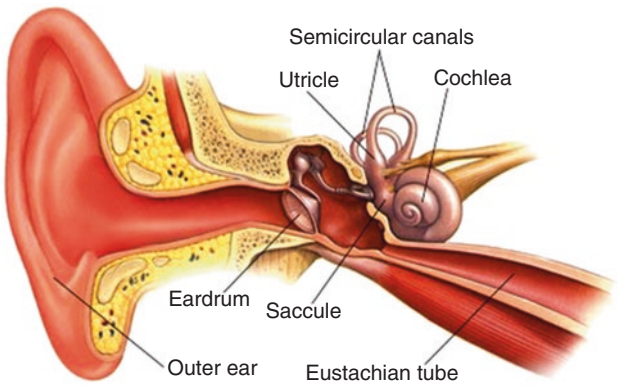

Fig. 6.1 The peripheral vestibular system. Five vestibular sensory end organs are housed within the inner ear: three semicircular canals and two otolith organs (saccule, utricle) (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

(Fig. 6.1) [2]. The bony labyrinth is the osseous outer wall of the inner ear located within the temporal bone. Inside the capsule is the membranous labyrinth which contains the vestibular sensory receptors. The bony and membranous labyrinths each contain a specific fluid. Perilymph provides a cushion between the bony and membranous labyrinths and has a high sodium concentration similar to cerebrospinal fluid. Endolymph is contained within the membranous labyrinth and has a high potassium concentration similar to intracellular fluid [3]. The membranous labyrinth contains two types of sensory end organs, the semicircular canals (SCCs) and the otoliths.

The SCCs detect angular acceleration, such as head turns. These curved tubes each contain an enlargement (ampulla) housing the sensory epithelium (crista ampullaris). The crista ampullaris is covered with the sensory epithelium. A gelatinous structure (cupula) arises from the crista ampullaris, extending across the ampulla to maintain a fluid tight seal. Because the cupula maintains the same specific weight as the surrounding endolymph, it does not respond to linear forces [4–6].

J. M. Bogle (✉)
Department of Otolaryngology – Head and Neck Surgery, Division of Audiology, Mayo Clinic Arizona, Scottsdale, AZ, USA
e-mail: bogle.jamie@mayo.edu

A. Zaleski-King
Department of Speech-Language Pathology & Audiology, Towson University, Towson, MD, USA
e-mail: acking@towson.edu

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The crista ampullaris contains the sensory hair cells responsible for encoding angular acceleration. The vestibular end organs are mechanoreceptors that translate mechanical force into neural potentials. Each sensory epithelium contains bundles of 20–100 stereocilia and one kinocilium. The cilia are linked in a stairstep pattern that allows the bundle to deflect together [7]. There are two types of hair cells—type I and type II. These different hair cells produce irregular and regular firing patterns, respectively [1], allowing for the broad representation of frequency and acceleration information needed to accurately identify acceleration profiles [8–10].

Vestibular system afferents produce high spontaneous resting rates which allows each sensory end organ to demonstrate firing patterns encoding both excitation and inhibition of the system [11, 12]. The three SCCs are oriented orthogonally in yaw, pitch, and roll planes. The vertical (anterior and posterior) canals form an approximate 45-degree angle with the sagittal plane [13]. Between ears, the SCCs are coplanar and are inversely excited in a push–pull fashion. For example, excitation of the anterior SCC in one ear corresponds to inhibition of the posterior SCC in the opposite ear. This arrangement allows for three-dimensional representation of rotational acceleration (Fig. 6.2) [14].

The two otolith organs, the saccule and utricle, lie within the vestibule in the center part of the bony labyrinth. Sensory neuroepithelium reside in each organ as a single patch of sensory cells, called macula. The maculae are positioned horizontally in the utricle and vertically in the saccule. The sensory hair cell bundles project into a gelatinous membrane which is embedded with calcium carbonate particles (otoconia). The additional weight provided by the otoconia means that the maculae are heavier than the surrounding endolymph. Linear acceleration generates force on the otoconia and gelatinous membrane, resulting in deflection of hair cell bundles. The utricle is stimulated by movement in the horizontal plane (e.g., head tilt sideways; lateral displacement) while the saccule is excited by movement in the vertical plane (e.g., sagittal plane upward, downward; forward, backward) (Fig. 6.3) [15].

While the SCCs and otolith organs are coplanar between ears [16], each otolith organ also encodes both excitation and inhibition for each linear acceleration. The otolith organs are divided into two sections of opposing polarity demarcated by the striola, a curved dividing ridge running through the middle of the macula. Head tilt results in excitation of a distinct subset of hair cells on one side of the striola and reduced afferent discharge from the hair cells on the other side. Additionally, a subset of afferent fibers encodes when the head is upright, increasing or decreasing the discharge rate with head tilt [17]. The otolith organs are limited in the capacity to distinguish between tilt with respect to gravity and linear translation. For example, the set of otolith cells that are activated by head tilt toward the right ear is also acti-

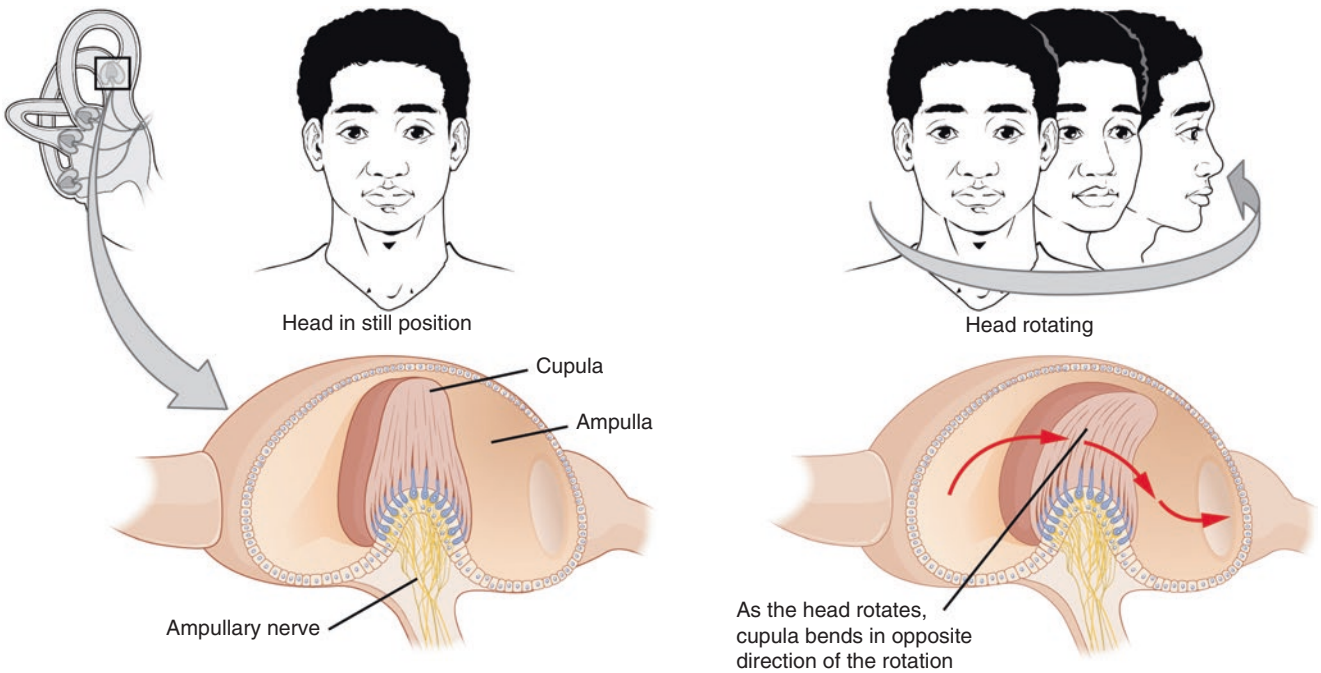

Fig. 6.2 Semicircular canal physiology. The semicircular canals encode angular acceleration. When the head is rotated, the endolymph lags, bending the cupula in the opposite direction and deflecting the underlying sensory hair cells to encode the acceleration (With permission from CFCF / Wikimedia Commons / Public Domain / https://commons.wikimedia.org/wiki/File:1410_Equilibrium_and_Semicircular_Canals.jpg)

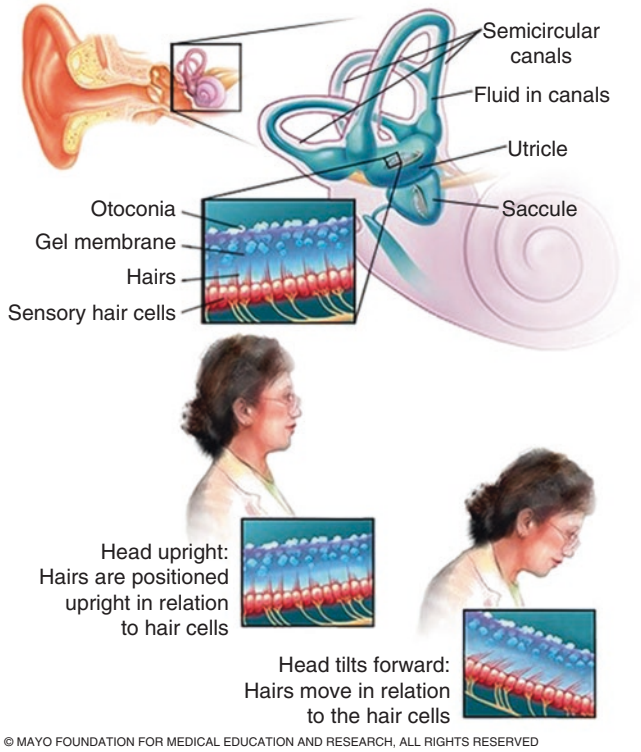

Fig. 6.3 Otolith organ physiology. The otolith organs encode linear acceleration induced by head tilt or linear translation. When the head is tipped, the otoconia are pulled downward, deflecting the underlying sensory hair cells and encoding the acceleration (Used with permission of Mayo Foundation for Medical Education and Research, all rights reserved)

vated by translational acceleration toward the left ear [15]. This is resolved by incorporating extra-otolith cues from SCCs, proprioception, and visual system information [18].

From the peripheral end organs, afferent projections travel along the vestibular nerve (cranial nerve eight, CN VIII) [19] and enter the brainstem at the pontomedullary junction. Central processing initiates as CN VIII enters the brainstem, the vestibular nucleus complex, and the cerebellum. These areas facilitate integration of input from each vestibular labyrinth, as well as from somatosensory and visual systems [1]. Otolith and SCC input continues to integrate at all central vestibular areas, from the vestibular nuclei to central vestibular processing centers [20].

Vestibular Reflex Function

The vestibular system is involved in a variety of functions, ranging from postural and oculomotor reflexes to spatial representation and cognition [21]. The vestibulo-ocular reflex (VOR) is the most well-described vestibular-mediated pathway. The VOR functions to stabilize images on the fovea by producing compensatory eye movements in the direction opposite a given head movement [1] at head rotations greater that 1 Hz [22, 23]. The VOR encodes the physical acceleration of the head into neural signals directing eye movement [1]. This reflexive eye movement is elicited at the first level of central vestibular processing through innervation of the vestibular nuclei. The resulting VOR response, or nystagmus, is used as a metric to quantify function.

Vestibular information is transmitted to the trunk and limbs for postural control through the vestibulo-spinal reflex (VSR). Most contralateral VSR inputs are part of the medial vestibulo-spinal tract (MVST) [24]. The MVST originates primarily from the medial vestibular nucleus, descends through the medial longitudinal fasciculus bilaterally, and terminates no lower than the mid-thoracic spinal cord [25]. Most ipsilateral excitatory pathways are part of the lateral vestibulo-spinal tract (LVST). The LVST originates in the lateral vestibular nucleus, descends through the inferior vestibular nucleus, and terminates on the anterior horn cells at various levels of the spinal cord. The MVST mediates head position by controlling neck and shoulder muscles, while the LVST controls postural adjustments to movement. When the head is tilted, both the SCCs and otolith organs are activated, transmitting impulses through the MVST and LVST to the spinal cord to induce extensor activity ipsilaterally and flexor activity contralaterally. An additional pathway originates in the reticular formation, descends to the spinal cord, and influences limb and trunk movement. The vestibular nuclei and reticular formation provide information to the spinal cord to maintain compensatory feedback responses to postural instability [1].

Central Vestibular Processing

Beyond stabilizing gaze and regulating postural control, the vestibular system also contributes to interpreting heading direction, localization of body in space, and distance traveled using inertial information obtained during displacement [26–34]. This information is uploaded and cross-referenced with other sources of sensory information.

Higher-order functions, such as spatial memory and self-motion perception, are associated with vestibular projections to the thalamus, which processes and relays sensory information to the cortex [16, 35–37]. These projections are multisensory and include convergent motor signals and proprioceptive feedback information [38]. The cerebellum maintains a key role in spatial orientation, motion perception, and vestibular reflex integration [39]. Vestibular system afferents directly project to the cerebellum [40], with afferent projections described from the SCCs to the nodulus and from the saccule to the uvula [41].

Vestibular sensory information ascends throughout the cortex, but unlike other sensory systems, there is no isolated

primary vestibular cortex in primates. Instead, there is a network of separate areas in the temporoparietal area—the parietoinsular vestibular cortex (PIVC)—that integrates vestibular, visual, and somatosensory input [42, 43]. There are also projections between the hemispheres, throughout the pontomesencephalic brainstem, and between the PIVC and visual cortex [43].

Vestibular system information becomes multimodal at an early stage of processing [36], as various sensory inputs within the brainstem generate a "best estimate" of body orientation and motion within the environment [44]. This integration is described as both multisensory convergence and multisensory transformation [45]. Convergence occurs as sensory information from various vestibular end organs combines with information from other sensory inputs. Transformation occurs when one sensory modality influences the integration of additional sensory modalities. This is illustrated by the known activation of the PIVC and simultaneous decrease in visual cortex activity with vestibular system stimulation [46]. Inversely, inhibitory vestibular-visual sensory interaction has also been described using large-field optokinetic stimuli to induce self-motion perception, finding increased activity in the occipital cortex and simultaneous decrease in PIVC activity bilaterally [47]. This relationship allows the dominant sensory input to shift from one modality to another, depending on the most reliable mode of stimulation [48]. Sensory integration and transformation are key to understanding central vestibular pathway compensation mechanisms.

Vestibular System Compensation

Reduced vestibular system function following peripheral or central pathology results in symptoms of dizziness and imbalance. These symptoms typically resolve over the following weeks due to the central nervous system's ability to compensate [49]. When a vestibular reflex pathway is altered, dizziness occurs due to an imbalance in vestibular nuclei resting neural discharge rate. During compensation, the resting rate is "rebalanced" as the commissural inhibitory system linking the vestibular nuclei modifies expectations regarding the current input [50]. Additional factors, such as altered vestibular nucleus neuron excitability, altered inhibition of vestibular networks via the cerebellum, neurogenesis in the ipsilesional vestibular nuclei, and adjustment of synapses in the vestibular pathways likely contribute to this process (for review, see [51]). Compensation allows for recalibration of altered vestibular sensory input and applies, in part, to the adaptation that astronauts experience upon and during exposure to microgravity. Regardless of the underlying cause, disruption of vestibular input leads to a compensatory response to reorganize and rebalance sensory input [52].

History of Vestibular System Evaluation in Spaceflight

Understanding the impact of microgravity on the vestibular system has long been at the forefront of space research. In 1961, Yuri Gagarin became the first man to enter space, completing an orbit in less than 2 h. He reported no significant vestibular concerns during his short exposure. It was GhermanTitov on the subsequent Vostok 2 mission who demonstrated the significance of microgravity on the vestibular system. Once in orbit, Titov described an abrupt onset of nausea and vomiting with lingering illness even after sleeping. Symptoms abruptly resolved nearing the end of his 25-h flight and he described feeling completely functional. Titov was the first human to experience space motion sickness [53, 54].

Initial reports of spatial disorientation experienced on Mercury and Gemini missions in the 1960s were minor and had minimal reported impact on operations. Therefore, initial work evaluating neurovestibular function focused on postural instability and reduced coordination post-flight, well-known challenges documented as early as the Apollo missions. Bedside balance and gait evaluations were completed before and after return from missions [55]. Specialized platform-based postural stability measurements were included as technology advanced [56]. Postural instability continues to challenge returning astronauts and these tools remain a useful metric to guide our understanding of imbalance.

The focus of neurovestibular research expanded as astronauts moved more freely within the capsule and as mission durations increased [57]. Symptoms associated with "space motion sickness" (SMS) or "space adaptation syndrome" were reported by both American and Soviet space programs, heightening concern for reduced operational performance that could endanger the crew as well as the mission [58–60]. The prevalence and severity of SMS were unexpected—astronauts were known for high levels of motion tolerance and had significant aviation training [61]. While initial reports described mild symptoms, later crew described symptom severity that could be quite severe [62, 63]. Today, ongoing research endeavors to better understand susceptibility and appropriate countermeasures to reduce SMS. Conclusive results are lacking, and SMS mitigation remains difficult. Astronauts continue to experience these effects. In mild cases, many wait out the symptoms, while nearly half report managing symptoms with vestibular suppressants [64–66].

Research describing vestibular system physiology in microgravity began in earnest in the 1970s and 1980s with the Skylab and Salyut space programs [67]. Researchers adapted technology commonly used on Earth to conduct comparable studies on the station, such as the rotational

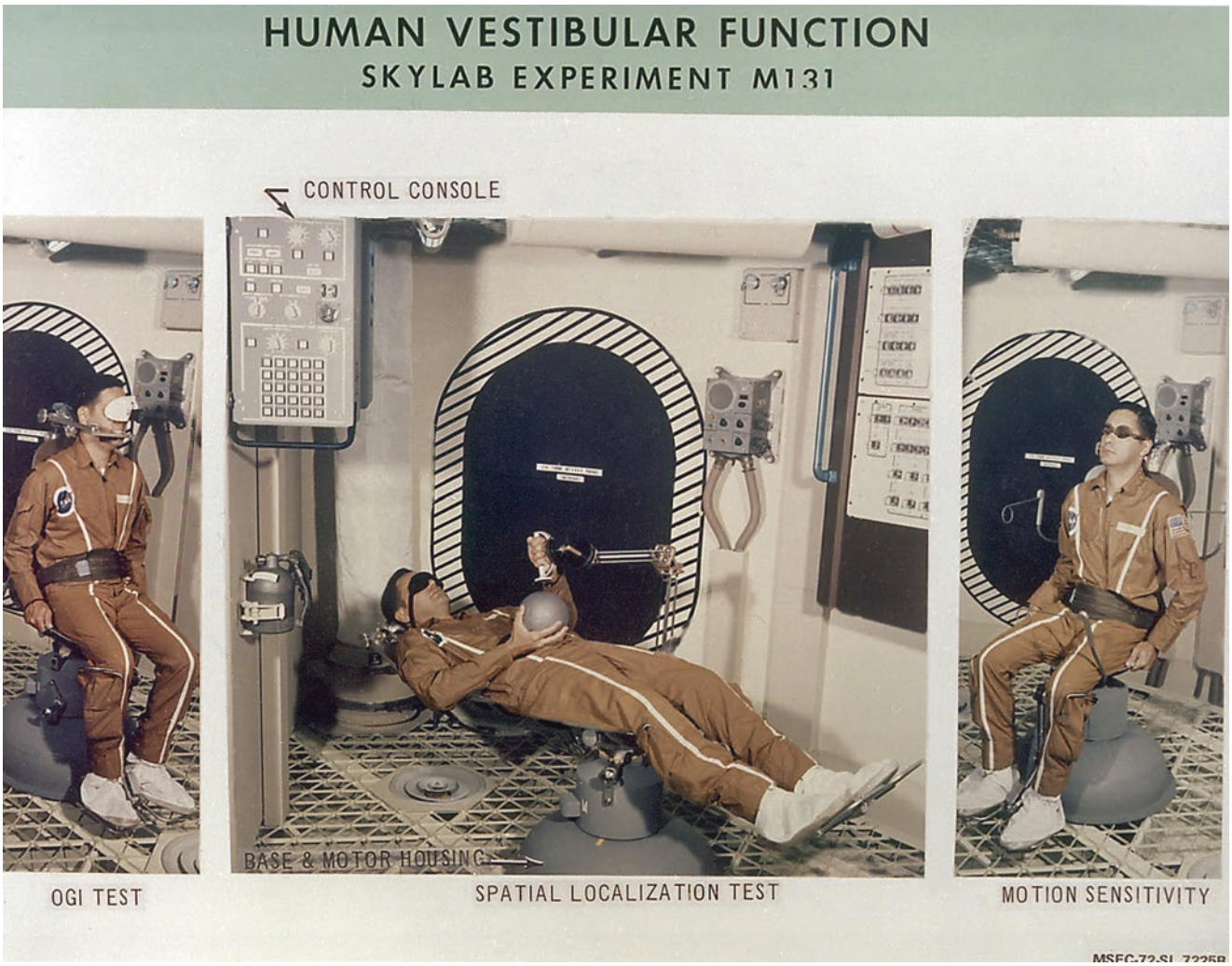

Fig. 6.4 Skylab's Human Vestibular Function Experiment 131. This study evaluated coordination function in long-duration spaceflight, focusing on susceptibility to motion sickness as well as otolith and semicircular canal function (With permission from NASA/Marshall Space Flight Center/Public Domain https://archive.org/details/MSFC-0102036)

chair used for Skylab Experiment 131 (Fig. 6.4). This study compared SCCs and otolith function on Earth and in microgravity conditions [68]. Later investigations conducted through the 1980s and early 1990s examined visual, vestibular, and visual-vestibular integration function of astronauts on both short- and long-duration missions [69]. Research conducted on the space stations evaluated how atypical vestibular system information altered various domains, including postural stability, motor control and adaptation, and operational proficiency [70, 71].

When the shuttle program began in the 1980s, astronauts were tasked with increased operational control during missions. In higher risk situations, such as the return to Earth, the sudden reintroduction of otolith reflex pathway information led to unique challenges not previously highlighted in capsule landings. The abrupt addition of otolith reflex pathway information led to overestimated perception of translation during and after landing [72]. An unexpectedly high proportion of shuttle landings occurred outside of preferred operational specifications, which was attributed at least in part to the somatogravic illusion. This illusion occurs when otolith reflex information is misinterpreted, resulting in altered attitude perception. Commanders and pilots were forewarned about this illusion, but it could not be replicated during simulation [73]. No significant events occurred during landing that were attributed to this illusion; however, the profound effect of reintroducing otolith information abruptly into overall spatial perception is a significant concern when altered perception may reduce operational performance.

Research continues to expand our understanding of the effects of microgravity on the vestibular system. The long-term presence of astronauts living on space stations has allowed scientists to further study these complex sensory interactions [59].

Techniques Used to Study the Vestibular System in Microgravity

While altered vestibular system function may lead to significant operational concerns, evaluating the vestibular system during spaceflight is challenging. Various methods have been used to evaluate the numerous reflexes associated with the vestibular system; however, these assessments are likely incomplete.

Animal Models

Because of the limited number of astronauts available for testing, along with the less than optimal test methodology, animal models provide an invaluable method for evaluating the effects of altered gravity in meaningful ways. Significant structural changes have been documented in non-human species, particularly related to the otolith organs. Histopathological studies have described increased otoconial mass in adult rodent utricles in as little as 1 week of microgravity exposure [74, 75], while saccular changes have been shown only with embryological or larval exposure in mollusks and newts [76, 77]. Conversely, hypergravity environments, such as prolonged centrifugation, reduced otoconial mass in mollusks, fish, and rodents [78–80]. Sensory hair cells and neural synapses have also demonstrated alterations. In rodent models, neurodegeneration has not been observed in short-duration spaceflight [74], but increased perinuclear and intercellular spaces have been found [78, 81]. Interestingly, another study using a rodent model found that there were significant changes in synaptic density for utricular areas associated with encoding low frequency and static changes in linear acceleration [82]. Longer duration missions have shown increased alterations in type I and type II hair cells. Specifically, hair cells have developed significantly more neural synapses in microgravity which reduced to baseline upon return to Earth [83–85]. These data suggest that the vestibular system will adapt—often quickly—to altered gravity environments, though the extent to which these changes occur in humans is not yet known.

Vestibular reflex pathway recordings are the standard method for documenting function. SCC-mediated VOR responses are stimulated by angular acceleration and therefore should not show altered function in microgravity. Animal models, however, provide evidence of transient angular VOR alterations. In monkeys, single unit recordings from the medial vestibular nucleus and flocculus have shown significantly reduced neural activation in the first few days of microgravity exposure [86]. Responses to linear acceleration have also demonstrated variability over the first few days, with increased neural activity recorded in the vestibular nucleus within hours of exposure. While activity levels return to baseline over the following day, another increase in neural response to linear acceleration has been recorded on days four and five, again returning to baseline. Responses to linear and angular acceleration have described variable time courses for adaptation and suggest that the otolith organs contribute to the adaptation mechanisms for the angular VOR pathways [86].

Earth-Bound Models

Few humans have been studied in an actual microgravity environment and the data collected from those human studies have often been inconclusive or contradictory. Earth-bound models can be utilized to improve our understanding of the effects of altered gravity conditions in larger groups of subjects.

Parabolic flight has been used consistently to evaluate vestibular reflex pathways. In this paradigm, 20–30 s of actual microgravity can be achieved per parabola. This method provides the only Earth-bound model to achieve actual microgravity, but study methodology is limited to those tasks that can be completed in this short duration [64]. Importantly, parabolic flight provides a method to closely describe vestibular system performance at the initial transition between gravity conditions, capturing the effects of sudden on- and offloading of otolith reflex information. Since this information has not been documented in actual spaceflight, parabolic flight provides valuable insight into this transition. Data collection during parabolic flight should be interpreted during this time course and not used to infer vestibular system function throughout spaceflight. Additional factors such as vestibular system adaptation and compensation, body fluid redistribution, diminished muscle mass, underlying anatomical changes, and prevalence of SMS cannot be replicated with this technique [64]. Parabolic flight continues to be useful in describing function during critical gravity transitions, but also leads to improved research questions and protocol development for missions where more detailed investigation may occur.

Prolonged head-down bed rest is used in various Earth-bound protocols to simulate the reduced sensorimotor input and altered cerebral hemodynamics found in microgravity [87]. This method allows for improved understanding of the somatosensory system and its influence on posture and motor control. Subjects evaluated using this analog demonstrate similarly reduced postural performance as astronauts evaluated after return to Earth [88]. This method not only has shown usefulness in modeling somatosensory changes, but also has been used to evaluate altered central integration. Advanced imaging methods such as resting state functional

magnetic resonance imaging (fMRI) have demonstrated altered connectivity between the motor, somatosensory, and vestibular systems when completing spatial orientation tasks [89], and even simple vestibular reflex pathways have shown reduced function [90]. Head-down bed rest provides a useful model to evaluate the effects of microgravity in a larger pool of subjects in controlled conditions that may not be replicated in spaceflight.

While microgravity receives more focus, astronauts are subjected to enhanced gravity during launch (~3.2 g) and upon return (~1.4 g). Enhanced otolith information also influences vestibular reflex pathways and may confound operational performance, as noted with the somatogravic illusion described in section "History of Vestibular System Evaluation in Spaceflight". Centrifugation has long been used as a method to evaluate the effects of hypergravity. Humans are generally only temporarily exposed to hypergravity conditions; however, this can have significant effects on operations. Atypical orientation perception has been reported as an overestimation of roll-tilt angle during hypergravity conditions, yet an underestimation during centrifuge-created hypogravity conditions [91, 92]. Performance variations have been described. For example, flight simulator performance has been significantly reduced in naïve subjects in hypergravity conditions, but not for trained aviators [93, 94], suggesting that training may assist in managing altered orientation effects.

Methodology

Technologically advanced methods for evaluating vestibular function were introduced during the Skylab missions in the 1970s [95, 96]. While direct assessment of each vestibular end organ is not possible using current techniques, there are numerous methods available to evaluate subsequent reflex pathways. These recordings therefore infer the functionality of the end organs. Vestibular system testing most commonly includes the VOR. Various methods of nystagmography (i.e., eye movement recording) have been used, including video cameras, scleral coils, corneo-retinal dipole potentials (e.g., electronystagmography), and infrared pupil recordings (e.g., videonystagmography) as technology developed and advanced.

VOR testing can be completed using various protocols. Caloric testing is commonly used clinically for the diagnostic evaluation of the vestibular system. It is a well-established technique but was not expected to be reliable in flight. Robert Bárány's work describing the thermo-conductive mechanism elicited by endolymphatic temperature change in the horizontal SCC [97, 98] suggests that the caloric response should be hindered in microgravity. This was supported by results obtained in parabolic flight, which found reduced nystagmus in microgravity and enhanced nystagmus in hypergravity conditions [99, 100]. Bárány's theory on the mechanism of this response was further evaluated with work completed on Skylab. These studies found no significant change in the nystagmus response from on-Earth measures [101–103], and led to alternative hypotheses for the underlying mechanism of this response [104]. Interestingly, work completed on Skylab-1 found consistent nystagmus responses in flight—except for one recording completed on the first day in orbit [105]. That individual datapoint suggested that there may be variability in VOR function over the course of adaptation to microgravity and was consistent with data collected in parabolic flight. Taken in context, the abrupt offloading of the otolith organs upon entry into microgravity is hypothesized to initially suppress the angular VOR response, returning to typical function over the course of a few days [106]. Therefore, the expected outcomes for VOR comparison will vary depending on the time post-entry into space.

While the caloric response is standard for evaluating the vestibular system on Earth, this test elicits a low frequency response (~0.003 Hz) [107] that is well below typical functional movement. Understanding the compensatory ability of the caloric response may not carry over into interpreting the higher frequency function needed for typical activities. Physiologically, frequencies are encoded differently, with low frequencies encoded by regular vestibular afferents and higher frequencies encoded by irregular afferents [107]. Rotational chair testing offers an ability to evaluate angular VOR function using various frequency and acceleration profiles. This technology has been studied in Earth-bound and microgravity environments [95], providing an understood model of bilateral vestibular system integration. This technology requires equipment capable of precise performance; however, there are limitations. For example, higher frequency oscillations can produce significant artifact in the recordings. Additionally, this method requires substantial equipment, challenging considering weight restrictions and available space on board the craft. Other methods are under evaluation. With advancing technology, higher frequency VOR responses will be evaluated, recording reflexive eye movements during head oscillations at target frequencies above those recorded with previous techniques [108]. Newer methods may prove more helpful in documenting change in angular VOR function over time while also using more compact equipment.

While the otolith system is key to understanding the effects of microgravity on the vestibular system, otolith reflex testing is challenging. Initially, there were no clinical protocols available to easily transition into assessing otolith information in flight. Earth-bound protocols were only available in specialized laboratories. These tools were modified

for use in orbit, with one of the first iterations used on Skylab. Early research utilized a "space sled" designed to evaluate the otolith system [109]. This device included a 6-m-long assembly mounted to the floor of Skylab to provide controlled linear acceleration. While this device provided the capability to perform precise experiments, it did require a significant footprint on board the laboratory [110].

Because of the technical limitations associated with linear translation paradigms on board, researchers assessed other possible methods for documenting otolith function. Otolith information is integrated into various additional pathways, including the VOR, and is required for appropriate neural representation of the VOR in pitch and roll. When the head tilts, the otolith reflex pathways induce ocular counter-roll (OCR) or torsional VOR. Absent OCR leads to atypical representation of the environment and contributes to spatial disorientation. OCR can be used to document otolith function using centrifuge [111] or retinal afterimage paradigms [112].

Otolith reflex pathways may also be evaluated using evoked potentials. This technology is newer but shows promise as a simple method to evaluate these reflex pathways. Vestibular evoked myogenic potentials (VEMP) evaluate the sacculo-collic (cervical VEMP) and utriculo-ocular (ocular VEMP) reflex pathways. These potentials can be quickly acquired with minimal equipment and provide information regarding descending vestibulo-spinal pathways not previously well-described. While clinicians have used this technique for years, minimal work has been done in microgravity. In parabolic flight, cervical VEMP responses have demonstrated greater amplitude in hypogravity than in normo- or hypergravity conditions [113], consistent with enhanced neural responses documented in animal models [114]. Further work with this technique is needed to evaluate its usefulness in understanding the otolith-mediated reflex pathways in prolonged microgravity environments.

Returning astronauts continue to experience challenges with postural stability [115] and are evaluated using a combination of bedside measures, computerized balance paradigms, and kinematic analysis of gait. Computerized methods have led to improved ability to understand the contributions of visual, vestibular, and somatosensory cues after exposure to microgravity in order to determine any prevalent sensory preference. Other methods have used objective recording of Hoffmann's reflex (H-reflex) [116] or electromyography (EMG). These techniques utilize the relationship between the otolith organs and vestibulo-spinal network to incrementally study these reflex pathways in weight-bearing muscles. Responses have been studied during and after exposure to vertical linear translation.

Effects of Microgravity on the Vestibular System

Once in orbit, the otolith organs are immediately offloaded, meaning that they no longer function as gravireceptors. The alteration in expected vestibular system input disrupts orientation, balance, and gaze control, affecting perception of self-orientation and motion [117] and requires the central nervous system to recalibrate and adapt [118].

Otolith Function

Most vestibular-related effects in microgravity occur after the abrupt loss of otolith-specific information. Under Earth-bound conditions, the otolith organs are stimulated by head tilt and translation that depend on head orientation relative to gravity, thereby eliciting the OCR reflex and aiding in the VSR. In microgravity, the otolith organs do not function properly as gravireceptors and cannot provide useful information about static head orientation (i.e., tilt). The microgravity environment does not exclude otolith information entirely as translation is still encoded. Additionally, otolith reflex pathways and the gravitoinertial analyzer are abnormally excited at least during the initial transition to microgravity [113, 114, 119], while low frequency otolith afferent information is suppressed by the central nervous system [120]. This is an important consideration: microgravity and vestibular dysfunction are not the same in terms of central interpretation. In microgravity, otolith information is still transmitted for linear translations, but not for head tilt, while we assume that vestibulopathy impairs both [114].

Initial evaluation of otolith reflex function in altered gravity was described using animal models in parabolic flight. In the frog, utricular neural activity varied closely with the magnitude of gravitational change. During the transition from 1 g to 0 g, there was an initial increase in spontaneous neural firing followed by a subsequent suppression of neural activity at 10 s into weightlessness. A large increase in neural firing was then noted in the hypergravity condition with a final restoration of baseline discharge rate after returning to the 1 g condition. In prolonged microgravity, it is presumed that the otolith organs "float" which overall should lead to decreased excitation [114].

The OCR is absent in microgravity conditions [121] and is reduced following long-duration spaceflight [122]. While those returning from short duration missions may not experience significant reduction [123], OCR may take several weeks to recover [122, 124–126]. There does not appear to be a lasting effect, however, and OCR eventually returns to pre-flight values [59].

Semicircular Canal Function

In contrast to the gravity-dependent otolith system, the SCCs should be unaffected by altered gravity environments [127–129]. Rotational chair testing has been used to describe angular VOR function and responses induced by trapezoidal acceleration several days into flight have not been significantly different from baseline. In-flight recordings to angular velocity changes have found nystagmus velocity (i.e., SCC response) as independent of linear acceleration [130].

While the SCCs may not be affected physiologically by changes in gravity environment, they are not completely immune to these effects. The otolith organs mediate these pathways. This was described early by evaluating the effect of "cross-coupling," or simultaneous stimulation of multiple vestibular end organs. Significantly, cross-coupling the SCCs did not lead to motion sickness in microgravity—an unexpected finding as this perception (i.e., Coriolis effect) is quite profound on Earth [95]—and was quickly associated with reduced otolith contribution to this integrated mechanism. Additional VOR responses, such as measures of the vertical SCC VOR pathways and central velocity storage mechanisms that prolong the VOR response to sustained motion, are reduced in microgravity [126, 131–133]. These paradigms provide evidence that the otolith-ocular pathway contributes to the integration and interpretation of the angular vestibular reflex pathways.

Research continues to evaluate alterations in vestibular system function. As previously discussed, traditional methods of evaluating SCC function focus on low frequency stimuli due to methodological limitations. Newer techniques are providing access to higher frequency VOR responses that more consistently align with typical head movements. Recent work has evaluated the recovery of angular VOR function using stimulus frequencies up to 1 Hz. Results suggest that there is a frequency effect to the angular VOR compensation process in flight, with higher frequencies requiring longer compensation time [108]. It is not yet known if full compensation can be achieved, even in long-duration flight, and what limitations may continue. As we learn more about these responses, our understanding of the influence of gravity on the angular VOR system will likely change.

Postural Stability and Sensorimotor Responses

Data from various laboratories have suggested that prolonged exposure to microgravity leads to postural instability for various reasons, including:

1. Decreased requirement for postural reflexes in weight-bearing muscles
2. Central nervous system reinterpretation of otolith reflexes
3. Reduced static and dynamic postural inputs from the proprioceptive system
4. Altered tonic activity in soleus and anterior tibialis muscles (for review, see [134])
5. Increased sensory weighting to visual cues.

Some level of disorientation during and after landing has been universally reported, with ataxic gait, inability to correct for postural errors, and concern for falling prevalent among returning astronauts. Furthermore, returning crew have described the need for slow and focused movements to stay upright and noted concern if quick responses were needed during an emergency [73].

Postural stability has been shown to decline with both short- and long-duration spaceflights, although the effects have been more pronounced and persistent with longer exposure [135]. Increased sway when in vision denied and/or disrupted somatosensory conditions has been described [136]. For a week post-return, postural stability tasks that included dynamic head movement on an unstable platform have been too difficult, suggesting a reweighting of balance ability to increased reliance on somatosensory cues [135].

Evoked potential recordings have demonstrated facilitation [137] or early potentiation [138, 139] of the H-reflex as a function of free fall or reduced gravity load. Prolonged free fall has been shown to facilitate sensory-motor rearrangement, and this adaptation may lead to central reinterpretation of otolith input. Similarly, rearrangement and reinterpretation have been proposed as a possible mechanism for muscle proprioceptive signal alterations that occur during prolonged exposure to microgravity [64]. These reflexes return to pre-flight values immediately after flight [138].

The effects of deconditioned otolith-spinal reflexes extend to gait and locomotion. Postural muscles contributing to upright stance have been shown to atrophy in microgravity [140]. Post-flight changes in step-cycle, walking speed, gaze stability, and amount of unrestricted head movement have all been reported [52, 141, 142]. Ataxia, disorientation in unstructured visual environments, illusory movement of the visual field, veered walking path, disruption of head stabilization in response to vertical translation [143], and decreased stability while turning corners have been demonstrated shortly after return [121, 144]. For short duration missions, these effects typically diminish within 12 h; however, for long-duration missions, it may take weeks for gait to return to pre-flight baseline [145].

Oculomotor Function

Although spatial orientation in microgravity shifts to increased dependence on visual and somatosensory cues, vision may be altered in microgravity as well. Detailed infor-

mation on changes to the ocular system is provided in Chap. 7. While altered VOR pathways in microgravity conditions were expected, research has found significant deficits in other oculomotor domains including gaze stability, saccade and smooth pursuit systems, and gaze fixation ability [146, 147]. Parabolic flight paradigms have described reduced precision and speed for smooth pursuit tasks, as well as prolonged duration for establishing stable gaze [148]. These results are consistent with returning crew who have consistently demonstrated reduced performance in acquiring visual targets, prolonged latency, and reduced eye and head movement velocity. Additionally, returning crew have demonstrated reliance on saccadic eye movement to manage smooth pursuit stimuli [144, 148, 149]. Oculomotor challenges have been described especially for vertical eye movements, consistent with known otolith involvement in these pathways [150]. Overall, recovery time of these metrics is similar to that of the OCR, with return to baseline over days to weeks [146].

Visual perception is another area of concern. Judgment of size and distance of objects is altered during [151] and following [152] several months of microgravity exposure, suggesting that mental depiction of three-dimensional space may be altered. Both close (<60 cm) and long (180 m, 1500 m) range distances have been underestimated by as much as 35% when compared to ground-based performance. Specifically, in this environment, the body is used to scale visual space as well as to perceive the size and distance of objects [152]. There may be significant limitations associated with this altered perception. For example, a review of 100 missions found that 20% of landings were above limits for touchdown speed, emphasizing the altered judgment of distance estimates [153]. These perceptual changes have implications for operational tasks and crew safety, especially during critical phases of the mission.

Other Consideration

To reduce the effects of altered otolith information, studies have evaluated the possible benefit of centrifugation while in orbit. This method was designed to stimulate the otolith pathways during the mission to maintain conditioning. Unfortunately, there have been mixed results using this paradigm as a method to significantly improve OCR function [111, 154]. There may be additional reasons to consider stimulating this pathway, however, as the vestibular system does interact with various other systems, especially the sympathetic nervous system. Most significant for this discussion include bone remodeling and autonomic reflex function.

Bone loss is a recognized sequela of spaceflight associated with the effects of prolonged weightlessness on the skeletal system. Bone loss occurs rapidly, within a few days after exposure and can be severe after two to five months in orbit. Upon return, bone is regained, however, bone density generally does not reach pre-flight levels. Therefore, astronauts may be at risk for accelerated bone loss leading to early-onset osteoporosis after a career in spaceflight [155]. Animal models have demonstrated reduced bone formation in microgravity, as well as enhanced bone development in hypergravity conditions [156, 157]. There are additional downstream effects associated with bone loss, including reduced magnesium, vitamin D, and protein available for absorption [158]. The relationship between the vestibular system and sympathetic skeletal projections that influence bone remodeling have been described in animal models noting significantly reduced bone formation and increased bone absorption in weight-bearing bones [156, 159]. While this work has been completed on Earth in animals with peripheral vestibulopathy, further investigating this relationship in altered gravity may lead to additional methods to address spaceflight-induced osteoporosis concerns.

Autonomic function may also be altered with atypical otolith input. Vestibulo-sympathetic reflexes, such as those involved in cardiovascular system regulation, may be impacted [160–162]. The otolith organs are especially involved in regulating blood pressure during orthostatic challenge. Carotid heart rate and mean arterial pressure are significantly altered in the various gravity environments obtained in parabolic flight paradigms, emphasizing the relationship of the otolith organs in regulating these responses [163, 164]. There has been a significant association reported between altered OCR during head tilt and reduced blood pressure response in symptomatic astronauts post-flight (Fig. 6.5) [165]. Animal models evaluating this relationship have found that microgravity-associated cardiovascular changes do not occur in those with vestibular end organ lesions [166–168], highlighting the likely association between unreliable otolith reflex information and these sympathetic responses. Impaired vestibulo-cardiovascular responses have been measured in humans for up to 4 days after return from long-duration missions, returning to pre-flight levels within 2 months. These data suggest that long-term exposure and deconditioning of otolith-mediated autonomic system reflexes may contribute to spaceflight-induced orthostatic intolerance [160, 169, 170].

Space Motion Sickness

Space motion sickness (SMS) affects nearly 70% of astronauts, developing within an hour after launch and resolving within 3–4 days. The sensation has some characteristics similar to motion sickness experienced on Earth, including nausea, drowsiness, and fatigue. The initiation and resolution of SMS though is quite different than on Earth (Table 6.1) [172–174], as most describe abrupt onset and offset of symptoms.

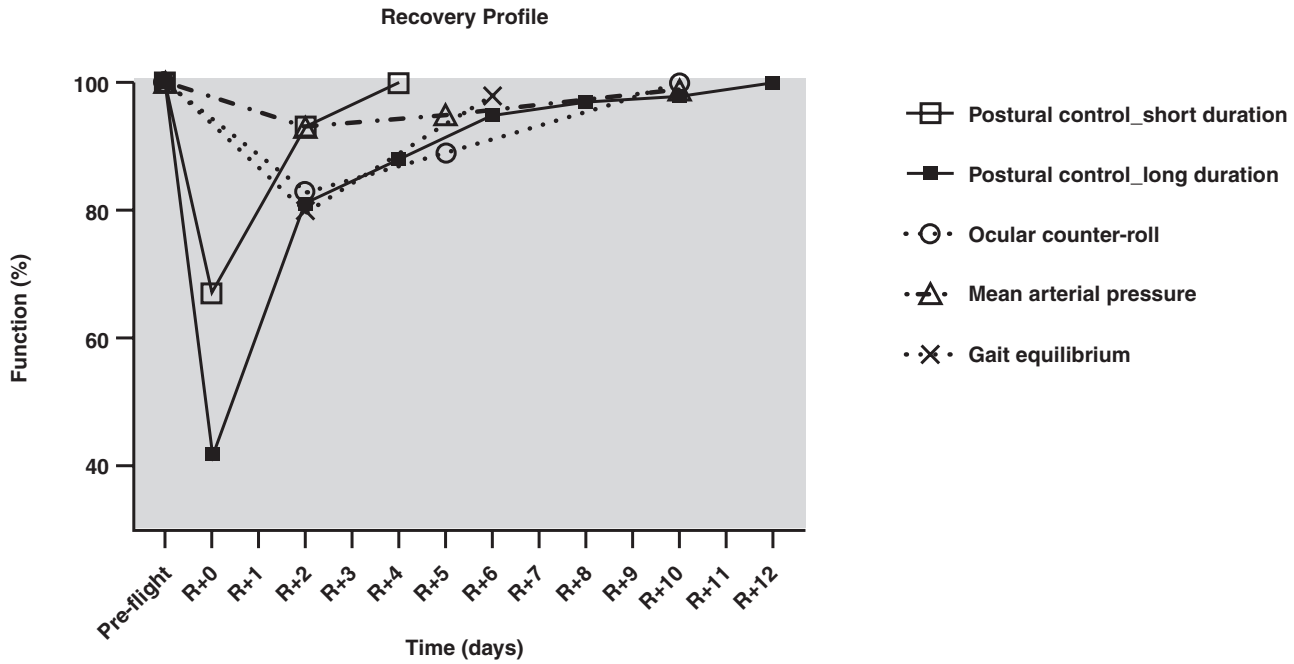

Fig. 6.5 Approximated depiction of post-flight recovery timeline for mean postural control after short- and long-duration spaceflight (adapted from [135]), OCR after long-term spaceflight (adapted from [165]), cardiovascular control measured via mean arterial pressure (adapted from [165]), and gait equilibrium measured via amplitude of lateral body displacement during the gait cycle (adapted from [171]). Change in function was approximated based on 100% pre-flight performance. The initial recovery phase is highlighted in the lighter box. Slower recovery phase is depicted in the darker box

Table 6.1 Characteristics of Earth-Bound motion sickness versus space motion sickness (SMS) [57, 191]

Characteristic	Earth-Bound (1 g) motion sickness	Space motion sickness (0 g)
Onset	Ramps up, symptoms added in sequence: salivation, pallor, cold sweat, stomach awareness, nausea, vomiting Rate depends on duration/intensity of stimulus	Sudden onset of vomiting, minimal warning Begins minutes to hours after entry to 0 g
Duration	Depends on duration/intensity of stimulus Most adapt to continued stimulus in days to weeks	8–72 h, typically 24–36 h Always resolves
Time Profile	Trapezoidal, height and slope depend on stimulus intensity	Similar to step function, consistent unless provoked by motion
Gastrointestinal Symptoms	Stomach awareness, anorexia, nausea, vomiting May be continual and severe with retching	Stomach awareness, anorexia, nausea, vomiting Usually mild, brief
Autonomic Symptoms	Skin pallor, cold sweats, abnormal gastrointestinal activity	Some flushing/warmth, abnormal gastrointestinal activity, constant ileus
Central Nervous System	Variable; some develop sopite syndrome with somnolence, lethargy, often physically/mentally impaired	Somnolence, lethargy, variable headache, averse to physical/mental activity Can adequately perform trained tasks
Resolution	Decreased symptoms over many hours	Rapid recovery (1–3 h) once begun Can recur on return to 1 g
Incidence	High variability with intensity	Up to 70%

Two theories have been proposed to account for SMS. (1) The fluid shift hypothesis suggests that SMS occurs when intracranial pressure, cerebrospinal fluid pressure, and/or inner ear fluid pressure increases and alters vestibular end organ function. This hypothesis suggests that central volume expansion lowers the threshold for vestibular stimulation, leading to increased motion sensitivity [175, 176]. (2) The sensory conflict hypothesis describes the conflict between actual and anticipated otolith signals, leading to a mismatch between visual and vestibular information [175, 177, 178]. Additionally, sensory feedback pathways also differ from the actual motor commands, enhancing the conflict. Sensory conflict is the most accepted mechanism for understanding SMS. Head movements, especially in the pitch plane [179],

unusual visual patterns, and adverse reaction to orientation illusions have also been associated with increased SMS symptoms.

Due to the high prevalence of SMS in astronauts, significant research has been conducted to predict who may be most at risk. Questionnaires [180], laboratory studies including provocative visual and vestibular stimulation [181], and personality trait analysis [182] have been used in attempts to predict the degree of SMS, all without significant success. Standard clinical measures of vestibular end organ function do not predict SMS [183]. Minimal association has been found between individuals who experience motion sensitivity during parabolic flight and those who later develop SMS [120, 184]. Interestingly, parabolic flight paradigms may have found a possible connection between changes in torsional ocular alignment associated with the effects of otolith reflex pathway asymmetry decompensation. When the otolith organs are offloaded, any underlying otolith asymmetry may be recovered [154, 185–189]. This has been documented in spaceflight as well and noted to persist throughout long-duration missions and upon return to Earth [190]. Further work continues to evaluate the predictive value of pre-flight evaluation of torsional ocular alignment as a metric to identify individuals at risk for significant SMS.

Perceptual Changes in Microgravity

Spatial disorientation is common in microgravity due to changes in otolith sensitivity and altered central integration of extra-vestibular inputs. Perceptual illusions were described initially in the 1960s as the "wrong position of the body in space" [192]. These sensations were highly variable, developed abruptly or gradually, and were present regardless of the eyes being open or closed. Illusions consistently resolve with acceleration changes and can be reduced with increased proprioception, such as using footholds to anchor oneself [192, 193]. Approximately 80% of crew members have described illusory sensations of self and the surrounding during active head movements [194], suggesting that internal estimates of verticality are unstable. This is likely to occur only in those with appropriate vestibular function; sensory illusions are not expected in those with vestibular areflexia [192].

Duration of microgravity exposure is important in the formation of perception change; however, nearly all crew members experience at least some disruption of spatial orientation on transitioning to microgravity [195]. In parabolic flight, individuals often have difficulty in determining "up" or "down," instead deferring to the position of the head as "up" and feet as "down" [196]. This inversion illusion [192] occurs early in the transition to microgravity as the otolith are abruptly offloaded and typically disappears with longer duration exposure as the body becomes the frame of reference for self [196]. Many describe the inversion illusion as a sense of tumbling backward upon entering microgravity, or as a prolonged sense of being upside down [195]. Describing internal perception of verticality can be done using a subjective visual vertical (SVV) task. On Earth, correct verticality estimates depend on visual, proprioceptive, and vestibular cues, weighted in proportion to reliability [197]. The otolith reflexes are heavily involved in this estimate [198, 199]. In microgravity, however, the lack of otolith input leads to a bias in verticality toward the body's midline, or the idiotropic vector [197]. Upon return, the mean ability to complete this task returns to baseline, however, there is a significant difference in pre-post flight variability or precision. This variability suggests that otolith input may not immediately integrate reliably into maintaining spatial orientation [200].

Post-Spaceflight Vestibular Adaptation

The transition between gravity environments, whether into or return from microgravity leads to significant alterations in coordination between sensory feedback and motor control. These changing environmental demands can be challenging as crew members return to on-Earth gravitational conditions. The significance of understanding these effects was well described by American astronaut Scott Kelly, who stated that after returning from his 340-day mission, "… Every part of my body hurts. All my joints and all of my muscles are protesting the crushing pressure of gravity…I struggle to get up. Find the end of the bed. Feet down. Sit up. Stand up. At every stage I feel like I'm fighting through quicksand. When I'm finally vertical, the pain in my legs is awful, and on top of that pain I feel a sensation that's even more alarming: it feels as though all the blood in my body is rushing to my legs…" [201].

The effects of abrupt reintroduction of otolith information into the vestibular system can be striking and immediate; however, evaluating vestibular reflex pathways and adaptation mechanisms has been challenging. The vestibular system demonstrates functional changes within the first hours to days following a transition between gravity conditions and therefore likely requires evaluation quickly upon return as well as over the next days to weeks. Additional variables, such as mission duration, are also likely to play a role in the ability of the vestibular system to quickly and adequately compensate (Fig. 6.5) [202].

Post-flight functional decrements have been documented since the Apollo era, and have included reduced postural control and motor coordination, ataxia, oculomotor deficits, and significant lightheadedness [203]. Gait and postural control have been extensively evaluated. Most returning astronauts have described perception of self or environmental

motion during the return flight and after landing [57]. While kinematic data have shown that pre-flight coordination between head and trunk are compensatory during locomotion, coordination between angular head movement in the pitch plane and vertical trunk translation and head orientation is moderated after flight (Fig. 6.5) [141, 171]. These post-flight postural changes have been associated with various compensatory strategies for locomotion, including wide-based gait, increased arm use, and shorter step length [204].

Static postural stability is expected to recover in at least 5 days and follows a predictable course. The initial recovery phase is rapid, accounting for approximately 50% of postural stability recovery, followed by a slower recovery phase occurring over the subsequent 100 h [134]. As we further evaluate these recovery profiles more granularly, it is likely that there will be additional variables and time courses to consider. For example, other metrics have suggested that while postural stability may recover quickly, neuromuscular control may take up to 3 weeks to return to baseline [205, 206]. Mission duration and crew member experience likely also contribute to the recovery profile (Fig. 6.5) [135]. Experienced astronauts demonstrate less severe post-flight postural instability than first-time astronauts, suggesting that prior exposure may facilitate learned plasticity for adaptive motor strategies upon return [207]. Problematically, however, functional balance and gait assessments have known high interindividual variability and there are numerous metrics available that may be used to define recovery. Refining these protocols will assist future research identifying difficulties in balance and gait.

SCC and otolith-mediated ocular reflexes have also demonstrated atypical function post-flight. Even after short missions, post-flight visual target acquisition velocity has been described as slowed and gaze stabilization as less accurate than pre-flight function [208]. While some have found no substantial change in angular VOR function [208], others have described significant reductions in the caloric response at 10-days post-flight [209]. Functionally, decreased post-flight dynamic visual acuity has been reported, meaning that astronauts may experience oscillopsia with typical head movement [210].

Studies evaluating the OCR have found 70% reduction in response compared to pre-flight levels. The recovery timeline of the OCR has been associated with mission duration, with longer durations requiring at least 11 days for recovery, while shorter durations require only a few hours. While much adaptation occurs quickly, these data suggest that reintroduction of otolith information may not be immediate, especially for longer duration exposure (Fig. 6.5) [122, 211].

Reinterpretation of vestibular input during landing and immediately post-flight has been associated with increased attention to remaining sensory signals, especially vision [120]. During exposure to altered gravity environments, attenuation of vestibular input leads to "visual dependence" and visual orientation illusions. The increased weighting of visual information experienced during as well as the readaptation upon return has been compared to the sensory reorganization experienced by patients recovering from vestibular pathology [21, 118]. Perception of self-orientation is also altered. Visual and tactile sensory modalities are weighted differently for each individual, and post-flight postural strategies vary from pre-flight strategies, describing a shift in sensory organization [212–215]. Understanding how these sensory inputs are reweighted to address changes in environment will lead to improved methods for reducing the possible challenges associated with these effects.

Future Directions

Vestibular system adaptation has proven challenging to astronauts and requires our attention to fully understanding the long-term consequences of altered gravity environments. There is incentive to enhance our understanding of vestibular reflex function to reduce the often-debilitating effects of SMS and to improve operational performance in challenging environments. Initiating appropriate and timely vestibular system compensation will allow for improved operational performance and reduce symptoms associated with spatial disorientation in critical transitions. Work in this area is promising. Because astronauts with multiple spaceflight exposures demonstrate improved ability to transition between these environments [207], it is possible that astronauts could be habituated to various gravity conditions pre-flight. Essentially, crew would be trained to maintain various adaptation profiles depending on the gravity input available [216]. Establishing a training paradigm to allow for fluid transition between gravity conditions may reduce concerns regarding operational performance, at least to some degree.

Exposure to otolith-mediated illusions pre-flight may also reduce concerns for high-risk transitions. Developing appropriate simulations so that the crew can recognize when to expect altered perception is key to improving performance. Methods such as galvanic vestibular stimulation (GVS) may be useful in various conditions. Disruptive GVS applied in training paradigms may lead to reduced perceptual errors and improved functional performance upon reentry [217–219]. While the current use of capsules may reduce the level of precise performance expected by the crew, understanding these sensory illusions will lead to overall safer returns, especially if emergencies arise. In orbit, GVS may provide a method for recoupling the VOR pathways to mimic those provided in 1 g environments with the goal of reducing spatial disorientation and perhaps severity of SMS [220].

More broadly, maintaining appropriate otolith reflex pathway conditioning may also lead to improved vestibulo-

sympathetic reflex function, reducing the impact on bone remodeling or orthostatic challenge. Other concerns may also be addressed by regulating vestibular reflexes. For example, sleep can be a considerable issue for astronauts. While there are numerous contributors to disrupted sleep in orbit, such as altered hemodynamics, reduced motor activity, environmental noise, and overall discomfort [221], vestibular-mediated autonomic alterations may also contribute. Recent research suggests that the vestibulo-sympathetic reflex pathways may contribute to reported challenges transitioning between sleep states [160] and may also be implicated in reduced sleep duration due to increased vigilance regarding altered gravity and continued effort to maintain appropriate posture [222–224]. More work in this area is needed to better understand how to improve sleep quality for crew members. Adaptation or management of altered vestibular system information may provide improved quality of on-board experience, especially with long-duration missions.

Human space exploration is advancing and understanding the significant impact of altered gravity is key to our success in these endeavors. With goals of long-duration missions to the moon or to Mars, or even the ability for civilians to enter space, understanding and mediating the effects of the vestibular system will continue to play a role in future exploration.

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Intraocular Pressure Considerations

7

Yeni H. Yucel and Neeru Gupta

What Is Spaceflight-Associated Neuro-ocular Syndrome (SANS)?

The ability to see well is critical to the performance of all astronauts during spaceflight. The phenomenon of transient or persistent vision impairment in astronauts during space flight or following return to Earth has been recognized as a health risk that needs close attention [1]. This condition, coined as spaceflight-associated neuro-ocular syndrome (SANS) [2], consists of a cluster of pathological findings on eye examination including optic disc edema, retinal thickening around the optic disc, choroidal folds, retinal folds, and cotton wool spots [3]. A hyperopic shift is also observed [3]. To understand SANS, research programs have recently engaged in systematic ocular imaging studies to characterize and quantify changes in the eyes of astronauts. Optical coherence tomography (OCT) images show significant peripapillary retinal thickness increase and optic disc changes after spaceflight [4]. Recent studies reveal that retinal and choroidal changes in the eye occur early during spaceflight, persist throughout the mission, and require 45–90 days after returning to Earth to recover to preflight levels [5]. Furthermore, post-mission reductions in axial length of the eye and decreased anterior chamber depth have been noted and are likely to be associated with the observed hyperopic shift [5].

Fluid Shifts and SANS

Although the exact etiology of SANS is not yet known, microgravity-associated headward shift of intra- and extravascular fluids are implicated in this condition [6]. Optic disc edema is likely due to excessive interstitial fluid accumulation in the optic nerve head. Possible sources of this excess fluid include leaking capillaries of the optic nerve head [7, 8], and the peripapillary choroid [9] as they lack an effective blood–tissue barrier. Additional possible sources of fluid entry into the optic nerve head may be cerebrospinal fluid entry via optic nerve perivascular glymphatics [10]. The spread of excessive water from the optic disc into the surrounding retina may contribute to an increase in peripapillary retina thickness (Fig. 7.1). Other possible origins of excessive water entry into the peripapillary retina include the blood circulation via altered blood–retina barrier integrity [11], the vitreous via Muller cell aquaporin-4 [12], and the peripapillary choroid. The intraocular pressure (IOP) and the cerebrospinal fluid pressure (CSFp) would both be expected to influence the inner nerve fiber layer, the prelaminar and laminar parts of the optic nerve. We believe that fluid drained from the aqueous humor (AH) across neighboring vitreous [9, 13], and exiting across the retinal pigment epithelium [14, 15] to the richly vascularized choroid, may contribute to the retinal and choroidal

Y. H. Yucel (✉)
Departments of Ophthalmology and Vision Sciences and Laboratory Medicine and Pathobiology, Unity Health Toronto, St. Michael's Hospital, Temerty Faculty of Medicine, University of Toronto, Faculty of Engineering and Architectural Sciences, Physics, Faculty of Science, Toronto Metropolitan University Institute of Bioengineering, Science and Technology (iBEST), Toronto, ON, Canada
e-mail: yeni.yucel@unityhealth.to

N. Gupta
Departments of Ophthalmology and Vision Sciences and Laboratory Medicine and Pathobiology, Unity Health Toronto, St. Michael's Hospital, Temerty Faculty of Medicine, Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada
e-mail: neeru.gupta@unityhealth.to

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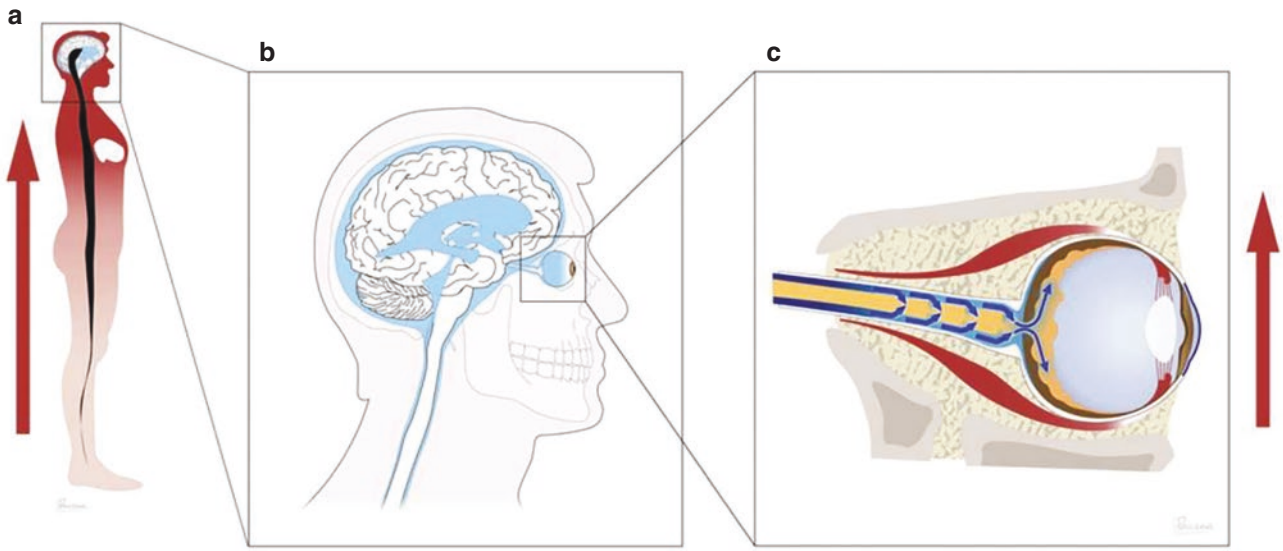

Fig. 7.1 The headward shift of fluid under microgravity conditions (**a**) moves cerebrospinal fluid (**b**) (blue) from the subarachnoid space around the optic nerve into the optic nerve head and retina (orange) and choroid (brown) via the glymphatic pathway (**c**) (blue arrows). The red arrows indicate the headward shift of fluid

changes. In addition to local hydrostatic pressure changes, this flow of fluid entry from the vitreous to the retina may be facilitated by a rise in oncotic pressure induced by plasma volume drops of 10%–15% while in flight [16].

Intraocular Pressure and SANS

Intraocular pressure (IOP) is a critical parameter to ocular function in health and disease states. It is a major risk factor for glaucoma, the leading cause of preventable irreversible vision loss projected to affect 111.8 million people by 2040 [17]. All treatments aim to lower IOP using a variety of pharmacological agents. The Ocular Hypertension Treatment Study showed that the incidence of glaucomatous damage increases with IOP [18]. Age greater than 40 years is also a risk factor for the development of both ocular hypertension and primary open-angle glaucoma, along with others such as myopia, ethnicity, and family history. Like any adult, it is recommended that all astronauts have regular eye examinations including IOP measurements and optic disc examination during and between spaceflights and post-retirement. Spaceflight-associated conditions including cardiovascular changes due to microgravity, hypercapnia, and low-grade radiation may be associated with IOP and glaucoma-like changes, and they should be taken into account with the above-listed risk factors. A critical review of the evidence regarding the role of IOP in the development of SANS is timely as private space companies (e.g., SpaceX, Blue Origin) aim to increase accessibility to spaceflight for civilian populations [19–21] with demographic and health characteristics that are different from those of astronauts.

The shape of the outer corneal-scleral shell is maintained by IOP which is finely regulated to prevent ocular hypertension and hypotony and vision-threatening conditions that arise due to swings in eye pressure. The light path to the retina depends upon optical characteristics of the cornea, AH, pupil, lens, and vitreous, all of which are also highly dependent on the IOP. The light-sensitive retina sits on the choroid, a pigmented and highly vascularized layer, supported by the underlying sclera which is an opaque and fibrous outer layer. Their shape and integrity also depend upon IOP. Various parameters such as the axial length between the cornea and retina, in addition to anterior chamber depth, can be altered during disturbances of globe shape. As IOP depends on both ocular hydrodynamics and hemodynamics, its measurements can inform us about both of these highly regulated systems. Although changes in IOP are not included in the definition of SANS, IOP and its hydro- and hemodynamics-determinants are fundamentally relevant to our understanding and prevention of this sight-threatening condition. Here we will review and tie together observations of IOP changes during and after spaceflight, discuss methods to measure IOP, and re-iterate the role of IOP as a physiological parameter that should be monitored as part of eye changes in SANS. This approach will guide studies on the efficacy and safety of SANS countermeasures.

IOP Conceptual Model: Ocular Pressure–Volume

Several conceptual models can contribute to our understanding of IOP. In the ocular pressure–volume model, IOP is an exponential function of the total ocular volume (Vt) and the elasticity (*E*) of the corneal-scleral shell (IOP = (Vt, *E*))—the theoretical basis for indentation tonometry and tonography [22]. Another model treats steady-state IOP as a function of aqueous flow (*F*), outflow conductance (*C*), or "facility" and episcleral vein pressure (EVP) [23]. This model (IOP = *F*/*C* + EVP) is the theoretical basis for understanding ocular hypertension and hypotony as well as current medical and surgical treatment to lower IOP to treat glaucoma. Both models provide insight into IOP physiology [24].

Aqueous humor and vitreous fluid, and uveal blood, especially choroidal blood are the main compartments generating IOP in "normal gravity" or 1g conditions (Fig. 7.2).

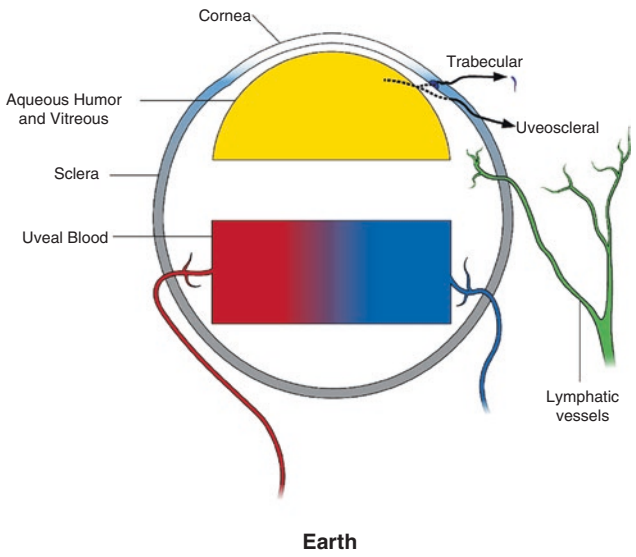

Fig. 7.2 Schematic of ocular hemodynamic and aqueous humor and vitreous fluid compartments generating IOP. Extraocular and intraocular arteries are represented in red, with extraocular and intraocular veins in blue. The uveal (ciliary body and choroid) blood compartment is represented by a red/blue rectangle. The combined aqueous humor and vitreous fluid compartment is represented in yellow. Trabecular and uveoscleral outflow pathways from the anterior chamber are indicated by black arrows. Trabecular outflow drains into episcleral veins (small blue). Lymphatic vessels in green drain fluid from the intraocular and extraocular interstitial tissue (white background). Figure adapted from Kiel et al. (2010) [24] and Watenpaugh and Hargens (1996) [25]

Aqueous Humor Dynamics and Regulation of IOP (Fig. 7.2)

AH hydrodynamics determine the quality of AH, its chemical composition, electrolyte balance, and pH. Circulating AH supplies oxygen and nutrients to the avascular tissues of the anterior segment such as the cornea, trabecular meshwork, and lens and subsequently removes metabolic waste products. Although difficult to measure with currently available techniques, some AH drains into the vitreous cavity [26] and provides regular water content to the vitreous. Compared to the plasma, the aqueous has a low protein level (about 0.02 g/ml compared to 7 g/ml) [27]. Briefly, AH secreted by the ciliary epithelium into the posterior chamber (also called AH inflow), passes between the anterior surface of the lens and posterior surface of the iris into the anterior chamber. The AH drains from the anterior chamber through several routes (also called AH outflow) [26, 28]. AH flows out of the eye either through the trabecular meshwork, eventually reaching the systemic blood circulation via the episcleral veins [29–31], or through the ciliary body into suprachoroidal spaces, and sclera via the uveoscleral route [32]. A growing body of evidence shows drainage of AH from the eye also via lymphatics [33, 34], with lymphatic channels in the human ciliary body identified using molecular markers [33]. Methods to measure the AH dynamics parameters including aqueous production, trabecular outflow, EVP, uveoscleral outflow [26], and lymphatic drainage [34] are available. The development of novel dynamic non-invasive techniques to assess specific outflow pathways to determine the drivers of intraocular pressure and their relative contributions will guide individualized care.

All currently used IOP-lowering glaucoma eye drops target aqueous inflow and/or outflow pathways. Common IOP-lowering pharmacological agents either reduce aqueous inflow by action on beta-adrenergic receptors and carbonic anhydrase inhibitors or increase outflow via their action on α_2-adrenergic receptors of the autonomic sympathetic system, prostaglandin $F_{2\alpha}$ receptors, and inhibition of Rho kinase [35].

Some aqueous outflow structures such as the trabecular meshwork, canal of Schlemm and episcleral vein; in addition to playing a filtering role, participate in cardiac-induced pulsatile aqueous outflow mechanisms with systolic expansion of the choroid [31]. Thickening of the choroid during spaceflight may cause reduced cardiac pulsatility-induced AH outflow, in addition to IOP increase due to increased volume effect.

Unlike increased IOP, low pressure in the eye known as ocular hypotony, especially after long-term or multiple missions has often been overlooked as a potential risk factor. Although the clinical signs and symptoms of ocular hypotony are usually reversible in acute and transient stages, chronically decreased IOP can have deleterious effects on intraocular tissue morphology and function [36–38]. An imbalance of aqueous production and outflow (trabecular, uveoscleral) after return to Earth after a long-duration mission may contribute to alterations of aqueous flow dynamics. These may be associated with compromised oxygen supply, nutrition, and metabolic exchange within the anterior chamber, and water content to vitreous, leading to ocular hypotony with complications of retinal [39] and choroidal folds, detachment [37, 40–42], and posterior pole and scleral flattening [43]. Close follow-up of IOP is required after landing to rule out prolonged ocular hypotension. Unfortunately, treatment options to manage ocular hypotony are limited.

IOP in Relation to Ocular Volume

If corneal-scleral elasticity is constant, acute changes in IOP must involve changes in ocular volume. AH and ocular blood volume changes are the most labile and are responsible for the greater part of IOP variation (Fig. 7.3). Uveal blood, especially choroidal blood and aqueous humor and vitreous fluid are the main compartments generating IOP in 1 G conditions (Fig. 7.3a). In this model, we have combined aqueous humor with vitreous given that the AH provides water content to the vitreous body [26]. In early microgravity, due to a headward shift of fluid, the volume of intraocular blood increases, leading to IOP elevation (Fig. 7.3b). During adaptation to microgravity, aqueous humor volume decreases with normalization of IOP (Fig. 7.3c).

During early space flight under microgravity conditions, there is an increase in uveal volume (ciliary and choroid) induced by congested blood vessels (Fig. 7.3b). There is also increased aqueous production and decreased trabecular outflow due to elevated EVP. Reduced uveoscleral outflow and lymphatic drainage would contribute to elevated IOP. Aqueous volume changes may occur with transient imbalances in aqueous production and outflow. Similarly, ocular blood volume changes may occur with blood flow imbalance into and out of the eye, especially at the level of the choroid [44], as evidenced by increased choroidal thickness observed in astronauts during spaceflight [5].

A decrease in aqueous production, with simultaneous increases in trabecular, uveoscleral and lymphatic drainage, would reduce aqueous and vitreous volume allowing a return to baseline IOP.

In early landing, uveal blood (Fig. 7.4a) volume decreases compared to adapted microgravity (Fig. 7.4b) with an IOP decrease. In late landing, the aqueous humor/vitreous volume is restituted with normalization of IOP (Fig. 7.4c). In landing, a decrease in volume of the uvea (ciliary and choroid), relative increase in trabecular outflow due to decreased EPV, and increased uveoscleral outflow with lymphatic flow would contribute to IOP lowering. A delayed increase in aqueous production with decreases in trabecular outflow, uveoscleral outflow and lymphatic flow would contribute to a return to baseline IOP. For individualized countermeasures and treatment, it would be critical to monitor specific components of AH dynamics and ocular hemodynamics.

Neurohumoral and local control mechanisms involved in the regulation of the resistance at the level of ciliary and choroidal vasculature are not fully understood. Autoregulatory myogenic [45] and autonomic neural mechanisms [46, 47] regulate ocular blood volume during changes in arterial pres-

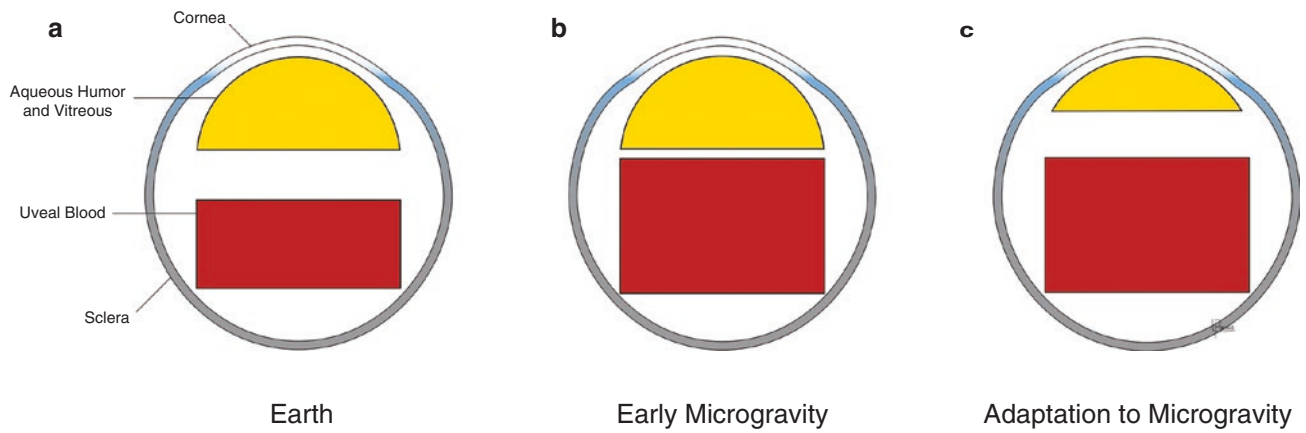

Fig. 7.3 Schematic of main ocular compartments generating IOP in Earth, Early in Space, and Adaptation in Space. Uveal blood, especially uveal blood (red), and aqueous humor and vitreous fluid (yellow) of the eye in 1g conditions. During early spaceflight under microgravity conditions, the volume of uveal blood increases due to a headward fluid shift. While in space, adaptation involves a decrease in aqueous humor/vitreous volume

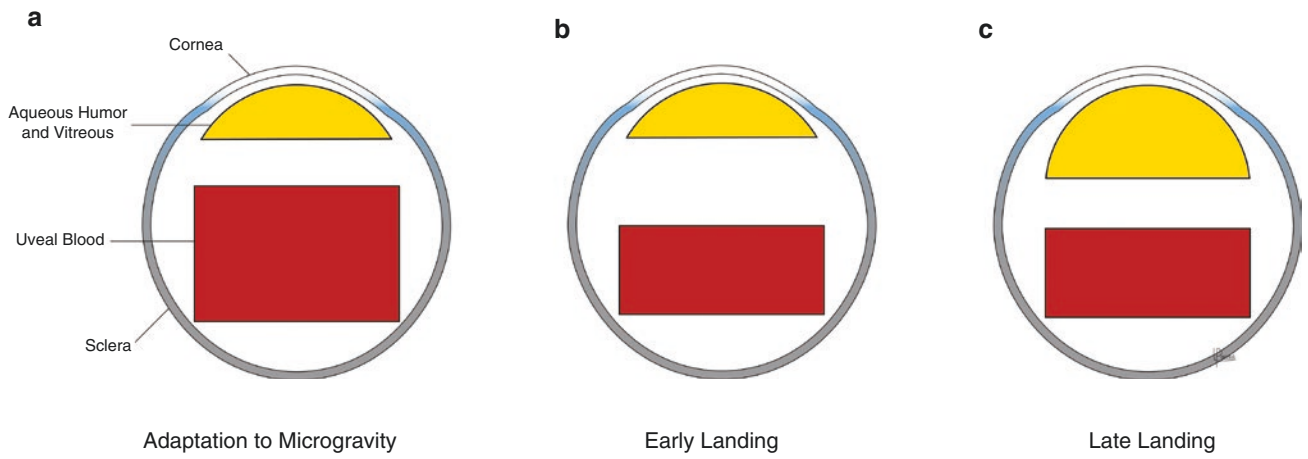

Fig. 7.4 Ocular compartments in transition to landing: Uveal blood (red), and aqueous humor and vitreous fluid (yellow) of the eye in adapted in space. In early landing the uveal blood component volume decreases. In late landing, the aqueous humor/vitreous volume increases

sure [45]. While increases in arterial pressure produce initial increases in IOP (Fig. 7.3b), this IOP elevation is not sustained. Instead, early elevated IOP increases the pressure gradient for aqueous outflow, causing a compensatory decrease of aqueous and vitreous volume so that IOP gradually returns to baseline (Fig. 7.3c) [45]. If the increase in blood volume is small, the compensation is relatively quick, whereas compensation for a larger increase in blood volume, takes longer. IOP falls below baseline when arterial pressure-induced distention of the vasculature is abruptly ended in early landing (Fig. 7.4b). This reflects a compensatory loss of aqueous and vitreous volume, which is gradually restored by continued aqueous production, until a return to baseline IOP (Fig. 7.4c). Raising arterial pressure elicits a modest increase in IOP under control conditions. A much larger increase is elicited when choroidal blood volume regulation is impaired by systemic vasodilation by pharmacological tools [45], by altered autoregulatory myogenic [45], autonomic neural mechanisms [46, 47], and neuro- and cardioendocrine mechanisms. Thus, ocular blood volume changes are strong influencers of IOP. Ocular blood volume changes are compensated by corresponding changes in AH and vitreous volumes which contribute to the IOP regulation.

IOP and Postural Changes

Postural changes are known to affect IOP with significant increases in IOP from the upright or sitting position to the supine position [48–50]. IOP has been shown to increase by 3–4 mmHg in normal subjects when lying supine, regardless of the time of the day [51, 52]. EVP is the only component of AH dynamics that is affected by body position, increasing by 3.6 mmHg from the seated to supine position. Mean IOP and mean EVP increase significantly from the sitting to the inclined position [53]. In contrast, the rate of AH formation is stable while subjects are alternated between an upright and inverted body position [54]. No changes to outflow facility are noted between sitting and supine positions [55].

IOP and Ocular Perfusion Pressure

Ocular perfusion pressure (OPP), calculated by the mean arterial pressure (MAP) minus the IOP [56], is an important parameter to assess tissue perfusion. To avoid the collapse of intraocular veins, IOP should remain below venous pressure within the eye. If IOP is higher than MAP, the perfusion of tissues fed by intraocular arteries will be reduced. Blood flow to the inner retina and optic nerve head by branches of the central retinal artery is mainly modulated by local autoregulation according to local metabolic demands as in other parts of the central nervous system. The outer and avascular portions of the retina receive nutrients and oxygen via diffusion from the choroidal blood vessels that do not receive feedback signals from the retina. The sympathetic and parasympathetic components of the autonomic nervous system substantially influence numerous ocular functions including ocular blood flow [47]. As postural IOP changes are larger in patients with autonomic failure compared with normal subjects [57], suggesting that the autonomic nervous system plays an important role in regulating IOP during postural changes. Continuous and simultaneous measurements of IOP and local mean arterial pressure (MAP) would be opti-

mal to monitor OPP during postural changes over time, during day and night cycles, and in microgravity conditions.

IOP, CSFp, and Translaminar Pressure Difference (TLPD)

Under normal physiologic conditions, the TLPD, the difference between IOP and the retrolaminar CSF, generates both a net posterior force on the surface of the LC and a hydrostatic pressure gradient within the prelaminar and laminar optic nerve. In glaucoma, pathology occurs at the level of the LC [58], and the TLPD has been proposed to be involved in its pathogenesis [59]. In addition, TLPD may be involved in conditions in which edema of the optic disc is prominent as in idiopathic intracranial hypertension, and obstructive hydrocephalus [60]. In vivo measurement of pressure directly around the LC is currently not feasible, proxies of the pressure in regions anterior and posterior to the LC, are IOP measured at the cornea and CSFp measured by lumbar puncture (LP), respectively. A limitation of these proxies to calculate TLPD is the difference in body position at which the measurements are taken. For example, Goldmann applanation tonometry is commonly carried out in the seated position while LP is performed in the lateral decubitus position. As both IOP and CSFp change with posture, measuring them in different conditions to calculate TLPD is problematic. TLPD in healthy controls is 1.4 mmHg when measuring IOP in the sitting position and the CSFp via LP in the lateral decubitus position [61]. However, a recent study in healthy subjects demonstrates that both CSFp and IOP change during postural changes. TLPD differences of 19.8 mmHg while seated, 12.3 mmHg while supine, and 6.6 mmHg while in the 9° head-down tilt position have been shown [62]. A limitation of this estimation is the assumption that CSFp at the lumbar level is similar to CSFp at the perioptic subarachnoid space. In addition, TLPD depends on LC thickness and its reduction in highly myopic eyes may be the histologic correlate of increased susceptibility to pressure-induced injury [63].

Continuous, simultaneous, and direct measurements of IOP and CSFp in nonhuman primates have shown that TLPD changes significantly and instantaneously from the supine to seated (+14 mmHg), supine to standing (+13 mmHg), and supine to inverted (−12 mmHg) positions. No significant TLPD change from the supine to prone positions is noted. CSFp showed greater relative change than IOP [64]. The 56% increase in TLPD during waking hours in nonhuman primates [65] was reported to match the increase in TLPD due to postural change from supine to upright in humans [62].

Orbital Pressure and IOP

The orbital soft tissue surrounding the globe is confined by the bony orbital socket and semi-rigid fascia-like tissue of the eyelid anteriorly. Most orbital blood vessels are tributaries of intracranial blood vessels, and are in direct contact with ocular blood vessels, and share similar autonomic control [66, 67]. They are also connected to extracranial blood vessels via anastomoses [68].

Orbital conditions including vascular malformation such as Sturge-Weber syndrome, orbital tumors, and endocrine orbitopathy can cause congestion of the orbital veins and a subsequent rise in EPV [69]. Large vessel venous obstruction (superior vena cava syndrome), cavernous sinus thrombosis, and carotid cavernous sinus fistulas can cause an increase in superior ophthalmic vein pressure and a rise in EVP [70]. Sturge–Weber syndrome in older children and young adults with port-wine stains (hemangiomas) on the face near the eye can include intrascleral or episcleral anastomoses that increase EVP [71] and in turn, IOP [72, 73]. Some of these conditions may also be associated with increased choroidal thickness [74–76]. Further volumetric imaging studies of the orbital tissue components, intra- and extravascular fluids in and around the globe, and CNS, are needed to understand changes in SANS [77]. Lymphatics in the orbit [78] are implicated in the drainage of fluid from the orbit and contribute to lymphatic drainage from the eye [35] and perioptic subarachnoid space [79] (Fig. 7.5).

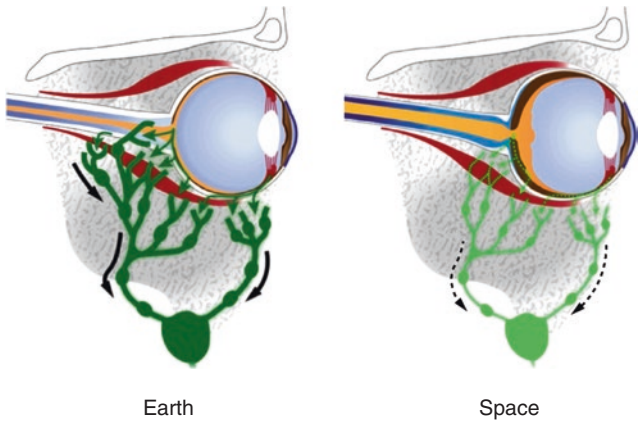

Fig. 7.5 Schematic of the globe and orbit with lymphatics draining excess fluid into regional lymph nodes (green) on Earth (left) and in space (right). Under microgravity conditions in space, lymphatic drainage from the optic nerve and the eye is reduced with fluid accumulation in the optic nerve and retina (orange), and choroid (brown). Extraocular muscles and orbital soft tissue are presented in red and gray, respectively. Black arrows represent lymphatic flow. The black arrow with dotted line represents decreased lymphatic flow in microgravity. The orbital bony socket is represented in white superiorly

Autonomic and Central Regulation of IOP

The autonomic nervous system (ANS) serves as an important interface between body, central nervous system (CNS), and external stimuli [80–82]. The ANS sympathetic noradrenergic system (SNS), parasympathetic cholinergic system (PCS), and sympathetic adrenergic system (SAS) together control visceral functions to maintain homeostasis. The SNS and PCS play key roles in regulating optimal cardiovascular function to maintain the physiological state of astronauts despite the stressors of spaceflight [83]. The role of the autonomic system in the regulation of IOP is complex, acting on both AH dynamics and ocular hemodynamics. Evidence for autonomic sympathetic and parasympathetic innervation of the anterior episcleral circulation comes from histological studies in primates [84] of trabecular meshwork and scleral spur [85]. In rodents, electrical stimulation of the superior salivatory nucleus elicits an increase in IOP and EVP [86] and choroidal vasodilation [87]. Changes in choroidal thickness due to vascular congestion during the flight [5] may contribute to altered thermal environment in the central retina [88, 89], especially when central body temperature is increased during spaceflight [90]. The action of topical adrenaline or epinephrine on the IOP, aqueous humor dynamics and ocular hemodynamics has been studied [91–94], however the role of adrenaline as a neurohormone of the sympathetic adrenergic system on the eye's physiology is not well elucidated.

Both sympathetic and parasympathetic systems are involved in the regulation of the systemic lymphatic system [95], implicating them in lymphatic drainage from the eye, orbit, and cerebrospinal fluid.

Mechanisms of central regulation of AH dynamics are underexplored. Early experiments in primates show that intracranial hypertension induced by inflation of an epidural balloon leads to an increase in IOP [96]. A recent study in rats demonstrated that a neural feedback mechanism driven by ICP regulates conventional outflow facility that leads to IOP increase [97]. Experimental studies have demonstrated the impact of the hypothalamo-pituitary-suprarenal system in the regulation of IOP [98–100]. Delivery of hypo-osmotic agents into the third ventricle resulted in IOP elevation, while the delivery of hyperosmotic agents lowered IOP [101]. Third ventricle injection of substance P [102], thyrotropin-releasing hormone (TRH) [103], or arginine vasopressin [103] also elevated IOP. Injection of a GABA(A) receptor antagonist bicuculline into the dorsomedial and perifornical hypothalamus in rats increased IOP [100].

Circadian Changes

In the general population, IOP ranges between 10 and 20 mmHg with an average of 15.5 mmHg. IOP is a dynamic parameter with distinct circadian rhythms and spontaneous variations [104]. Diurnal variation for normal eyes is between 3 and 6 mmHg. IOP undergoes nocturnal elevation due to circadian rhythm, independent of posture changes [50, 105–107] and variations of 24-h IOP in the right and left eyes are similar [108].

AH flow also demonstrates a circadian rhythm with a peak in the morning and at night [109, 110]. The role of the central circadian clock via melatonin and the possible role of the ocular circadian clock are active areas of research [111]. Recent studies in mice suggest that IOP rhythm entrainment is mediated by a systemic rather than local signal [112] and that intact adrenal function [113], glucocorticoids, and the sympathetic system [114] are required for manifest circadian rhythms of IOP. At this time, it is unknown whether circadian rhythm changes observed in spaceflight [115, 116] contribute to IOP changes.

IOP Changes in Space

Given the immediate increase in IOP noted upon entering weightlessness, studies of IOP are of great interest. The first inflight IOP readings performed during a D1 Spacelab mission showed a rise of 20–25% in IOP 44 min after entry to microgravity conditions [117]. A subsequent study documented a 92% increase in IOP after 16 min entry in microgravity (German–Russian MIR mission) [118]. A 114% increase in IOP was reported during a D2 Spacelab mission [119]. Furthermore, data acquired on the first day of six different space shuttle missions for 11 subjects revealed an increase of 4–7 mmHg [120]. While IOP has been reported to return to baseline values within the first week of microgravity exposure [118–120], a mean IOP rise of 26.3% in a woman astronaut was still present at day 8 during spaceflight [121]. Thus, currently published data suggest that IOP increases upon entering weightlessness [118, 119]. Chronically elevated IOP has not been observed in astronauts during long-duration ISS missions. Tonometry data from the Lifetime Surveillance of Astronaut Health study of 15 subjects suggested no change in IOP on day 30 in flight, and 30 days prior to return to Earth compared to pre- or postflight. The IOP among subjects with optic disc edema on fundoscopy upon

return to Earth did not differ from remaining crew members [121]. After return from long-duration spaceflight, IOP values were similar to preflight measures (10–14 mmHg vs. 10–16 mmHg, respectively) [3]. IOP measured after landing on Earth may be lower than preflight levels as suggested by postflight decrease of IOP compared with preflight measurements observed in Apollo astronauts [123].

Despite the sustained headward fluid shift and cardiovascular changes during the first few days of spaceflight, the immediate IOP increase followed by a return to baseline within the first week suggests compensatory mechanisms that are not yet fully elucidated. If we assume this early IOP increase is due to headward fluid shift and cardiovascular adaptation leading to an increased in intravascular volume, especially in the uvea, the compensatory mechanisms may relate to aqueous inflow and outflow changes that decrease AH volume. Understanding these compensatory mechanisms are important to understanding the long-term effect of these changes.

During long-duration missions, cardiovascular changes of decreased mean arterial pressure (MAP) and increased cardiac output (CO), indicate a lower systemic vascular resistance (MAP/CO) [124]. These changes alter ocular blood volume and exert influence on IOP. Neurohormonal changes implicated in the cardiovascular adaptative process may also influence both ocular hemodynamics and hydrodynamics. Thus, IOP changes are an integral part of the development and progression of ocular changes during flight, and recovery after landing. While determinants of IOP such as ocular hydro- and hemodynamics in the development and progression of SANS remain relatively unexplored, IOP is an important parameter to include in future studies to understand, prevent and treat SANS.

IOP decrease below baseline after landing may also be explained by a decrease in choroidal vascular congestion and delayed recovery of decreased aqueous volume by changes in aqueous inflow and outflow. Measurements of episcleral pressure changes, and outflow facility performed after landing can help to understand these compensatory changes.

IOP is a dynamic parameter with many influences, with distinct circadian rhythms, and spontaneous variations [104]. Its measurement depends on the devices used to evaluate IOP before, during, and after flight. In addition, the training of operator with the device, time of the day, body position, are critical to insights into IOP elevation. In most IOP studies in astronauts, details regarding IOP measurement methodology are lacking. Future studies should disclose this important information per subject rather than reporting only group differences. Long-term spaceflight-induced IOP changes may be in the order of a few mmHg, so more sensitive IOP measuring devices can better assess IOP changes.

Elevated CSFp was previously believed to be related to SANS given the swollen optic disc appearance of papill-edema and optic nerve edema observed [125, 126]. The observation that CSFp does not go up under microgravity conditions has questioned the role of high CSFp in astronauts [127]. There is no evidence of sustained IOP increase [3, 117, 128] or decreased CSFp. Carefully designed studies with simultaneous IOP and CSFp measurements will allow correlation of their changes with retinal, optic nerve, and choroidal changes observed by ocular imaging during and after flight.

In addition to microgravity, other extreme conditions such as hypercapnia [129, 130] and various type of exercise regimes [131–144] likely contribute to IOP changes during flight and to SANS development. Whether chronic low-dose radiation exposure is associated with IOP changes and SANS also need to be studied.

Countermeasures such as exercise with or without the Advanced Resistive Exercise Device (ARED) and Lower Body Negative Pressure (LBNP) suit are used to mitigate microgravity-induced bone loss, muscle atrophy, and cardiac deconditioning [145].

The effects countermeasures on IOP and SANS are not yet known. Studies in experimental models and on-ground analogs that mimic microgravity conditions will help to unravel the relationship involved in changes of IOP to SANS and the efficacy and safety of countermeasures.

IOP in Microgravity Models

Ground-Based Analogs

As space missions are costly and low in number, human studies in ground analogs are good alternatives for gravitational research that can complement and inform research studies in space [146]. The main ground-based analogs are head-down tilt bed rest and dry immersion.

Head-Down Tilt (HDT) Bed Rest

HDT bed rest is the most common ground-based model used to study the physiological effects of microgravity on the cardiovascular and musculoskeletal systems [147]. The HDT bed rest mimics cephalic fluid shift, immobilization, confinement, and inactivity. The subject remains in the supine position at −6 degrees HDT bed rest for either short periods (from 1 week to 1 month) or sometimes longer periods (>1 month). HDT bed rest may be used to understand eye changes during headward fluid shift. Subjects who underwent 70-day −6° HDT bed rest showed an increase in OCT peripapillary retinal nerve thickening [148], unlike subjects who underwent 4.5-h-HDT at −6°,−12°, and −18° tilt angles or 14-day exposure to −6° HDT bed rest [149]. Healthy subjects undergoing strict HDT bed rest showed a larger increase in peripapillary total retinal thickness compared to 20 astronauts during ~30 days in spaceflight [150]. Interestingly, choroid thickness shows a larger increase in astronauts compared to the strict HDT bed rest subjects.

−6° HDT bed rest studies have shown inconsistent findings regarding IOP. Early studies showed normalization or lower IOP within 5–6 days [151], while more recently, an increase of 2 mmHg after 10 days has been reported [149]. One −6° HDT study of 14- and 70-days observed an increase in IOP with +1.42 and +1.79 mmHg from baseline, respectively. Systematic comparisons of spaceflight IOP data and HDT bed rest studies with close attention to IOP measuring device, body position and time of the day, are needed. The sympathetic system is decreased in HDT bed rest and not in spaceflight [152], suggesting differences that should also be considered.

HDT bed rest studies may also help to study possible risk factors for SANS such as myopia [153], and its effect on the water content in the vitreous using MRI [154].

Dry Immersion

In the dry immersion model of microgravity, the subject remains immersed in thermoneutral water covered with an elastic waterproof fabric, isolating the subject from the water. Thus, the subject floats freely while remaining dry. One of the main features of dry immersion is that it imitates the absence of any supporting structure for the body, centralization of body fluids, immobilization, and hypokinesia observed during spaceflight [155]. Dry immersion rapidly induces a wide range of physiological effects of weightlessness including cardiovascular alterations [156] associated with sympathoexcitation [157] and possible effect on intracranial pressure (ICP) effects [158]. During 5-day dry immersion experiments, although IOP did not differ from baseline in the healthy eye, intraocular fluid production rate (F) was decreased in 60% of cases by day 1 [159].

Ground-based analogs such as HDT bed rest and dry immersion represent an opportunity to better understand IOP with rigourous IOP measurement technologies.

Countermeasures

Exercise

To mitigate muscle atrophy due to microgravity, astronauts undergo 2.5 h of intensive resistance and aerobic exercise nearly every day onboard the ISS [160].

Short-term exercise overall has an IOP-lowering effect [161]. Dynamic exercise has a greater IOP-lowering effect than isometric exercise [133], and the IOP-lowering effect of exercise increases with its intensity [134, 135]. Anaerobic exercise also seems to decrease IOP [136, 137]. With strenuous exercise, it appears that IOP is inversely related to plasma osmolarity during and after strenuous exercise [137]. Dehydration during strenuous exercise and elevated colloid osmotic pressure significantly reduced IOP compared with hydrated subjects with normal colloid osmotic pressure [162].

Although choroidal blood flow increases somewhat in the immediate post-exercise period [163], it is not yet known whether exercise-induced choroidal changes contribute to IOP changes during and after exercise.

Certain types of exercises such as weightlifting or exercise at maximal exertion can increase IOP. One study compared weightlifting with and without subjects holding their breath and found that IOP increased more prominently when the subject hold their breath [142]. Another study concluded that elevated ICP reduces ocular venous outflow in weightlifting subjects who are essentially performing a Valsalva maneuver, contributing to raise in IOP [143]. During maximal exertion, subjects are essentially performing a Valsalva maneuver known to increase IOP in the absence of other factors [144].

NASA's integrated resistance and aerobic training during a 70-day non-hypercapnia strict −6° HDT bed rest protocol was not associated with a significant difference in retinal thickening or signs of optic disc edema compared to a con-

trol HDT bed rest group though IOP was slightly higher in the exercise group [164]. Interestingly, −15° HBT bed rest for less than an hour was associated with a decrease in IOP in subjects undergoing either moderate-intensity aerobic, resistance or high-intensity interval aerobic exercise [165]. These differences highlight the impact of countermeasures that depends on duration and tilt angle of HDT bed rest. Integrating results from different HDT bed rest models is needed to better understand the short- and long-term effects of countermeasures.

Astronauts follow a rigorous exercise regime [160], so it is important to consider the effect of exercise in subjects who undergo regular exercise programs. A regular exercise program lowers baseline IOP, and diminishes acute decreases in IOP in the post-exercise period [140, 141, 166]. Exercise regimes may differ in type and intensity which may alter baseline IOP and their relative risk profile. IOP measurement before, during, and after spaceflight should consider time of the day in relation to exercise and should report individual data rather than strictly between groups, compared to the age-matched general population.

Lower Body Negative Pressure (LBNP)

LBNP using the Chibis Suit is commonly used by cosmonauts to counteract cephalic fluid shifts [167]. This countermeasure mitigates headward fluid shift, attenuating ocular changes (choroidal engorgement) associated with cephalad fluid shifts seen in HDT bed rest [168–170]. 15° head-down tilt increases IOP, while application of LBNP significantly reduces IOP [52]. The effect of LBNP on IOP during-6° HDT bed rest for longer periods is not yet known.

Artificial Gravity

Exposure to artificial gravity (AG) either continuously or intermittently simulates gravitational states on board the spacecraft. Enhancing adaptation during the mission to Mars gravity and re-adaptation to Earth [171], AG offers a countermeasure with the potential to address bone loss, cardiovascular deconditioning, and muscle weakening [172, 173]. AG is considered an integrated countermeasure because it addresses all of these systems [174] and can be combined with other countermeasures [172]. AG has been proposed as a potential countermeasure for SANS [171]. IOP increases observed in the supine position remained elevated under AG conditions in healthy volunteers [175].

Animal Models

Experimental animal studies both in space and on the ground may help us to better understand the role of IOP and the determinants of AH dynamics and ocular hemodynamics.

Animal Experiments in Space

Recent studies in mice on ISS at the Japan Aerospace Exploration Agency's mouse housing unit [176] demonstrated molecules involved in the regulation of intraocular fluids and of the blood–retina barrier. Immunohistochemical analysis of the retina revealed increased expression of aquaporin-4, a water channel mainly seen in the CNS, as a strong indication of altered blood–retina barrier integrity after spaceflight compared to controls. There was also a significant increase in the expression of platelet endothelial cell adhesion molecule-1 (PECAM-1) and a decrease in the expression of the BRB-related tight junction protein and Zonula occludens-1 (ZO-1) after spaceflight [11]. It is interesting to note that aquaporin-4 is implicated in the outflow of water from the vitreous into the retina [12].

Animal Ground Models

Nonhuman primates have been used in spaceflight to understand microgravity effects [177], and are also used in biomedical research to study IOP and AH dynamics-related h, based on their similarities with humans [178–181]. The nonhuman primate model has been used for continuous monitoring of IOP and ICP to evaluate posture-related IOP changes [64, 65]. Head-out water immersion experiments in primates show some similarities to cardiovascular deconditioning [182]. Similarities to man regarding CNS and CSF dynamics, eye and brain anatomy and physiology [179–181] make the nonhuman primate model may also be adaptable to study SANS with capacity to develop and validate of new non-invasive IOP measuring technology that can be used during spaceflight.

An experimental ground model of hindlimb unloading in rodents that mimics microgravity conditions has been developed by NASA to study bone loss, muscle atrophy, and cardiovascular changes observed in astronauts [183, 184]. Changes in gravitational forces and central venous pressure likely alter passive lymphatic flow [185, 186], and there is evidence that the active pump of cervical lymphatic vessels is inhibited [185]. The mouse model shows similar AH dynamics to men [187] and its small size has multiple advantages for biomedical science [188]. The mouse hindlimb

unloading model may be adapted to study eye changes induced by headward fluid shift and to study the interplay between the eye, cardiovascular system, and central nervous system. Recent studies show CSF entry into the optic nerve along small perforating pial vessels through sleeve-like paravascular spaces between vessel walls and aquaporin-4-positive astrocytic endfeet [10]. AH drains into cervical lymph nodes [35, 189], and these coincide with those into which CSF is also drained [190, 191]. Non-invasive in vivo quantitative techniques in mice [192, 193] and studies of these elusive fluid pathways in hindlimb unloading experiments may help to inform otherwise more expensive studies on Earth and in space.

Non-invasive IOP Measurement and Devices

Tonometry is used to measure IOP based on the relationship between the IOP and the force necessary to deform the cornea by a given amount. Several types of tonometers are used during spaceflight and in-ground analog experiments. Some are slit-lamp mounted devices, while others are portable. While a comprehensive review of tonometers is beyond the scope of this chapter, the main instruments been used on astronauts are highlighted below.

Goldman applanation tonometry (GAT) has been the standard in clinical practice for the measurement of IOP. It is, however, largely influenced by ocular properties and variations in corneal biomechanics [194]; it is subjective and prone to learning; its use outside clinical settings is limited by the need for topical anesthetic, fluorescein, and a slit-lamp microscope to perform measurements. The portable version of this is the Perkins tonometer. A portable applanation self-tonometer specifically designed for spaceflight used by Draeger and coworkers is based on an automatic measuring procedure and an optical sensor that replaces the eye of an examiner [128].

The Tono-pen is a handheld portable tonometer that determines IOP by making contact with the cornea by way of a probe tip, causing applanation/indentation of a small area. Topical anesthesia eye drops are used. After four valid readings are obtained, the average measurement is given together with the standard error. Some studies have reported that the Tono-Pen underestimates postural IOP responses [51, 195–197], while other studies do not during spaceflight [121].

Rebound tonometry (RT) (iCare, Tiolat, Helsinki, Finland) is portable and easy to use. Although it is a contact tonometer, topical anesthesia drops are not required and the tonometer has a disposable tip to minimize cross-infection. The device processes the rebound movement of a rod probe resulting from its interaction with the eye; rebound increases (shorter duration of impact) as the IOP increases. Six measurements are taken and their average is displayed. RT shows high reproducibility and less dependency on ocular characteristics [198–200]. RT has been used in a 7-day-HDT best rest study [151].

The TON-1 compact eye tonometer-tonograph in an impression tonometric method. The device is designed for easy and rapid measurements of true IOP, and quantitative monitoring of intraocular fluid and blood in the eye, and calculates tonometric, tonographic, and sphygmographic characteristics [201]. The TON-1 was used in a 5-day dry immersion experiment [159].

A pressure phosphene tonometer that is applied to the eye with closed eyelids has also been used during spaceflight [122]. It was reported that phosphene tonometer measurements may be influenced by eyelid skin edema due to fluid shifts [122].

Dynamic contour tonometry (DCT, or Pascal) is a slit-lamp mounted and contact IOP measurement device that may present some advantages. It contains a sensor tip with concave surface contour and a miniaturized pressure sensor. The results and quality score measures are provided digitally. DCT is considered an accurate technique [202], and is less influenced by central corneal thickness compared with GAT [203–205]. Additionally, it measures the ocular pulse amplitude which is the difference between the mean systolic and diastolic IOP. These characteristics may present some advantages for ground analog experiments.

Tonometry data is collected as part of medical testing requirements for astronauts, GAT mounted on a slit-lamp, measures pre- and postflight on subjects while seated, and the handheld Tono-pen is used by crew members on each other during spaceflight [121]. Understanding the principles, advantages, and limitations of various IOP measuring devices and effects of different contexts before, during, and after flight or in ground analog experiments is an important area of future research. Low-mass, low-volume devices that can be used during flight requiring to allow self-IOP assessment, or use by another astronaut, are important considerations.

IOP measurements during space flight are based on the assumption that the compliance of the cornea and sclera remain unchanged. However, it is not yet known whether biomechanical properties of cornea and sclera may also change. Rich in glycosaminoglycans [206–208], the corneal stroma may be altered in microgravity and this in turn, may affect corneal tissue elasticity, corneal thickness, and its deformation during IOP measurement. Variations after corneal refractive surgery are known to limit interpretability of tonometric readings [209, 210].

A single IOP measurement cannot accurately assess IOP, as measurements vary depending on the conditions under which they are taken (e.g., supine vs. erect, resting vs. exercise, on Earth vs. microgravity) as well as the state of the patient (e.g., underlying disease state, hydration status, medications, comorbidities, and stress).

Current IOP measuring devices used in clinical settings provide measurements at a single timepoint and are not able to represent the range of spontaneous IOP variations during a 24-h cycle or daily activities in an ambulatory setting [211, 212]. This is a limitation that prevents the ability to distinguish between spontaneous IOP changes and the effects of experimental or therapeutic interventions or of extreme physiological conditions such as microgravity. Contact lens sensors [104, 213–219] and implantable intraocular IOP sensors [220, 221] that can be used by telemetry to monitor IOP continuously represent an active area of research and development.

IOP measurements should ideally be performed with the same device with adequate calibration before, during, and after spaceflight, and by the same operator. Difference between operators depending on their level of training may be associated with significant disagreement [222]. Devices that are portable, user-friendly, sensitive to monitor minor IOP changes continuously without being affected by corneal conditions are needed. The development of a reliable and sensitive IOP measuring or surrogate measuring device with [223] or without a contact lens adapted to spaceflight would offer considerable information regarding important eye changes. Grounds analog experiments should be leveraged for the development and validation of new IOP measuring technologies. The advancements are highly relevant to understanding SANS and io developing countermeasures.

Future Directions for In-Flight Studies and Ground studies

The ambitious plans for future missions to MARS will present new eye health challenges in healthy and productive astronauts and need careful consideration. Long-duration spaceflights will introduce increased ocular risks that include IOP changes.

In preparation for these missions, space agencies must accomplish the following:

1. Assess IOP-associated risk for the eye health during their active life and after retirement of astronauts.
   1a. Improve IOP measurements in spaceflight: The design and the development of a compact and sensitive IOP measuring device and techniques adapted to IOP changes during spaceflight should be a high priority as current devices do not respond to these requirements.
   1b. Design and develop a wearable device to monitor IOP and other IOP-related parameters in an ambulatory setting that allows simultaneous and continuous measurements of other physiological parameters such as blood pressure.
   1c. Develop novel non-invasive devices to assess specific AH dynamics components including blood flow in and around the eye underlying IOP changes to guide personalized countermeasures.
   1d. Leverage ground analog experiments to study and assess IOP-related risk, assess potential sex-differences, and develop and validate IOP and related parameters as biomarkers of SANS with an interdisciplinary approach.
   1e. Develop individualized analysis methods to assess the relationship between IOP changes over time and other eye changes dependent on systemic, CNS and ANS physiology under varying doses and duration of microgravity conditions.
2. Develop or adapt rodent and nonhuman primate models to study SANS in relation to determinants of IOP regulation: ocular blood flow, fluid homeostasis in ocular and orbital tissues, lymphatic drainage, and their modulation by autonomic nervous system and hormones. The nonhuman primate model can help to validate new miniaturized IOP measurement devices under non-invasive conditions and in a continuous manner.
3. Develop and/or adapt pharmacological and other countermeasures to prevent eye changes in SANS including IOP-related risk, and evaluate the efficacy and safety of countermeasures.
4. Evaluate the efficacy and safety of multisystem countermeasures such as exercise regimes and LBNP or their combinations to prevent IOP changes and the development of SANS.

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Central Nervous System Neoplasms in Microgravity

8

Kolaparambil Varghese Lydia Johnson, Alex P. Michael, and Terje Saehle

Introduction

Since humans first inhabited the International Space Station (ISS) over two decades ago, the duration of space missions per astronaut have been limited to 1–12 months. Astronauts in low Earth orbit are also partially protected from galactic cosmic radiation (GCR) due to the Earth's magnetic field. The next steps in human exploration will include long-duration missions beyond low Earth orbit (LEO) and higher concerns for harmful effects of space radiation. Prolonged exposure to microgravity may also alter the central nervous system at the cytoarchitectural level [1], and it has been suggested that microgravity may even inhibit proliferation [2] of malignant glioma. Therefore, with the aim to protect astronaut's health and exploit space environment conditions to potentially develop on-ground countermeasures, the need to understand the behavior of the central nervous system (CNS) in space has emerged. The dismal knowledge regarding the characteristics of the combined effects of microgravity and space radiations arises interest in researchers, especially regarding the long-term risk to develop neurodegenerative diseases and cancer. Recent progression in aerospace medicine and research opened several questions regarding the behavior of the neoplasms in microgravity and under ionizing radiations and a potential treatment window [3, 4].

Central nervous system (CNS) neoplasms are solid tumors arising from the brain, meninges, or spinal cord with different prognosis dependent on their location and histology.

CNS neoplasms are considered to be rare but lethal tumors as they account around 30% of cancer deaths in children and young adults [5]. The 2016 World Health Organization (WHO) classification categorizes CNS neoplasms based on histogenesis and molecular parameters to help aid in identification and prognostication [6]. The grading of some CNS tumor according to this classification is consultable in Fig. 8.1.

The treatment and prognosis of CNS neoplasms vary according to the location, severity of symptoms, and the type of neoplasm. In adults, the majority of primary CNS tumors are malignant in nature and treated with a combination of surgery, radiation, and chemotherapy depending [7]. Unfortunately, even after initial disease control, the majority of malignant tumors progress and the mortality rate remains high [8].

In this chapter, two main areas of cancer research in the spaceflight environment will be covered: (1) Central Nervous System malignancies tumorigenesis and (2) tumor suppression. We will analyze the molecular bases of tumorigenesis in terrestrial gravity and hypothesize on the tumorigenesis in microgravity with close attention to the contribution of radiation. We with further evaluate the tumor suppressive characteristics of microgravity in the treatment of CNS tumors. The chapter aims to review the currently available literature regarding these arguments and to identify the role of microgravity on CNS neoplasms behavior.

Alex P. Michael and Terje Saehle contributed equally with all other contributors.

K. V. L. Johnson (✉)
Faculty of Medicine and Surgery, Università degliStudi di Perugia (Terni), Perugia, Italy

Space Medicine Group, European Society of Aerospace Medicine (ESAM), Cologne, Germany

A. P. Michael
Neurological Surgeon, Mercy Clinic Neurosurgery, Saint Louis, MO, USA

T. Saehle
Space Medicine Group, European Society of Aerospace Medicine (ESAM), Cologne, Germany

Norwegian Civil Aviation Authorities, Bodø, Norway

European Space Agency Medical Board, Cologne, Germany

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WHO grades of select CNS tumours

Diffuse astrocytic and oligodendroglial tumours	
Diffuse astrocytoma, IDH-mutant	II
Anaplastic astrocytoma, IDH-mutant	III
Glioblastoma, IDH-wildtype	IV
Glioblastoma, IDH-mutant	IV
Diffuse midlineglioma, H3K27M-mutant	IV
Oligodendroglioma. IDH-mutant and 1p/19q-codeleted	II
Anaplastic oligodendroglioma, IDH-mutant and 1p/19q-codeleted	III
Other astrocytic tumours	
Pilocytic astrocytoma	I
Subependymal giant cell astrocytoma	I
Pleomorphic xanthoastrocytoma	II
Anaplastic pleomorphic xanthoastrocytoma	III
Ependymal tumours	
Subependymoma	I
Myxopapillary ependymoma	I
Ependymoma	II
Ependymoma, *RELA* fusion-positive	II or III
Anaplastic ependymoma	III
Other gliomas	
Angiocentric glioma	I
Chordoid glioma of third ventricle	II
Choroid plexus tumours	
Choroid plexus papilloma	I
Atypica choroid plexus papilloma	II
Choroid plexus carcinoma	III
Neuronal and mixed neuronal-glial tumours	
Dysembryoplastic neuroepithelial tumour	I
Gangliocytoma	I
Ganglioglioma	I
Anaplastic ganglioglioma	III
Dysplastic ganglioeytoma of cerebelium (Lhermitte-Duclos)	I
Desmoplastic infantile astrocytoma and ganglioglioma	I
Papillary glioneuronal tumour	I
Rosette-forming glioneuronal tumour	I
Central neurocytoma	II
Extraventricular neurocytoma	II
Cerebellar liponeurocytoma	II
Tumours of the pineal region	
Pineocytoma	I
Pineal parenchymal tumour of intermediate differentiation	II or III
Pineoblastoma	IV
Papillary tumour of the pineat region	II or III
Embryonal tumours	
Medulloblastoma(all subtypes)	IV
Embryonal tumour with multilayered rosettes, C19MC-altered	IV
Medulloepithelioma	IV
CNS embryonal tumour, NOS	IV
Atypical teratoid/rhabdoid tumour	IV
CNS embryonal tumour with rhabdoid features	IV
Tumours of the cranial and paraspinal nerves	
Schwannoma	I
Neurofibroma	I
Perineurioma	I
Malignant peripheral nerve sheath tumour (MPNST)	II, III or IV
Meningiomas	
Meningioma	I
Atypical meningioma	II
Anaplastic (malignant) meningioma	III
Mesenchymal, non-meningothelial tumours	
Solitary fibrous tumour/ haemangiopericytoma	I, II or III
Haemangioblastoma	I
Tumours of the sellar region	
Craniopharyngioma	I
Granular cell tumour	I
Pituicytoma	I
Spindle cell oncocytoma	I

Fig. 8.1 Grading of central nervous system tumors (2016 WHO). Reprinted from [6] with permission

Environment

Microgravity

The space environment is hazardous, outlined by high vacuum, extreme radiation of galactic and solar origin, and extreme temperatures [9]. Perhaps the most obvious unique influence on the pathophysiology of CNS neoplasms during spaceflight is that of microgravity. Microgravity or zero-g is used to describe the condition of weightlessness experienced during spaceflight [10]. The term does not necessarily refer to a reduced level of gravity in an absolute sense, but to the lack of counteracting inertial g-forces or any other forces than gravity. Microgravity is expressed as a fraction of g, where g is the gravitational acceleration at Earth's surface, on average 9.81 m/s^2. This should not be confused with gravitational field. At ISS altitude, the gravitational field is around 90% of that on the Earth's surface. However, the ISS orbits the Earth in a constant free fall and with almost negligible air resistance. The inertial g-forces on ISS are therefore virtually absent and equivalent to micro-fractions (10^{-6}) of the normal force exerted on an individual on the surface of the Earth due to gravity. The lunar gravity of 0.16 g and Martian gravity of 0.38 g induce less gravitational forces than the Earth's gravity at ISS altitude, but the astronauts based on the surface of Moon or Mars are still exposed to higher gravitational load as compared to the microgravity environment experienced during orbit.

From now onwards, we will refer to the spaceflight gravitational environment as microgravity [11].

Space Radiations

The next largest hazard to take in consideration is that of ionizing radiations. Ionizing radiations are particles with a sufficient amount of energy which can totally discard an electron from its orbit, consequently generating a more positively charged atom. On the other hand, the non-ionizing radiation (Low energy) does not have adequate energy to separate

electrons. There are three naturally occurring types of ionizing space radiations; galactic cosmic rays (GCRs) originating beyond the solar system, localized trapped particle belts of electrons and protons (ERBs)—known also as Van Allen radiation belts—and solar particle events (SPEs) [12]. The Galactic cosmic rays (GCRs) are an isotropic flux of charged particles originating from sources beyond the solar system with unidentified origins which can penetrate through a typical spacecraft or an astronaut [13]. When the particles strike the spacecraft, hadronic cascades are also initiated and result in secondary particles. The average GCR absorbed per day in a mission to Mars has estimated to be around 1.75–3.0 mSv/day [14, 15]. The Van Allen radiation belts or ERBs are two zones confining the Earth in which energetic charged particles are trapped due to the Earth's magnetic field [16], and the planetary magnetic field various among other planets in our Solar System [17, 18]. The majority of the inner Van Allen Belt is located beyond the ISS orbit and protects the station from incoming particles. However, the South Atlantic Anomaly (SAA) is an area where the inner belt dips closer to Earth and expose ISS to large amounts of radiation. The Solar Particle Events (SPEs) are made mostly of protons with a high-value flux representing a risk for astronaut health, however, in contrary to the GCRs, they are feasible of defense [19]. The SPEs are shielded by the Earth magnetic field, so they are of greater concern for planetary and interplanetary missions. Very large SPEs are rare, but challenges in prediction of their occurrence may impose significant operational constraints or radiation risk to the crew.

To grasp the impact of ionizing radiations, it is crucial to distinguish the Low Earth Orbit (LEO) and the interplanetary space beyond LEO. In this section, the suborbital flights are not considered, as they operate at a low altitude avoiding the ERBs. On the ISS (LEO), the astronauts are partially protected from SPEs and GCRs due to the magnetosphere [20]. While in deep space, missions do not benefit from the protection against planet atmospheres against SPEs or GCRs. Consequently, SPEs and GCR will stumble the spacecraft with fluxes in a position-dependent manner. The average radiation dose-equivalent rate is around 4.3.84 mSv/day, three times higher than in LEO [14].

Lack of a strong global magnetic field and the thin atmosphere on Mars result in only minimal protection from radiation on the surface of Mars. According to the MSL-Rad workshop data, Mars surface and ISS radiation dose rates are similar, 0.213 mGy/day and 0.240 mGy/day, respectively [21]. The current maximal exposure of an astronaut to radiation, according to NASA indications, is set to 3% of the risk of exposure-induced death (REID) cancer fatality with a 95% confidence interval (C.I.) [22].

CNS Neoplasms Overview

The term central nervous system neoplasms refer to a group of heterogenous benign and malignant tumors [23] which ranges from an extremely invasive and nearly untreatable Glioblastoma multiforme to a non-invasive and treatable pilocytic astrocytoma. The CNS tumors can either be primary or secondary. They are the most common solid tumors in children in the USA, and responsible for approximately 15–20% of all childhood cancers. They are the leading cause of death in children between 0 and 14 years [24–26]. CNS tumors are estimated to occur with an incidence rate of 23.8 per 100,000 people in adults, and they account for 2% of all cancers [24].

The classification of this group of tumors has always been challenging, and it has been under constant revision and update since Bailey and Cushing's publication in 1926 [27].

Currently, the WHO 2016 Classification—in comparison to the WHO 2007 classification based exclusively on histogenesis [28]—categorizes CNS tumors into four grades also basing on molecular markers and genetic factors [6]. Moreover, new changes to the classifications of diffuse glioma have been suggested by the cIMPACT (the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy) with an upcoming fifth edition of WHO Classification in the current year 2021 [29, 30].

The criteria of WHO Classification are: (1) anaplasia, (2) mitotic activity, (3) endothelial cell proliferation, and (4) necrosis [31]. Thus, the grading of a CNS tumor is based on these criteria.

Grade I tumors do not meet any criteria, they are benign and slow growing tumors with a good prognosis, i.e., Juvenile Pilocytic Astrocytoma. On the contrary, Grade II tumors fulfill the criterion of anaplasia. They are either malignant or non-malignant slow growing tumors with the potential to recur as higher-grade tumors. For instance, diffuse astrocytoma falls in the Grade II category. Anaplasia and mitotic activity are the two criteria met by III grade tumors like anaplastic astrocytoma. They are malignant tumors that can progress to higher-graded tumors. Grade IV tumors, such as glioblastoma multiforme (GBM), meet all three or four of the above-mentioned criteria. They have a rapid reproducing rate and they are considered to be aggressive malignant tumors [32]. These CNS Grades are predicted to be switched into Arabic numeral nomenclature according to the WHO fifth edition preview [29]. The grading of some selected tumors is consultable in Fig. 8.1.

Glioma, a category of malignant brain tumors that includes high-grade glioma or glioblastoma and low-grade gliomas, is the most common histological form of primary

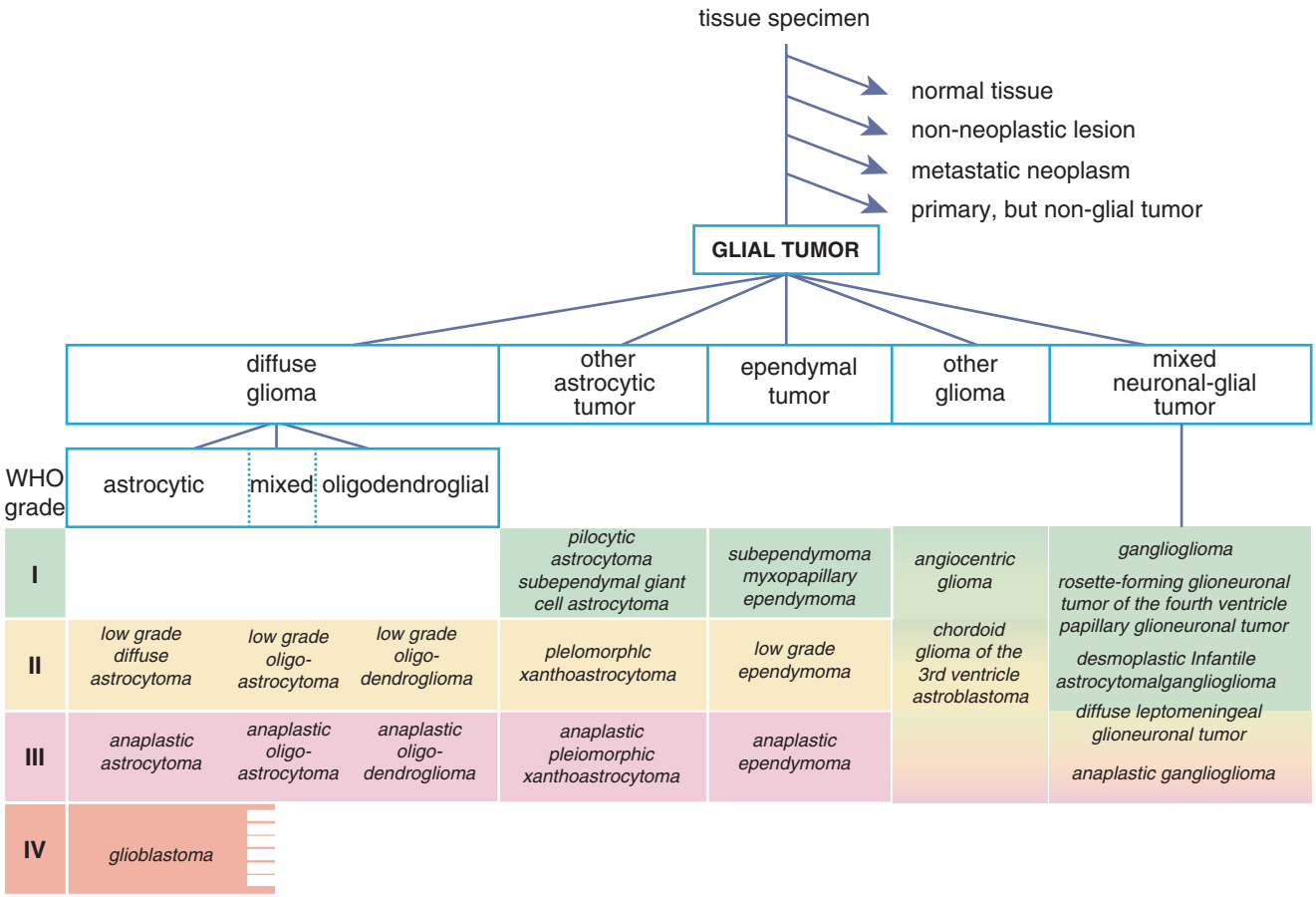

Fig. 8.2 Decision tree for histologic diagnosis of glial and neuronal-glial central nervous system neoplasms. Reprinted with permission from [34]

CNS cancer, therefore, this chapter will be focusing mainly on their classification and description [33]. Gliomas originate from progenitor glial cells or stem cells, and they mirror the glial characteristics after undergoing neoplastic transformation. There are several kinds of glial tumors, i.e. diffuse glioma, other astrocytic glioma, ependymal tumor, other glioma, and mixed neuronal-glial tumor (Fig. 8.2) [34].

Diffuse gliomas account for the vast majority of glial neoplasms in adults. They are defined by diffusive infiltration growth and tumor cell migration into the CNS parenchyma over large distances. The WHO grade II and grade III astrocytic tumors, the grade II and III oligodendrogliomas, the grade IV glioblastomas, and the associated diffuse gliomas of childhood are all classified as diffuse gliomas. The main molecular markers employed in the diagnosis of glioma are isocitrate dehydrogenase (IDH) mutation, chromosomal arm 1p19q deletion, O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation, telomerase reverse transcriptase (TERT) promotor mutation, alpha-thalassemia retardation syndrome linked (ATRX) mutation or loss of nuclear expression, and tumor protein p53 (Tp53) [6]. Other markers introduced by the cIMPACT are H3 K27M mutation and H3.3 G34 mutation, EGFR amplification, CDKN2A homozygous deletion, and +7/−10 genotype [35].

Briefly, IDH marker is at the core of differential diagnosis between glioma and gliosis, and in astrocytoma, oligodendroglioma, and even in 10% glioblastoma, it is positive. Mutation in both IDH 1 and 2, known as IDH Mutant, while the negativity to both forms of IDH is referred to as IDH wild type [36]. The 1p/19q co-deletion, on the other hand, is correlated with the diagnosis of Grade II and Grade III (anaplastic) oligodendroglioma. It plays an important role also in the prognostication of the outcome, and it is linked to procarbazine–lomustine–vincristine (PCV) chemotherapy sensitivity [37]. Basing on these two markers, diffuse gliomas have been classified into diffuse astrocytic tumors IDH-wildtype, diffuse astrocytic tumors IDH-mutant and oligodendroglial tumors IDH-mutant and 1p/19q-codeleted. Where it is not possible to conduct proper molecular testing, the tumor falls into the category of not otherwise specified (NOS).

In gliomas, TERT mutations in the promoter region (C228T and C250T) predict poor survival and radiotherapy resistance, especially in glioblastoma and oligodendrogli-

oma [38]. On the other hand, the methylation of the O^6-methylguanine-DNA methyltransferase (MGMT) gene promoter acts as a positive prognostic factor in GBM patients [39].

Grade II, diffuse astrocytomas, known also as low-grade infiltrative astrocytomas, can be IDH mutant or wild-type [40]. It affects mainly young adults with a mean age of 35 years. In almost 40% of the cases this grade II CNS tumor presents with seizure, and depending on the location and size of the lesion, it can induce focal neurological disfunctions [41, 42]. According to the cIMPACT-NOW recommendations, Astrocytoma IDH-mutant WHO grade II, would be graded as Astrocytoma, IDH-mutant, WHO grade 2, characterized as well-differentiated, lacking histologic features of anaplasia and with low or absent mitotic activity. Microvascular proliferation, necrosis, and CDKN2A/B homozygous deletions are absent [43]. A safe total resection and radiographic follow-up are indicated in this type of gliomas [44].

Grade III, anaplastic astrocytoma (AA), is a rapidly growing, diffusely infiltrating tumor with a median age of onset around 41 years [28]. It can also be IDH mutant or wild-type. Depending on the location of the tumor, the clinical manifestation is mutable. The symptoms include focal or generalized neurological deficits, headaches, visual and sensory impairment, strength loss, and gait disturbances; seizures are less common in anaplastic astrocytomas in comparison to low-grade gliomas [45]. The new recommendations characterize AA IDH-mutant WHO grade III glioma as an Astrocytoma, IDH-mutant, WHO grade 3 that manifests focal or dispersed anaplasia in concomitancy of significant mitotic activity. Microvascular proliferation, necrosis, and CDKN2A/B homozygous deletions are absent [43, 46]. Where necessary and regardless of the mutational status of the IDH gene, the first therapeutic strategy in the treatment of AA is a maximal safe surgical resection along with radiographic follow-up and chemotherapy as per Stupp protocol [47].

The previously classified oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, WHO grade II would be remain oligodendroglioma, IDH-mutant, and 1p/19q-codeleted, WHO grade 2 in the new recommendations [43]. Oligodendrogliomas constitutes around 5% of primary brain tumors and in most of the cases the symptoms are non-specific such as headache. Seizure is experienced in around 35–85% of the cases. Surgical therapy, chemotherapy, and radiation therapy are the main treatments of oligodendroglioma [48].

Glioblastoma (GB), a grade IV glioma, is one of the most aggressive brain tumors, with an estimated survival time of just 15 months after diagnosis [6]. This tumor can be either primary—in case of a de-novo development—or secondary, progressing from a low-grade glioma [49]. The former is denominated in the 2016 WHO Classification as IDH wild-type, while the latter as IDH-mutant for its various pathways of progression [50]. Both forms of GB have the same characterization, such as necrosis, pleomorphism, and vascularization. Early relapse is caused by its high resistance to radiotherapy and chemotherapy, as well as incomplete surgery due to diffuse invasion of the guerrilla cells [50, 51]. The main symptoms referred by the patients are headache—due to high intracranial pressure—seizure, cognitive impairment, and nausea. The therapeutical indications consist in a safe total resection followed by radiation and temozolomide. This type of tumors is very hard to treat, therefore, various clinical trials and studies are in progress. The main sword of Damocles in the treating of GB is represented by the heterogeneity dictated by the glioblastoma stem cells (GSCs) which were first described in 2003 [52]. These GSCs, as "the apex of a dynamic network," are renominated for their two key features being self-renewal and differentiation [53]. The heterogeneity which consists in the unpredictability of cancer cells' subtypes across individual tumors, de facto, seems to limit the efficacy of selective targeting of oncogenic pathways and of tumor microenvironment [54]. According to the new recommendations, glioblastoma, IDH-mutant, WHO grade IV should be renominated as Astrocytoma, IDH-mutant, WHO grade 4, and the previous wild-type grade II diffuse and anaplastic astrocytomas, as well as glioblastoma, IDH-wildtype, WHO grade IV are suggested to be classified as glioblastoma, IDH-wildtype, WHO grade 4 for their poor outcome predicted by TERT, EGFR and + 7/−10 genotype [43]. The glioblastoma, IDH-wildtype, WHO grade IV, can moreover be classified as Diffuse hemispheric glioma, H3.3 G34-mutant, WHO grade 4 in the presence of a missense mutation in the Histone H3.3 protein, codon 34.

Methodology of Studying CNS Neoplastic Behavior in Space

Real microgravity studies are expensive and rare; thus, on-ground simulated microgravity (SMG) is more prevalent. Several contemporary devices are used to simulate microgravity such as random positioning machine (RPM), rotating wall vessel (RWV), and fast rotating clinostats (Fig. 8.3) [55, 56].

The main tools utilized in the studies taken in consideration in this chapter are: the 2D clinostat system and the 3D clinostat system. The 2D clinostat system is a 3-dimensional rotational device which rotates around 1 (2D) axis (Fig. 8.3). Essentially, it is a rotating device which prevents the biological system from achieving a sustained gravitational acceleration vector [57, 58]. A random positioning machine (RPM), known also as 3D clinostat, is a simulator based on the principle of vector averaged gravity [59]. This simulator is often compared to the 2D clinostat although it has several differ-

Fig. 8.3 Random positioning machine (**a**) and 2-D Clinostat (**b**). Copyright: © 2015 Svejgaard et al. This is an open access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited

ences. The 3D clinostat presents two axes of rotation and a major swimming velocity [55]. The RWV, instead, is a bioreactor of 5–20 cm diameter with liquid-filled container that rotates around a horizontal axis at 10–20 rpm [60].

Most of the studies are made in vitro on 2D or 3D cultures. 2D cultures are well known to be simple, with a low time of culture formation, and low-cost maintenance but they have the disadvantage of not portraying faithfully the natural structures of tumors. Further disadvantages lay in the diverse phenotype loss, lack of representation of the cell-cell and cell-extracellular interactions and a monolayer composition which translates into an unlimited metabolic resource on contrary to the in vivo cells [61]. The other limitation of 2D cultures, as reported by Birgersdotter et al., is the change in gene expression and splicing, topology and the cellular biochemistry [62]. On the other hand, 3D cultures are beloved for the faithful imitation of in vivo tissues and organs, and for the recreation of proper interactions of cell–cell and cell-extracellular environment [61]. Also, the morphology, the phenotype and cellular reproduction phases, as well as the molecular mechanisms, are preserved in 3D cultures in contrast to the 2D cultures [62, 63]. The limitations of 3D cultures reside in a longer time of culture formation, in a worse performance in culture quality and in expensive costs [64, 65].

The analysis part of each studies varies depending on the type of cells and the objective of studies.

The ideal method to observe the behavior of CNS cancer in space would be to have in vivo models analyzed in space. In Cancer and Health research in space, a conference paper, it was intended to examine human GBM derived cancer stem cells (GSCs) in space. The GCSs would be inoculated into mice brain and subsequently, 12 healthy mice, as control, and 12 mice with GBM, sent on the ISS, whereas 24 mice would be maintained in on-ground laboratories under observation for the corresponding on-ground experiments.

Procedures involving animals and their care would be conducted in accordance with the national and international guidelines of the National Institutes of Health Guide (NIH) for the care and use of laboratory animals. On board the ISS, mice will be kept in special cages, previously used by Japan Aerospace Exploration Agency (JAXA) [66], and they would be monitored 24/7 with internal cams. Cages will be equipped with automatized systems to provide food and water, hygiene

and adjust sleep/wake cycles. At the end of the mission, mice would be examined with behavioral tests through our specifically projected maze to evaluate their cognitive abilities and scanned with MRI to rate the volumetric variation in dimension and vascularization of the tumor mass. Furthermore, tumor mass would be explanted and study at morphological, cellular, molecular, and genetic levels. The core point of this project consists on the possibility to study cancer models in vivo, rather than in vitro, on the ISS. Unfortunately, for economic restrictions the project is in stand-by. Recently, Larose et al. published a paper on their intention to analyze tumors in space. They intend to observe by 2025 human organoids on the Chinese space station [67].

CNS Neoplasms Behavior in Space

Carcinogenesis in Space

Carcinogenesis in space may differ in comparison to the carcinogenesis on-ground. Thus far, no experiments have been conducted in high linear energy transfer (LET) due to obvious limitations, and our knowledge regarding carcinogenesis derives from studies made in low LET. Consequently, there are no sufficient studies on CNS neoplasms carcinogenesis stages in space. Most of the studies are done on survivors of the atomic bomb from Japan.

Initiation under HZE ions—high energy nuclei originating from GCRs or SPEs [68]—differs from the initiation process described earlier. It produces cluster damage in DNA helix strands, causing multiple lesions, instead of non-clustered lesions [3, 69]. These radiation-induced lesions translate into a genomic instability due to the activation of multiple pathways affecting different carcinogenesis stages.

Promotion and progression stages are also different due to the duplex promoter and initiator role of radiation [70]. As reported by Hanahan and Weinberg, the above-mentioned genetic instability promotes the carcinogenesis through several mechanisms, such as evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, and limitless replicative potential [71]. Other factors deemed to contribute to the carcinogenesis are the extracellular matrix remodeling, persistent inflammation, and oxidative damage [22, 72]. According to Cucinotta et al. fatal cancer risks are less than 10% at upper 95% of confidence interval, deducing that the risk model is accurate. In the hypothesis that the risk model is incorrect, the percentage of fatality could approach 20% with significant life loss [73].

Nevertheless, the risk assessment of carcinogenesis in space, and in particular of central nervous carcinogenesis, is so far, not possible due to a lack of sufficient data and studies. As a matter of fact, mechanisms and inter-species variations are still poorly understood.

Tumor Suppression in Space: A Dual Theory

In the past couple of decades, particular attention has been given to the cancerous cell behavior in microgravity. Sahebi et al. defined microgravity as a dual edge sword as it is still not clear the exact function of microgravity in relation to cancer [74].

It is hypothesized that microgravity impacts the cancerous cells by repressing survival signaling pathways and inducing apoptosis. De facto, the role of microgravity in cellular viability and apoptosis is demonstrated by the inhibition or downregulation of BCL-2 and Bnip3 anti-apoptotic proteins, and by the enhancement of Bax, p53, Caspase -3, 7,8, and PARP pro-apoptotic proteins [74–76]. Another characteristic of microgravity consists in the ability of preventing the formation of spherical colonies and cell proliferation due to a downregulation of ATM/ATR and CDK1/2 proteins which prevents the transition from the cellular phase S to G2 [74, 75, 77]. A key factor is also the induction of early alterations of cytoskeleton, of extracellular matrix (ECM) and focal adhesions [78–80], as a matter of fact, many studies reported a spheroid formation in some types of cancers [81]. Spheroid cultures are cell clusters organized in 3D which alters some signaling pathways and gives a greater differentiation potential in microgravity to stem cells [82]. Furthermore, it seems that this remodeling of cytoskeleton and ECM is an adaptive response to microgravity [74] and that actin microfilament structures are sensitive to microgravity leading to an alteration of signal transduction [83].

Concerning the CNS neoplasms, several changes in cell viability, proliferation, and apoptosis were studied in the past few decades. Especially, U251MG glioma cell line and U87 cells were analyzed in simulated microgravity in a time-dependent manner. U251 cells and U87 derive both from a malignant glioblastoma tumor but with different phenotypes and variances in nicotinamide nucleotide metabolic process regulation, RNA splicing, glycolysis, and purine metabolism [84, 85].

Deng et al. reported a time-dependent inhibition of U251 cell viability by SMG as well as a blockage of cell cycle in G2/M phases. Additionally, an upregulation of cleaved caspase 3 and 9, and a downregulation of BCL-2 and BNIP-3 were evident after a Western blot analysis [86]. Similarly, Zhao et al. identified an upregulation of p21 and a downregulation of Insulin-like growth factor binding protein-2 (IGFBP-2) (Fig. 8.4) [87]. An upregulation of p21 translates into a major tumor suppression, hence to an increased apoptosis. The Insulin-like growth factor binding protein-2, instead, is one of the over-expressed factors and a biomarker in high-grade glioma. A downregulation of IGFBP-2 is linked to an inhibition of glioma cells proliferation [88]. Additionally to the changes in proliferation, apoptosis, and morphology, SMG effects also the migration and the inva-

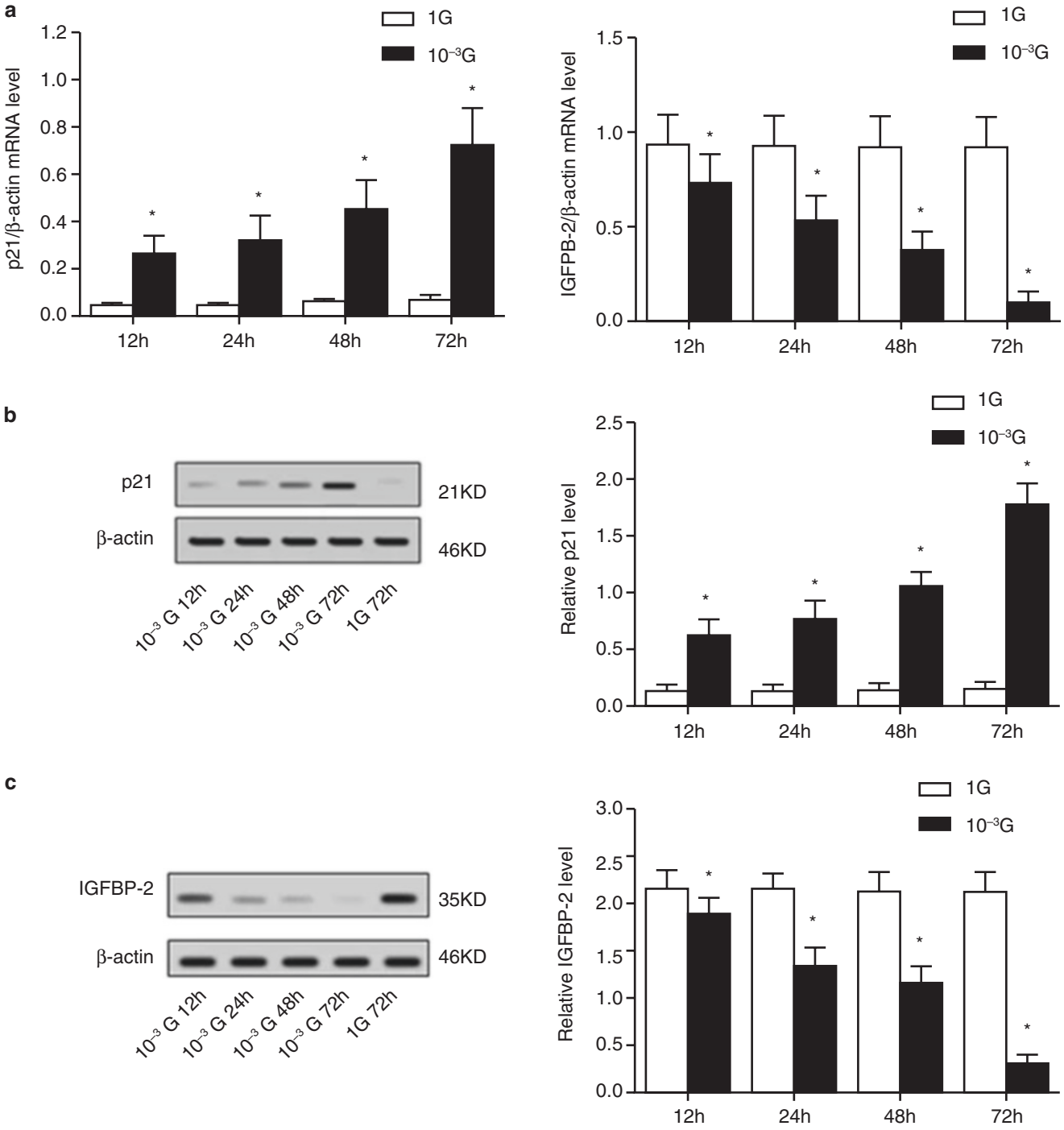

Fig. 8.4 Expression of on p21 and of Insulin-like growth factor binding protein-2 (IGFBP-2) in simulated microgravity vs. normal gravity. (**a**) The bar graph shows the ratios of p21 (left panel) and IGFBP-2 (right panel) mRNA relative to the amount of β-actin mRNA. The western blot images of p21 and IGFBP-2 are, respectively, shown in (**b**, left panel) and (**c**, left panel). The right panels represent the densitometric analysis of the data. β-Actin was used as a loading control. Reprinted and cited with permission from the authors [87]

sion of U87 and U251 cells [86, 89]. In fact, SMG was associated to an inhibition of focal adhesion kinase (FAK), and to a reduced RhoA/Rock signaling and Nek2 expression which transposes into a decreased viability and migration of U251 glioma cells [86] (Fig. 8.5). Focal adhesion kinase (FAK) is an integrin-based focal adhesion tyrosine kinase and it has a crucial role in the regulation of cytoskeletal networking and cellular signaling [90]. Moreover, FAK appears to be overexpressed in highly invasive tumors and it is interconnected with RhoA/Rock pathway which regulates the cytoskeleton

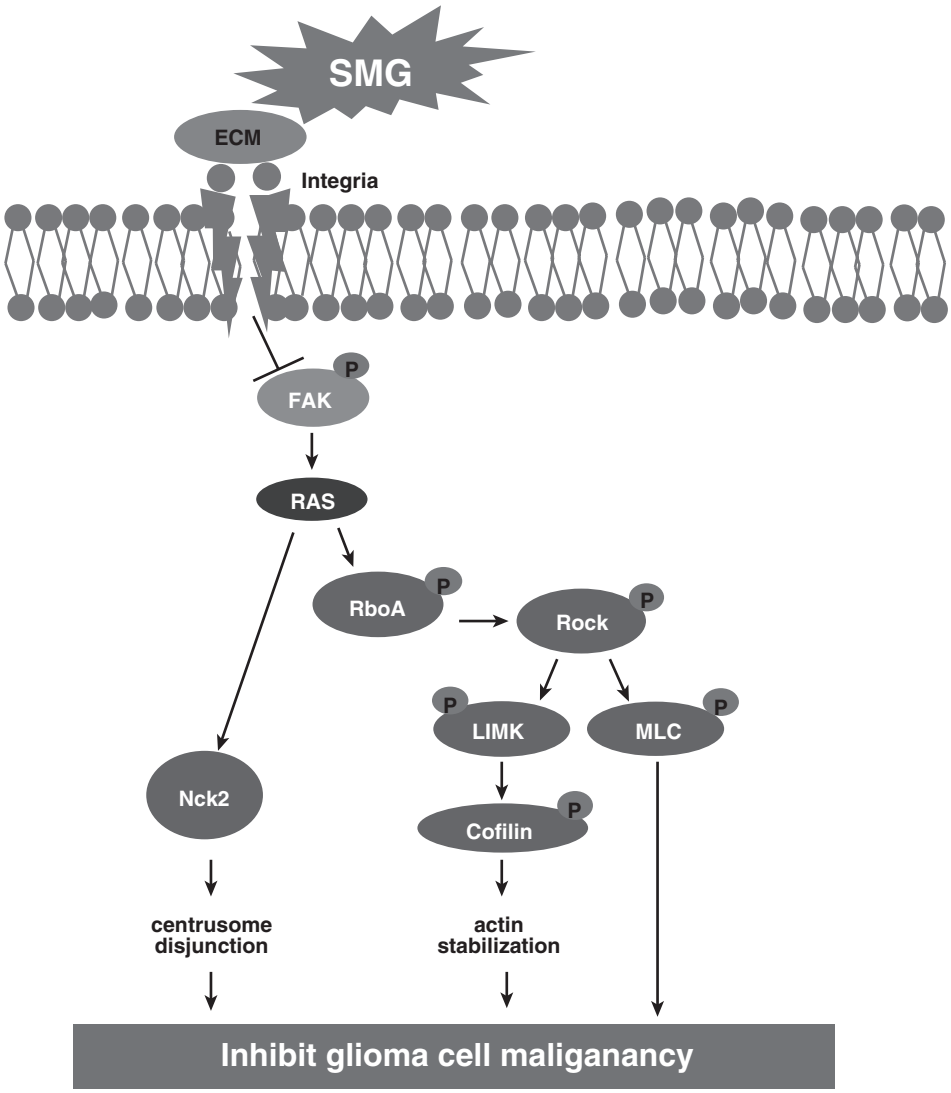

Fig. 8.5 Systematic diagram of the signaling pathways affected by SMG in glioma cell via FAK activation. Reprinted with permission of the authors [86]

and morphology [91]. By the inhibition of FAK by SMG, also GTP-RhoA gets inhibited with a consequent arrest of Rock, LIMK, MLC, and Cofilin phosphorylation which along with the Nek-2 inhibition results into an inhibited glioma cell malignancy [86]. Likewise, the invasion and migration potentials of U87 cells were found to be effected by SMG, through an inhibition of store-operated Ca^{2+} entry (SOCE) and a subsequent downregulation of Orai1, a cell membrane pore structure, and expression [92, 93].

Overall, majority of the studies in simulated microgravity suggests an inhibition in the glioma cell malignancy which could contribute to the development of therapeutical possibilities. Conversely, ionizing radiations are deemed to enhance the carcinogenesis [94–96]. As a matter of fact, according to Hanahan and Weinberg, the space radiations could lead to DNA damage with subsequent mutations and genomic changes, and to epigenetic changes, i.e., methylation, altered replication or inflammatory responses. These could potentially lead to a genetic instability which could trigger mechanisms that could lead to an incremented carcinogenesis (Fig. 8.6) [71].

Another important aspect to take in consideration while analyzing the effects of microgravity on tumor suppression is the enhanced sensitizing of cancer stem cells (CSCs) to chemotherapeutic agents [97]. Kelly et al. performed experiments on CSC in a hydrofocusing bioreactor (HBR) and in the rotary cell culture system (RCCS). The HBR is constituted of a 50 mL fluid-filled sphere that rotates at a set speed to furnish a particular hydrofocusing capability that, in the absence of gas bubbles, permits for a low-shear culture conditions in which cells can grow in simulated microgravity [98]. The RCCS is also 50 mL horizontally rotating culture vessel that decreases the shear and turbulence caused by traditional stirred bioreactors, reducing mechanical cell damage, and simulating microgravity [99]. The result of the study indicates that potentially, basing on the core concept of elimination of cancer stem cells which are reputed to be the responsible of tumor recurrence after

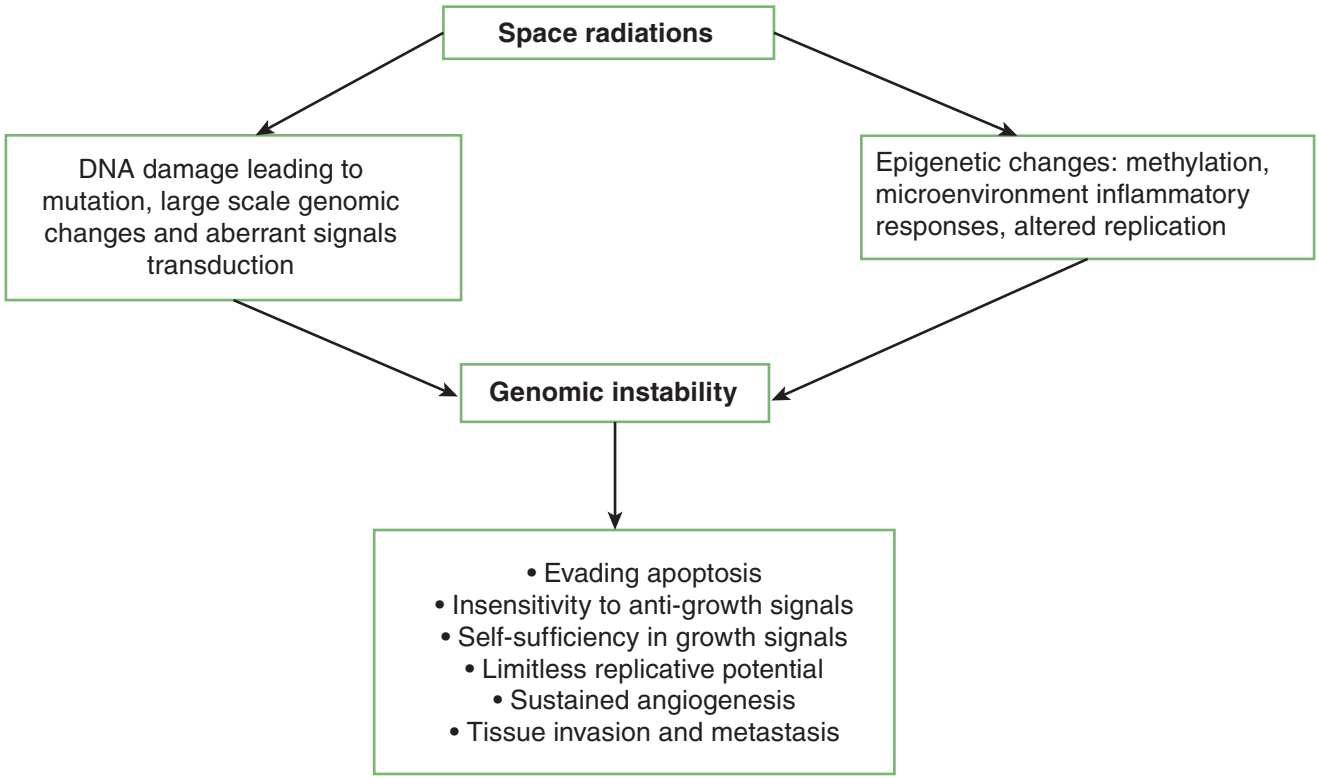

Fig. 8.6 The hallmarks of cancer and possible mechanisms of radiation damage that lead to these changes observed in all human tumors. Readapted from Hanahan and Weinberg, 2000

invasive therapies, it might be possible to develop an anticancer therapy through microgravity. As a matter of fact, in T98G, U87MG cell lines CD133 (+) in HBF appear to be more sensitive to chemotherapeutics in comparison to RCCS and normal gravity. Not many studies have been conducted on CD133—positive stem cells, even if they could be an ideal target for further therapy implementations [100]. Also, Takeda M et al. reported an increased chemosensitivity to cisplatin in microgravity in GBM cells, suggesting microgravity might serve as an expectable role of protection for GBM patients [2]. These results were confirmed also by Yuan et al. in their study as well [101]. Unfortunately, studies on other solid CNS tumors in microgravity is lacking. No other relevant studies were found after researching PubMed, Cochrane or Google Scholar databases. This constitutes a limit in the understanding of CNS neoplasms behavior in space.

As the radiation has been largely considered as an initiator of cancer through induction of DNA mutation, and on the other hand given the potential tumor suppressive and sensitizing to chemotherapeutic characteristics of microgravity, the questions is whether to protect or to expose. Thus, given the dichotomic outcomes predicted, reported in literature, the main question would be if the astronauts are subject to incremented risk of malignant CNS tumors following prolonged space missions, or if exposure of patients with CNS neoplasms to the space environment will result in tumor suppression? Will tumor suppression effect of microgravity balance the potential carcinogenesis mediated by ionizing radiations? To answer to this dilemma, further studies are needed to analyze the combined effects of microgravity and ionizing radiations in pharmaceutically treated, non-treated, and control subjects.

History of Literature

Several studies have addressed the effects of spaceflight on CNS [1, 102, 103], but, hitherto, no clear view has been obtained regarding the behavior of CNS neoplasms or generally, of cancer, in space.

Already in 2001, Cucinotta et al. have expressed their perplexity regarding the lack of knowledge and the uncertainty deriving from it in matter of cancer behavior and risk assessment [104]. In late 90s, several researches addressed the possibility of a higher cancer induction due to high-LET radiations in space compared to the normal X-rays (Low-LET radiations) with the consequence of a permanent damage to the CNS independently from the site and typology of tumor [105, 106]. Uncertainty remains the key word also today regarding the risk assessment of carcinogenesis in space. As discussed earlier the effect of radiations depends also on the type of radiation taken

in consideration, the amount of radiation on LEO (ISS) or Mars surface is different to the one in deeper space [14, 107]. In addition to the studies related to radiation and cancer risk assessment, further studies have been made on the role of microgravity. As discussed in the tumor suppression part, up to day, it is possible that simulated microgravity inhibits the malignancy of high-grade central nervous system cancers [86, 87]. Whereas, it still remains unclear the combined effects of radiations and microgravity in space, placing a shadow on the results and the future of long-term space colonization.

Literature Review Methodology

Concerning the CNS Neoplasm tumor-suppression part, a literature review has been conducted by May 2021. PRISMA guidelines were the point of reference for the literature review. PubMed was the database of reference and several keywords were utilized. Keywords employed were: "Central nervous system neoplasm AND microgravity"; "Central nervous system neoplasm AND spaceflight"; "Solid tumor AND Microgravity"; "Cancer stem cell AND microgravity"; "Glioblastoma AND microgravity"; "Glioblastoma AND spaceflight"; "Cancer Stem Cell AND spaceflight"; "Tumor suppression AND spaceflight"; "Tumor suppression AND microgravity."

Foreign language literature was excluded. Zotero software was used to manage citations, abstracts, and documents.

The search strategy returned 124 references. Of these 26 were eliminated as duplicates, and a further 82 were excluded at the title and abstract screening stage. The remaining 16 papers were included for full-text screening. Of these 16 papers 7 were included in the study. An additional study was included through citation searching (Fig. 8.7).

Limitations

Several limitations have to be addressed in this chapter. As discussed earlier, a clear view of the CNS neoplasm behavior is not currently available. This may be due to financial or ethical concerns.

Despite extensive space radiation research, significant uncertainties remain in predicting the biological consequences for humans as terrestrial simulations differ from an actual spaceflight environment [108]. As reported by Chancellor et al., it is arduous to properly simulate the spectrum of energies, ion species, concentrations, and dose rates found in the space radiation world.

Additionally, the information available for extrapolating radiation risk concerning the spaceflight is restricted by several factors such as limitations in the emulation of the radiation environment, and choice of surrogate animal model. Also the impossibility to delivery of sufficient complexity, rate, and magnitude of doses can be considered as important limitations [108].

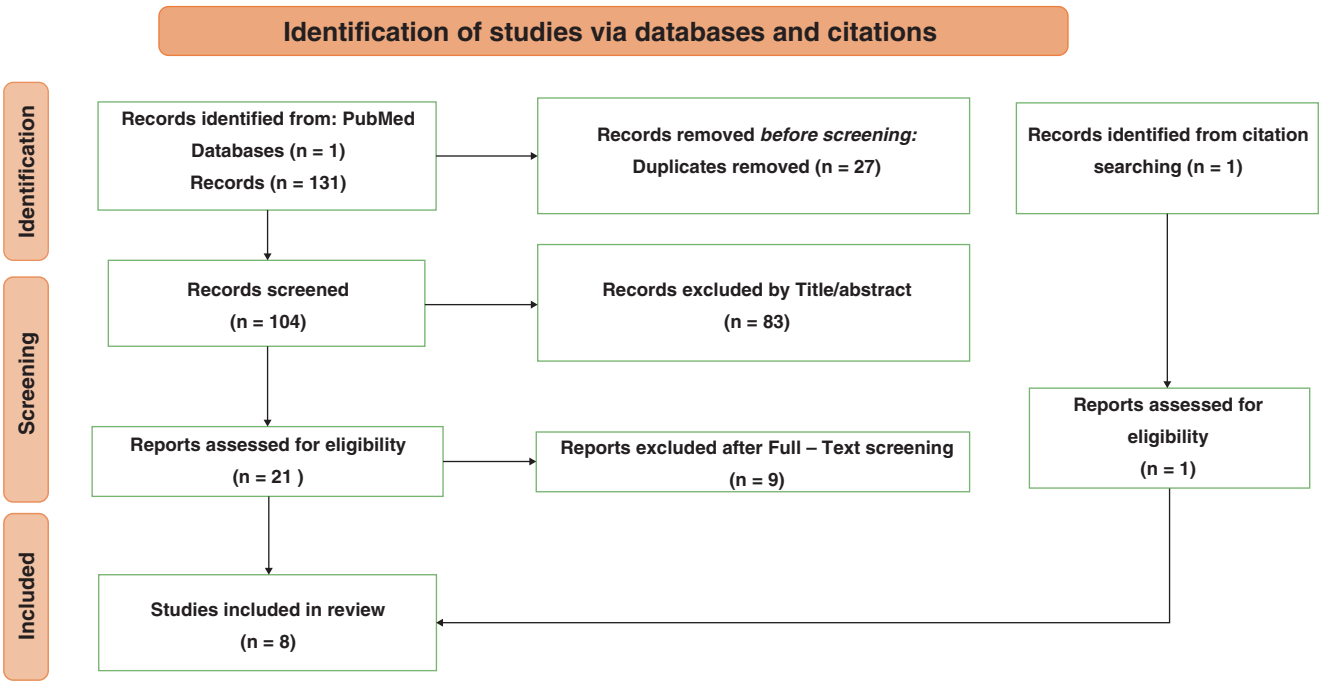

Fig. 8.7 Literature review methodology: Readapted from PRISMA 2020 flowchart

Furthermore, observations in studies conducted in a simulated microgravity environment on Earth may differ from real microgravity. The principle of clinostats and random positioning machines is to vary the gravity between −1 g and +1 g with the purpose of achieving an overage of 0 g over time [109]. Hydrostatic gradients are still present, even if the vector varies. This is different from a real and sustained microgravity.

Conclusion

Heretofore, the precise behavior of central nervous neoplasms in space is dismal. Currently, experiment results in simulated microgravity seem to be auspicious for a possible usage of microgravity as a tool for therapies. The role of microgravity in space is hypothesized to be akin to the simulated microgravity. The correlation between microgravity effects and space radiations remains obscure, given the speculated propension of a carcinogenesis enhancement under ionizing radiations. Several questions remain still open. With the current data, it would be preliminary to declare that extended missions would increase CNS cancer risk, and it is not possible to assert that microgravity could lead to tumor suppression. The dual sword theory reamin pertinant. The CubeSat to study Solar Particles (CuSP) spacecraft, on board of Artemis, might reveal further information in terms of space radiation, widening the understanding, thereby, also of the related cancer risks. Further researches are neded to clarify the aspects and questions raised in this chapter, also in the light of the information which will be obtained from the upcoming missions.

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Space Renaissance and Neurodegeneration

9

Davide Marotta, Jana Stoudemire, Twyman Clements, Jeanne F. Loring, Paula Grisanti, Scott A. Noggle, and Valentina Fossati

Introduction: A Brief History of Space Exploration

Humans originated around 200,000 years ago and evolved on Earth under the action of gravity. From their origins in Africa, our ancestors populated the Earth, journeyed to new lands, sailed across unknown seas, and went from gazing at the stars to exploring beyond our planet [1, 2]. While exploration has always been a defining element of human identity, it is only during the past 60 years that space exploration has become a reality. Humans in space face many challenges; radiation, microgravity, isolation and confinement, hostile environments, and distance from Earth all affect biological processes, with phenotypic and physiological impacts on the cardiovascular, immune, and central nervous systems [3]. Understanding these biological effects and their implications for human health is critical for developing sustainable strategies to expand space exploration.

Over the last three decades, the space economy has created increasing opportunities for space accessibility. As a result, life-science research has flourished onboard the International Space Station (ISS), a unique laboratory to conduct investigations that impact human health both in low Earth orbit (LEO) and on Earth [4–7]. Research on the ISS largely focuses on radiation and microgravity, the space environment's two primary hazards. Microgravity induces cellular and molecular adaptations and alters physiological responses, including changes in the immune system, heart, bones, and muscle [8]. Thanks to spaceflight investigations, we have greatly improved our understanding of certain pathological processes such as bone loss, skeletal-muscle atrophy, and vestibular dysfunction [3]. Moreover, new medical technologies that have been developed for space research, such as artificial limbs [3, 9] have directly impacted lives on Earth. It is also well known that cosmic radiation affects the central nervous system (CNS), and the first animal studies in LEO suggested that the damage caused by irradiation has similarities to neurological aging and neurodegenerative disease [10]. Thus, the ISS is an ideal platform for research on neurodegeneration to develop countermeasures for future long-term space missions and to better understand neurological disease on Earth. In this chapter, we hope to convey the sense of promise and excitement for the pioneering studies with human CNS cells onboard the ISS that we, and others, have been developing over the past few years. Our goal is to better understand the role of neuroinflammation in neurodegenerative disease, using neuron-glia organoids derived from pluripotent stem cells. Our program involves an interdisciplinary team that combines neurobiology, stem cell biology and hardware and software engineering to enable long-term, fully automated cell cultures in LEO. We will highlight the limits and challenges of the current approach and anticipate future advancements.

Neurodegeneration and Neuroinflammation

With an increasing average human lifespan, the prevalence of neurodegenerative diseases is on the rise worldwide. The National Institute of Neurological Disorders and Stroke lists more than 600 neurological disorders; nearly 50 million people are diagnosed each year in the USA alone. The most common neurodegenerative disease, Alzheimer's disease (AD), currently affects over 40 million people worldwide. More than 5 million people in the USA are living with Alzheimer's today, which is expected to rise to nearly 13

D. Marotta · S. A. Noggle · V. Fossati (✉)
New York Stem Cell Foundation Research Institute, New York City, NY, USA
e-mail: vfossati@NYSCF.org

J. Stoudemire · P. Grisanti
National Stem Cell Foundation, Louisville, KY, USA

T. Clements
Space Tango, Lexington, KY, USA

J. F. Loring
National Stem Cell Foundation, Louisville, KY, USA

Scripps Research, La Jolla, CA, USA

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million in the next 30 years [11]. At present, there are no curative therapies for diseases such as AD, Parkinson's disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and frontotemporal dementia (FTD). Current medications can only manage and improve some symptoms, but do not stop, slow or reverse the neuronal degeneration and loss that occurs during disease progression. Understanding the pathogenesis of neurodegenerative diseases is an urgent unmet need for the development of effective therapeutic options.

Increasing evidence indicates a critical role for glial cells, the non-neuronal CNS cells, in neurodegeneration (Fig. 9.1). There are two types of glia that are actively involved in the inflammatory processes that accompany neurodegeneration, with different developmental origins: astrocytes derive from neuroepithelial progenitors [12], while microglia originate from hematopoietic common myeloid progenitors in the yolk sac and migrate to the neural tube during the early stages of embryogenesis [13]. Astrocytes are the most abundant cells in the CNS and are much larger than microglia. Both cell types are highly dynamic and have numerous motile processes that are used to interact with other cells (astrocytes) or scan the microenvironment and detect dangers (microglia). Despite their differences, astrocytes and microglia work closely together to promote developmental synapse formation, function, and pruning [14–18], and support neurotransmission [19, 20]; they both quickly adapt to changes in the local environment to maintain brain homeostasis [21, 22]. When the brain is perturbed, astrocytes and microglia react with a pronounced transformation [21, 23–31] that can hinder or support CNS recovery [22, 23, 32, 33] through neuroprotective and/or neurotoxic actions [34]. For example, gene expression analysis of reactive astrocytes has shown that brain ischemia triggers a molecular phenotype with beneficial activity, while reactive astrocytes induced by inflammation have detrimental activity [23]. Dysfunctional microglial pruning correlates with neurodevelopmental disorders, including schizophrenia [35] and autism [36]. Mutations in microglia-specific proteins such as TREM2 are associated with increased AD risk, and conventional genetic and computational approaches have converged on microglia-driven immune-inflammatory events [37, 38] in AD. The roles of microglia in the pathogenesis of AD are highly complex and variable, with hypoactivity aggravating pathology at some points in disease progression but ameliorating pathology at different points. Microglia may facilitate or instigate neuronal degeneration by releasing inflammatory enzymes, peptides, and oxygen radicals. Reactive astrocytes and microglia are abundant in multiple sclerosis (MS) [39, 40], PD [41–43], and other neurodegenerative disorders [44]. Our research team has been investigating the role of microglia and astrocytes in progressive MS and PD by developing in vitro models of human CNS cells. We have adapted these systems to investigate the effect of microgravity on the interaction of glial cells and neurons to improve our understanding of pathogenic mechanisms of neuroinflammation as triggers of neurodegeneration.

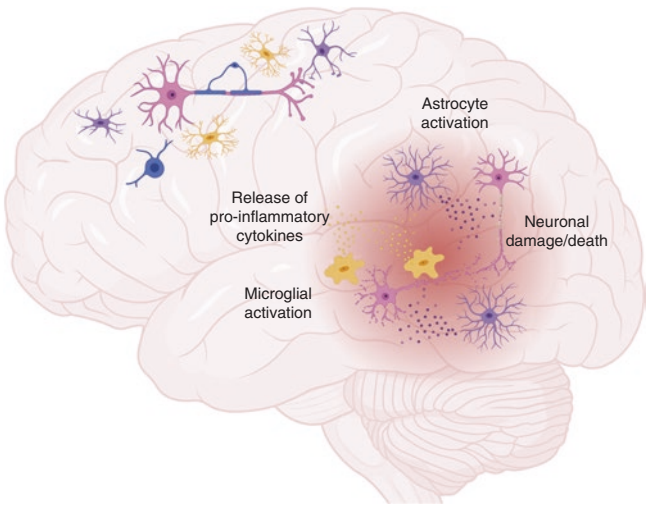

Fig. 9.1 Neuroinflammation in neurodegeneration. Neurodegeneration is often accompanied by inflammatory mediators, released by activated microglia (yellow) and reactive astrocytes (purple) in response to homeostatic imbalance (red spot)

MS is an autoimmune disease characterized by neuroinflammation and neurodegeneration. Multiple genomic loci and environmental factors are thought to contribute to disease susceptibility and severity [38, 42, 45]. Immunomodulatory agents can reduce the infiltration of immune cells into the CNS in the relapsing-remitting form [46], but other manifestations of MS, primary progressive (PP) and secondary progressive (SP) MS, are more difficult to control [47–49]. Currently, no definitive treatments are available for progressive MS patients. Recent evidence indicates that chronic activation of microglia and astrocytes plays a major role in driving progression and long-term neuronal damage [50, 51]. In MS, reactive astrocytes have been associated with local toxic glutamate levels [52, 53], reduced energy supply, and anti-oxidative defense of neurons [52, 54]. Therefore, targeting astrocytes and microglia in addition to peripheral immune cells may lead to novel therapeutic approaches for the progressive forms of MS [55, 56].

PD is marked by a significant loss of nigrostriatal dopaminergic neurons, associated with a glial response by activated microglia and reactive astrocytes [57, 58]. Genetic variants implicated in familial PD risk, including in the genes PINK1, PARK7, PARK8, FBXO7, and GBA, are found in ~15% of patients [59] and expressed in both neurons and glia, supporting the possibility that their pathogenic impact may be mediated through glial dysfunction [60]. In PD, microglia and astrocytes are activated, leading to the production of pro-inflammatory cytokines [61] reactive oxygen spe-

cies (ROS), and enhancement of microglial phagocytosis [61–64]. Astrocytes, activated by microglia, increase the levels of inflammatory complement component 3 (C3) [23]. Therefore, inflammatory crosstalk between microglia and astrocytes may severely impact dopamine neuron survival during PD; this may also be true in MS, in which C3 mediates microglial activity leading to synapse loss [65]. The current standard of care for PD is the biochemical precursor to dopamine, L-DOPA, which enables the remaining neurons to release more dopamine. This treatment does not prevent the continued loss of dopaminergic neurons, and there is no disease-modifying therapy for PD. Targeting microglia may be a source of novel therapeutic options [66].

iPSC Modeling and CNS Organoids to Study Neurodegenerative Diseases

Many experimental organisms such as mice, fruit flies, roundworms, and yeast have been used to model aspects of neurodegenerative diseases, providing critical insights into the pathogenesis of these disorders. However, non-human studies fail to recapitulate many of the clinical manifestations of these diseases and human-specific disease-related genetics, which underscores the urgent need for species-specific models. Over the past decade, induced pluripotent stem cell (iPSC) technology has transformed research and development across academic labs, biotechnology, and pharmaceutical companies by generating cells that carry the patient's genetic information. Skin and blood cells are easily reprogrammed using overexpression of transcription factors to generate personalized stem cells in culture (Fig. 9.2); iPSCs are essentially equivalent to embryonic stem cells in their ability to self-renew and differentiate into any mature cell type [67, 68]. Human iPSC models are being constantly improved as a result of evolving differentiation protocols and optimized culture systems. iPSC-derived cells are increasingly used for precision medicine and drug discovery, to predict responses in individual patients, and to select subgroups most likely to benefit from an experimental or established drug [69–71]. Furthermore, large-scale iPSC studies with hundreds of patient lines are beginning to unravel differences linked to sex, ethnicity, and age.

In the context of CNS diseases, iPSCs can be used to generate all major CNS cell types, including multiple subtypes of neurons, astrocytes, microglia, and oligodendrocytes [72–80]. iPSC-derived neurons from familial PD patients have revealed phenotypes associated with their mutations, including altered mitochondrial dynamics and decreased dopamine production (reviewed in [81]). To better understand the interactions between neurons and glial cells, more complex 3D tissue models—often referred to as brain organoids—have been recently established. Brain organoids generate a compendium of neural cell types and mimic broad features of the developing brain, such as radial organization of cell types around ventricles (as found in the early neural tube), and the generation of subcellular populations specific to distinct brain regions. Brain organoid studies have revealed distinct human features of the developing brain [82, 83]. Furthermore, human brain organoids have been engineered to carry specific disease-associated mutations and used to model schizophrenia [84], neurodevelopmental disorders [85], and neurodegenerative disorders. Relevant to neurodegenerative disease, organoid cultures containing astrocytes and microglia may now be used as a human analog of neuroinflammation to study the crosstalk between glial cells and their role in neurotoxicity.

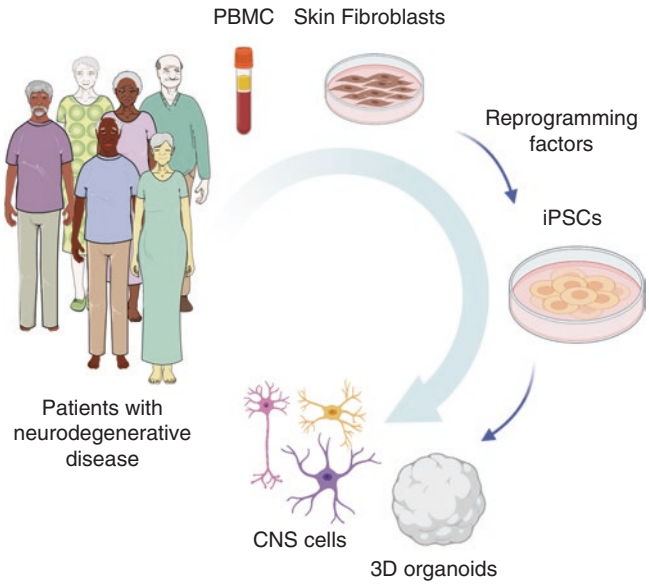

Fig. 9.2 Modeling neurodegenerative diseases using iPSC technology. Somatic cells–such as skin fibroblasts or blood cells– from patients with neurodegenerative diseases can be reprogrammed in vitro to become iPSCs. iPSCs can be differentiated into specific CNS cell types, or through 3D organoids, into a compendium of neuronal and glial cells that recapitulate brain development. PBMC = peripheral blood mononuclear cells

The Effects of Microgravity on Immune and Brain Cells

There is still scant information about the specific effects of microgravity on different types of human cells [3, 86–93]. Most studies to date have investigated the effects of microgravity on musculoskeletal degeneration [94–96], while only a few have focused on the impact of microgravity in neurodegeneration [97]. It is known that dementia is accelerated in elderly bedridden patients; hypokinetic effects on patients are partially analogous to microgravity effects on astronauts [98]. Hence, there is a possibility that astronauts may experience a

similar decline in the health of their nervous systems. Neurons may be predisposed to degenerate under microgravity [99], and cosmic radiation may also amplify neurodegeneration. Similarly to AD, spaceflight impairs vestibular function, influencing cognition, and other biological processes [100]. Protein folding and aggregation are affected by microgravity and might be a potential risk for astronauts on long-term missions, considering that protein accumulation is a hallmark of AD and many other neurodegenerative diseases [97]. Thus, there is a strong rationale for further studies on neurodegeneration in LEO.

Research conducted on 28 astronauts during long-duration stays onboard the ISS reported an increase in the plasma concentration of inflammatory cytokines in the absence of any apparent infection, as well as increases in chemokines relevant to microglia migration and activation [101]. Similarly, a recent twin study showed increased inflammatory cytokines and upregulation of immune-related pathways linked to innate immune response in an astronaut on a year-long mission compared to his Earth-bound twin [4]. The changes in the peripheral immune system may be mirrored in the brain's immune system. The ability of monocytes—a blood cell type analogous to microglia—to phagocytose bacteria has been reported as suppressed in astronauts [102].

Microgravity may interfere with the ability of microglia to react to injury by inhibiting the activation process or cytoskeletal rearrangements necessary for locomotion or phagocytosis. Microglia activation is associated with extensive changes in morphology and cytoskeletal rearrangement. These changes are likely to be necessary for locomotion and phagocytosis, critical to the function of activated microglia and may be affected by microgravity (reviewed in [103]). Research in LEO thus provides a unique opportunity for investigating the regulation and dysregulation of neuroinflammation using iPSC-derived microglia and astrocytes in a complex 3D model of the human brain.

Enabling Human Cell Cultures in LEO: Engineering Meets Cell Biology

iPSC culture and differentiation require specific and controlled conditions for growth. These include a sterile environment, a stable temperature of 37 °C, stable oxygen and CO_2 concentrations, and appropriate enclosed containers (e.g., flasks, multiwell plates) and cell type-specific media. Cell culture medium mimics blood or other physiological fluids and contains all the nutrients necessary for cells survival and proliferation [104]. Media for human iPSC differentiation into CNS cells and human brain organoids also require specific patterning agents that drive differentiation toward the desired cell lineage when provided at very specific time points during the differentiation protocol. Thus, experiments conducted on Earth with iPSC cultures require an incubator, a cell culture hood to perform media changes, bottles to prepare fresh media and collect waste, and refrigerators to keep the media and other reagents at required temperature. All these components must be effectively replicated for studies of human cells in LEO, necessitating innovative engineering solutions.

One approach that we have tested was to develop, along with our space flight partner Space Tango, a miniaturized laboratory system that is sent to the ISS and autonomously maintains traditional cell culture conditions (i.e., 37 °C, 5% CO_2 control), performing media exchanges and enabling experiments like drug challenges under sterile conditions. There are a few unique challenges to consider when doing automated cell culture work in space. Microgravity creates issues with heat dissipation due to the lack of natural convection and the difficulty of removing bubbles in fluid lines or containers. When performing organoids cultures, single organoids need to be plated into distinct wells; alternatively, agitation is required to avoid fusion when multiple organoids are cultured together. There are also critical operational constraints to consider. A typical timeline from hardware handover to installation on the ISS can be as short as 2.5 days or as long as 5 depending on launch scrubs, phasing of the spacecraft, and astronaut schedules.

For experiments involving cell cultures, the miniaturized system can be installed within a Space Tango Paul Ascent Utility Locker (P.A.U.L.), which connects directly to the SpaceX Dragon capsule and provides power and a data interface for monitoring the experiment until it is installed on the ISS. This capability allows for continual maintenance of the environmental parameters in the incubator as well as regular media exchanges during the pre-launch or voyage phases to the ISS phase.

Pioneering Experiments with MS and PD Brain Organoids in LEO

Leveraging our current protocols to generate iPSC-derived microglia [72] and 3D cultures of dopaminergic [105] and cortical neurons [106], we established the first long-term cultures of patient-specific neural cells in LEO to study neurodegeneration (Fig. 9.3). Our first proof-of-principle experiment involved four iPSC lines, generated by reprogramming skin fibroblasts derived from one primary progressive MS patient and one PD patient and their age/sex-matched healthy controls. We differentiated the iPSCs toward microglia and neuronal progenitors—cortical for MS and dopaminergic for PD—on Earth. Microglia progenitors were integrated with neuronal progenitors to form 3D cultures that were shipped to the laboratory at Kennedy Space Center (KSC). Upon their arrival at KSC, the cultures were

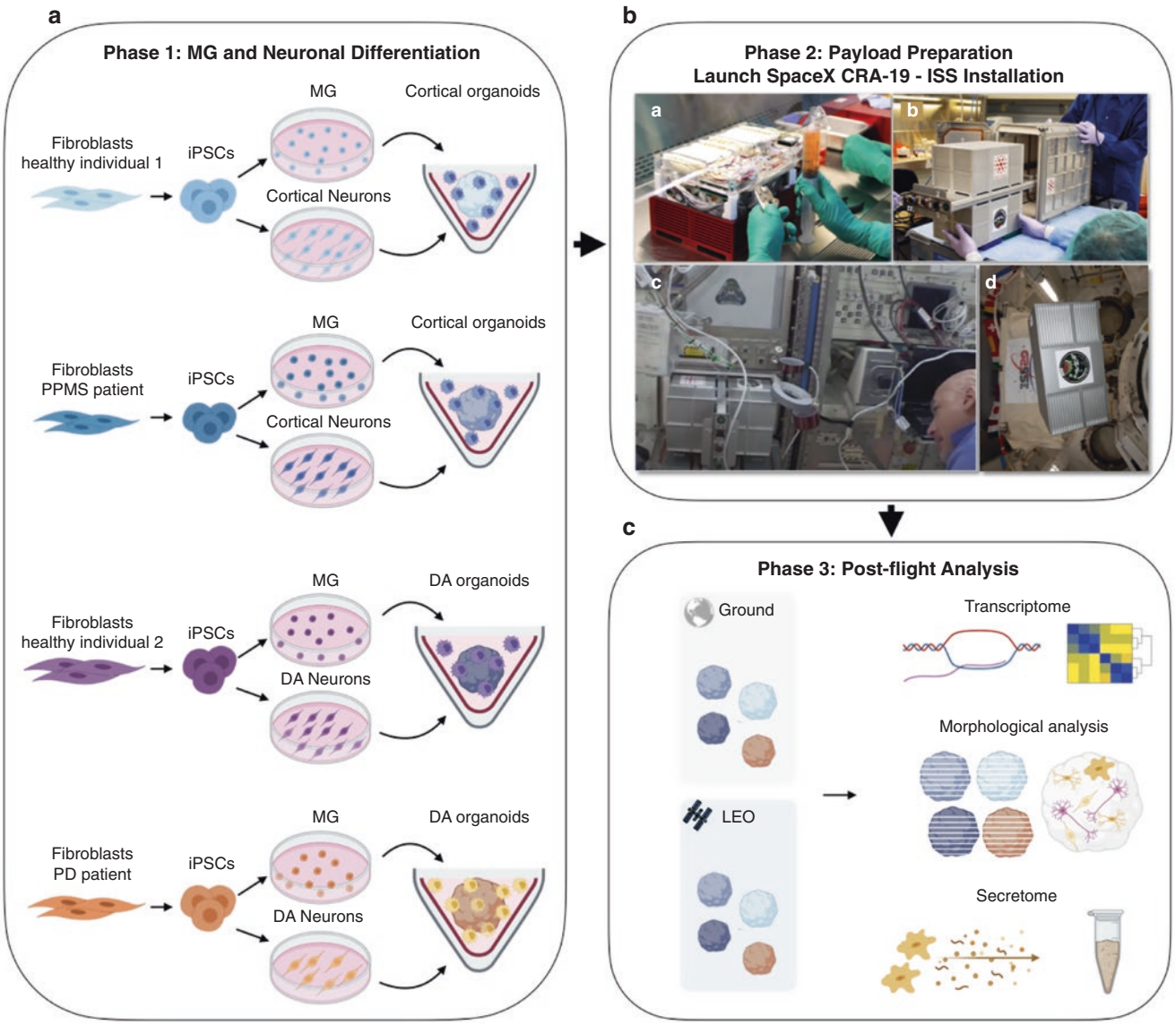

Fig. 9.3 Patient-specific organoid cultures in LEO: experimental diagram. In *Phase 1*, we reprogrammed fibroblasts from healthy individuals and PPMS and PD patients into iPSCs. We then differentiated the iPSCs into dopaminergic or cortical neurons and microglia. Neural progenitors were cultured in ultra-low attachment 96 V bottom plates to facilitate organoid formation. Following organoid formation, we added microglia progenitors to each organoid. In *Phase 2*, at the Kennedy Space Center, we loaded the brain organoids co-cultured with microglia progenitors into the CubeLab (**a**) for spaceflight and ground experiment. Picture shows two CubeLab modules loaded into a P.A.U.L. facility before launch (**b**). After 96 h, the payload reached its destination and astronauts installed it onboard the ISS <credit: NASA> (**c**). CubeLab Module floating on the ISS after removal and before placed into cold storage for return to Earth <credit: NASA> (**d**). In *Phase 3*, organoids returned to Earth and organoids from the ground control experiment were analyzed. Some organoids were sectioned and stained for morphological analysis, and the remaining samples were used for RNA sequencing analysis. The supernatant medium was used for analysis of the secretome

transferred to the CubeLab and launched onboard a SpaceX Falcon 9 rocket as part of the 19th SpaceX Commercial Resupply Services mission for NASA on December 5th, 2019. A counterpart CubeLab was kept on the ground for postflight analysis and comparison. After the experiments were completed on orbit and the cells fixed, the CubeLab was moved to 4 °C storage for the remainder of its time on ISS and during its trip back to Earth. Some tubes containing individual organoids were brought down to Earth as live cells.

The cultures returned to Earth onboard the Dragon capsule that splashed down in the Pacific Ocean on January 7th, 2020. Some of the living organoids were placed into culture immediately after their return and showed robust neural outgrowth, indicating that they thrived during the month-long culture in microgravity. Our ongoing analyses are focusing on identifying the impact of microgravity on different cell types and on cell behavior. Neural progenitor cells may proliferate more, or microgravity may drive differentiation and maturation; microglial migration within the organoid

may be altered and microglial morphology may change to reflect their state of activation. Based on the inflammatory responses of peripheral blood immune cells in space, we anticipate an altered secretome from microglia with an increased release of pro-inflammatory cytokines. This may result in stressed/damaged neurons, which could be used in the future as a platform for drug screens to identify compounds that promote neuronal survival. It will be important to evaluate whether patient-specific cells show differences in phenotype compared to cells from healthy individuals; although the PD and MS-derived cells do not carry known disease-causing mutations, they may have susceptibility variants that could affect their response to microgravity.

Our first launch served as a proof-of-principle experiment, with only one iPSC line of each type. We envisage forthcoming larger-scale studies that will enable statistical observations on progressive MS and PD-specific alterations. We are also contemplating changing the timing of pre-orbit organoid culture to analyze the effect of gravity on older cultures. Neuron differentiation time depends on the type of neuron, and glial cells require months to mature and recapitulate adult biology. The first organoids we used were relatively young (1 month old) and maintained in LEO for 28 days, with an overall time that is not usually sufficient to generate astrocytes (which typically arise after about 70 days of culture) [107, 108]. Overall, the results of these experiments are laying the groundwork for further and more complex studies to dissect the fundamental mechanisms underlying neuroinflammation in neurodegenerative diseases and to understand the impact of microgravity on these disease-relevant processes.

Challenges and Future Perspectives

The first-in-kind ISS studies on neurodegeneration using brain organoids derived from MS and PD patients required an innovative approach to traditional research. This foundational work provides an opportunity to create a human model system that can accelerate our understanding of neurodegenerative disease related to aging here on Earth—and the effects of spaceflight on the brain related to long-duration missions. While the protocols used to create this human brain organoid model systems are thoroughly tested in our laboratories before spaceflight to ensure flight readiness and reduce the risk of challenges on orbit, several factors need to be addressed to effectively adapt these experiments for reduced gravity environments like the ISS or on future platforms on the Moon or Mars. Considerations include maintaining the health of the organoids during transit, sustaining long-duration culture once on orbit, developing nanofluidic systems able to perform drug challenge on orbit, and collection and transmission of data in real-time. Capabilities to further support organoid research that will expand the use of these models in space are in development.

Maintaining organoid health during transit time A rocket can transport payloads (and astronauts) into space about eight minutes after launch, but for missions carrying only supplies and research, it takes 3–4 days to dock with the ISS. Missions to the Moon take about the same time, but a journey to Mars can take anywhere from 6 to 8 months. Loading experiments on rockets for flight requires turnover of payloads in advance of launch. For ISS missions, late-load timing of biologically sensitive payloads like organoids can be anywhere from 24–36 h before launch. For missions to the Moon scheduled for 2021–2023, the current late load timing is seven weeks. Launch windows can also be pushed or scrubbed for various reasons, including technical and weather challenges. For our experiments on the ISS, we developed a protocol using reduced temperature to slow the metabolic activity of the cells and migration of microglia for up to 96 h. The CubeLab containing our experiments can be maintained at 4 °C on ascent. Once it reaches the ISS, it can be installed into on orbit facilities that provide power to maintain a constant temperature of 37 °C and perform automated medium exchanges. As previously described, Space Tango also has developed the Powered Ascent Utility Locker (P.A.U.L.) to provide power and data monitoring of complex biological experiments while on ascent and on the ISS. The powered locker allows the CubeLab temperature to be maintained at 37 °C and medium exchanges to be performed in transit to the ISS so that the experiment in microgravity can begin exactly eight minutes after launch, with no need to wait for the payload to be received and installed on the ISS.

Real-time data collection and transmission Currently, to capture the full impact of microgravity on organoids while on the ISS, samples need to be fixed or preserved on orbit and postflight analyses are conducted on Earth. While this is a way to limit the changes that may result from the return to a 1g environment, systems that enable analyses on the ISS would significantly enhance the potential of future studies in microgravity. These analyses include, but are not limited to, immunostaining, live imaging, transcriptome, secretome, and proteomic profiles. Real-time data collection and transmission will also be an increasingly important capability for longer-duration missions to the Moon or Mars, where maintaining long-duration culture and sample return may take an extended time or prove impossible.

Maintaining organoids with increasing complexity in space The conventional differentiation of iPSC-derived brain organoids can require months, with the intervention of an operator performing media exchange and providing

properly timed signaling for differentiation into specific CNS cell types. In LEO studies, automated hardware needs to replace manual processes, enabling maintenance of short (~30 days) and long-duration (6 months or more) cultures. These capabilities will be essential on future missions for experiments that cannot be human-tended. In the specific case of neural organoid cultures with integrated microglia, a system that could integrate microglia progenitors on orbit (rather than on Earth before launch) would be ideal for both the ISS and future missions to the Moon or Mars. Extended culture periods in LEO would enable studies of more complex organoids that include astrocytes and oligodendrocytes, the myelinating cells of the CNS generated after 100 days [107] using traditional differentiation protocols on Earth. The role of myelin and oligodendrocyte dysfunction in several neurodegenerative diseases is being increasingly recognized [109] and human models will need to include this component to faithfully recapitulate human CNS pathology.

Drug challenges In addition to understanding the biology of age-related diseases, organoid models provide an opportunity for accelerating drug discovery for the treatment of neurodegenerative diseases. This includes testing existing or emerging drugs as potential countermeasures for the biological impacts of microgravity on astronauts and future space travelers. The development of nanofluidic systems for drug delivery at varying concentrations, along with a fully automated system for high-throughput, real-time image analysis for phenotypic investigations, would enable Earth-based studies of the effects of microgravity on cell survival and differentiation that could influence the development of new therapeutic targets or treatments.

Applications of automated platforms on Earth
All automated platforms devised for LEO studies have great potential for improving studies on Earth. We have previously shown that standardization and automation of iPSC cultures can reduce experimental variation and noise inherent to manual procedures, which are major confounding factors in high-content screening assays and phenotypic analyses [110]. Automated platforms are essential for high-throughput analysis. They would also hold value for standardized cell production in cell replacement therapies such as stem cell-derived dopaminergic neurons to treat PD and retinal pigmented epithelial cells to treat macular degeneration.

Astronaut analog models and development of countermeasures Astronaut analog models provide a unique opportunity for further accelerating exploration goals. Generating iPSC lines and organoids from astronauts would be critical for:

1. Studying the effects of spaceflight on virtually any cell type, in various radiation and microgravity conditions (e.g., low Earth orbit, the Moon, and Mars). This is especially important for studies of CNS cells, which cannot be sampled for analysis.
2. Integrating genetic, morphological, and phenotypic data from iPSC-cells and specimens such as blood, urine, or saliva collected during missions.
3. Developing personalized countermeasures in advance of a mission.

Future opportunities for stem cells in space Given the amount of ongoing research focused on establishing new stem cell therapies for patients on Earth and the potential benefit of using human organoid models to better understand the effects of space travel, it is conceivable that future expansion in the ISS or on the new space station or the Gateway station orbiting the Moon, will include the creation of stem cell facilities.

Future colonization Machines have already landed on Mars, and this year we witnessed the first flight on another planet by the Ingenuity helicopter. Artemis missions—to return to the Moon—are scheduled and being prepared for launch, and a human presence on the Moon and Mars is expected to be the next step. Still, the question remains: what are the effects of long-duration spaceflight on the human brain? How can we intervene to impede neurodegeneration? Which capabilities are missing for us to study these effects?

The ISS provides an opportunity to build the foundation for future studies as it is a unique platform to answer these questions. Generating a substantial amount of data on every flight and mission is critical to maximizing the opportunity to assess health risks during spaceflight and improve life on Earth. Sending human models, iPSC-derived brain organoids, to the Moon and Mars to study the effects of reduced gravity on brain health and disease will pave the way for future exploration and colonization. We will need to become even more innovative in our approaches to living and working in the space environment. It is not difficult to envision sending human cellular models to space in bioreactors, floating in a hibernation medium [111] and contained in automated hardware able to "wake them up" once destinations beyond low Earth orbit are reached, then re-hibernate them on the way back to Earth. Knowing what happens to the human brain in these extreme conditions is critical and using organoid models may hold the key to understanding the human risks of spaceflight.

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Summary and Future Directions

10

Timothy R. Macaulay

Introduction

The information presented thus far includes various studies conducted on the nervous systems and related structures of astronauts, cosmonauts, and animal models before, during, and after spaceflight missions. Further details of these experiments can be found in recent reviews [1–3]. These missions range from a few days to more than a year in low Earth orbit (~400 km above the Earth's surface) as well as nine lunar missions that landed 12 crewmembers on the lunar surface for up to 3 days. We have covered transient changes in spatial orientation, sensorimotor coordination, and cardiovascular dynamics, as well as adaptive responses or long-term changes in sensorimotor/vestibular function, cardiovascular physiology, cellular processes, cognition, and behavior.

Even with the past 60 years of human spaceflight research, missions to Mars will present unprecedented challenges. The first missions will likely be up to 3 years in duration, at distances from Earth of 10–20 light min. These conditions will likely exacerbate the impact of spaceflight hazards on the nervous system compared to current standard missions (~6 months) to the International Space Station (ISS). The primary spaceflight hazards include altered gravity (long periods of microgravity, intermediate Mars or lunar hypogravity, transient hypergravity during g-transitions, and readaptation to Earth's gravity), radiation exposure (such as high-energy protons produced from solar particle events and heavy ions contained in galactic cosmic rays), isolation and confinement, distance from Earth, and hostile/closed habitats [4]. International groups of scientists from physiological, behavioral, and aerospace medicine disciplines will need to continue efforts to mitigate the novel risks that crewmembers on board these missions will be exposed to.

This knowledge will also need to be supplemented by well-designed studies conducted in ground-based simulations and analogs. Methods such as centrifugation or performance of tasks under loading/unloading schemes allow changing gravity constraints, and techniques involving galvanic vestibular stimulation or virtual reality can alter spatial orientation. Each of these conditions have limitations and do not remove Earth's constant gravitational reference. However, they are extremely valuable given the limited time and resources available in long-duration spaceflight studies. Parabolic flights also provide valuable data related to short-duration responses to weightlessness. The ~25-s repeated exposures to 0 g predominantly induce neurovestibular effects and other phenomena with short time constants, but are also used for training and countermeasure evaluation [5]. In addition, parabolic flights could be used for studying a continuum of partial gravity levels (including Lunar 0.16 g and Mars 0.38 g). Longer duration analogs help to accelerate the characterization of, and countermeasure development for, physiological changes in spaceflight environments. Examples of analogs include head down tilt bed rest, dry immersion, isolation stations, and irradiation facilities [6].

The National Aeronautics and Space Administration (NASA) and other national space agencies such as the Japan Aerospace Exploration Agency (JAXA), the European Space Agency (ESA), the Canadian Space Agency (CSA), and Roscosmos State Corporation for Space Activities (ROSCOSMOS) continue to invest heavily in research and technology development activities to prepare for exploration missions. Two of the primary objectives of human spaceflight research are to (1) enable the definition and improvement of human spaceflight medical standards and (2) develop capabilities, necessary countermeasures, and technologies in support of human space exploration, focusing on mitigating the highest risks to crew health and performance. Next, we will explore the future directions of nervous system research and technology development as they relate to these primary objectives. Finally, we will examine the planned exploration missions that this work will be applied to.

T. R. Macaulay (✉)
KBR, Houston, TX, USA
e-mail: timothy.r.macaulay@nasa.gov

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Establishing Crew Health and Performance Standards

Many of the nervous system studies conducted to date have focused on understanding responses of physical and biological systems to spaceflight. This characterization of the effects of spaceflight helps determine what the risks are to the crew or their missions. Further characterization studies are needed to prepare for new mission lengths and destinations. In addition, robust assessments are needed to establish crew health and performance standards that provide a quantitative index of crew health and readiness to perform key operational tasks.

From a medical perspective, neurovestibular, cardiovascular, and spine health risks are highest during and shortly after g-transitions, whereas the risks to other nervous system related functions increases with mission duration [7, 8]. However, much of that is projected from data collected in shorter duration (2–3 weeks) missions [9] and standard duration (6 months) ISS expeditions. To prepare for exploration missions, longer-duration (1+ year) spaceflight neuroscience studies are needed that include repeated testing to construct a temporal profile of adaptations in anatomy, electrophysiology, morphology, behavior, cognition, and operational performance. If the observed consequences are more deleterious after longer duration spaceflight than estimated from short and standard durations, then relevant countermeasures will be required to enable exploration missions.

Ongoing, standardized monitoring of the nervous system and related structures requires several new measures to be developed. For spine health and intraocular pressure, the challenge is to develop devices that are compact and user-friendly. A wearable device to monitor surrogate markers may be a viable alternative solution. For cognitive performance, test batteries must be down selected to those most relevant and sensitive to spaceflight risks. Other tools must be developed for monitoring changes in brain-behavior relationships. Multiple distinct tools may be necessary since changes at the brain level might precede changes in behavior, and vice versa, due to functional compensation. The new measures and assessment techniques can be developed using ground-based simulations and analogs [10], then refined in spaceflight environments.

Stem cells and model organisms are critical for studying the effects of spaceflight on neurodegeneration and cancer risk. Brain organoids and neoplasms provide a unique opportunity to use actual human tissue for this research. To date, most of this work has been performed in analogs [11], with planned studies on the ISS. Several factors need to be addressed to adapt more experiments for spaceflight (e.g., maintenance during travel and real-time data collection). Studying these stem cells in low Earth orbit and exploration missions will help us narrow the large uncertainties that exist in neurodegeneration and cancer risk projection models [12].

In addition to continued research in each of the core areas described in this book, there is an increasing recognition of the importance of characterizing the risks in an integrated manner with transdisciplinary expertise. Multiple spaceflight hazards affect the nervous system, and it is possible that these effects could present interactive or synergistic risks to crew [13]. For example, the simultaneous exposure to isolation and confinement, space radiation, and altered gravity may have combined effects on brain structure and function and underlie changes in cognitive and sensorimotor functions [14]. Having integrated neuroscience research projects could help identify the common cerebral pathways that link vestibular responses, fluid cognition, mood states, and cardiovascular changes. Therefore, an integrated strategy is needed to assess and characterize how the combined effects of spaceflight hazards affect crew health and performance [1].

Developing Methods of Meeting Standards

As central nervous system risks and standards are further refined, the priority shifts towards developing methods of mitigating those risks and meeting those standards. Capabilities, countermeasures, and technologies are needed, particularly focused on mitigating the highest risks. Candidate countermeasures and technologies must be developed and refined using ground-based studies prior to validation in spaceflight missions. Once validated, these methods are an essential element in ensuring and optimizing crew health and performance during exploration spaceflight missions, including pre, in, and post-flight operations.

Several countermeasures have been proposed to mitigate central nervous system risks; however, few have been thoroughly evaluated in a long-duration spaceflight environment. These countermeasures are generally focused on pharmaceutical and/or non-pharmaceutical mitigation of sensorimotor decrements as well as a variety of training and rehabilitation approaches [3]. Most of the countermeasures tested to date have focused on reducing motion sickness. In addition, the countermeasures covered in previous chapters range from radiation shielding to electrical stimulation for recoupling vestibulo-ocular reflex pathways. Although countermeasures have been traditionally focused on specific outcomes (e.g., motion sickness, manual control, postural control, and intraocular pressure), there is increasing recognition of the need for countermeasures to be more integrated across risks and multi-disciplinary where feasible.

Multi-disciplinary and integrated countermeasures may be necessary to optimize the efficiency of risk mitigation and may have additional indirect benefits. The most established

multi-disciplinary countermeasure is exercise training. Although in-flight aerobic and resistance exercise protocols are primarily designed to prevent muscular and cardiovascular deconditioning, there are also several benefits to the nervous system and related structures, for example, postural control [15] and intraocular pressure [16]. However, the extent of these benefits, and the attributability to specific exercise modalities, is unclear because all crewmembers exercise. Because exercise capabilities will differ in exploration spaceflight vehicles, it is important to determine what countermeasures can be effectively integrated with exercise [17]. Lower-body negative pressure [18] and artificial gravity [19] are two additional countermeasures that have received considerable attention, are inherently multi-disciplinary, and can be integrated with other countermeasures such as exercise. Further design and development efforts are needed before these integrated countermeasures can be implemented in exploration spaceflight.

Pre-flight crew selection standards and targeted training provides another avenue for mitigating central nervous system risks. The high degree of variability across crewmembers in terms of neurological symptoms and the ability to adapt sensorimotor states suggest that these methods could be quite effective [15]. However, the selection criteria for sensorimotor function remain mostly limited to neurological screenings of reflex functions consistent with standard aviator flight physical examinations due to a lack of validated assessment tools [20]. Certain motor behavioral, genetic, and brain imaging measures may have predictive power for adaptability to G-transitions and the spaceflight environment [21]. This ability to predict individual symptoms and operational performance would allow for tailored training and countermeasures [22]. Currently for motion sickness susceptibility, there are promising terrestrial predictors, but the only reliable predictor of susceptibility is motion sickness experienced during a previous spaceflight [23]. For sensorimotor function, improved adaptability demonstrated by crewmembers with multiple spaceflight experiences suggests that astronauts could be habituated to various gravity conditions [24]. Developing assessment tools and individualized training will likely become even more critical with the added nervous system impacts associated with new missions and vehicle designs.

Future Missions

The ISS has served as a testbed and stepping-stone for exploration missions. It has allowed investigators to study the effects of spaceflight hazards on the central nervous system in a controlled spaceflight environment. Moving these experiments to the Moon will allow investigators to study the effects of spaceflight hazards in the context of exploration missions. Many of the standards and countermeasures developed for crew health and performance in analogs and simulations [10] will need to be reevaluated as additional data become available and warrant updates.

Agencies plan to return crewmembers to the lunar surface in the mid- to late-2020s. The Moon will be used to test and develop new deep space exploration technologies and increase the fidelity of research for long-duration spaceflight [25]. For investigators, the Moon will provide opportunities to understand how the nervous system responds to a true deep space environment before committing to the years-long journey to Mars. Hazards will be more extreme compared to on the ISS. In particular, the radiation environment in a lunar orbiter and on the lunar surface is characterized by both higher doses and increased particles [26]. Long-term colonies and stem cell samples will be needed to determine the detrimental effects of this type of radiation environment. In addition, the effects of additional gravity transitions are not fully characterized. Crewmembers will be exposed to four gravity transitions (Earth, microgravity, and lunar gravity) and need to perform operations in a novel partial gravity environment [27]. Finally, lunar missions will involve further distances than the ISS (days from home rather than hours) with decreased vehicle volumes and capabilities.

Overall, these lunar missions will allow investigators to test and refine standards and countermeasures that will enable human exploration of Mars as early as the 2030s. They can also serve as a training ground for Mars missions. If crewmembers remain in orbit for 6 months before simulating Mars surface operations on the Moon, this could validate the ability of crews to perform critical tasks after the physiological deconditioning that occurs during a 6-month Mars transit. These tests could aid in the design of countermeasures and technologies for Mars.

In addition to the increased scope of exploration spaceflight, there will also be a higher frequency of commercial astronauts in low Earth orbit. As space tourism increases, the incidence of neurological and visual pathology may rise with the increase in civilian space travelers who are not as physiologically adept. Furthermore, health issues become more concerning in someone who has a predilection, or underlying disease process, that may be exacerbated by in-flight or post-flight problems. Efforts to capture the health data of these crew and other retired astronauts will greatly increase the sample size for research analytics. Having such data repositories available will enable researchers to refine prediction models for the susceptibility to spaceflight risks and improve the determination of long-term health impacts from exposures to spaceflight environments [28]. This work would offer the unique opportunity to study the various components of long-term nervous system functions that are intrinsically linked to spaceflight risks.

Finally, although the spaceflight neuroscience research conducted to date has been focused on operational impact and protecting crew health and performance, these data collected under limited resources and small sample sizes have had positive implications for research on Earth as well. For example, fundamental insights have benefited studies on patients with equilibrium disorders, studies on patients suffering from neurodegenerative diseases, the development of new ocular health measures, and the development of sensory aides for patients with balance disorders. With the progression of next-generation commercial space stations and increased populations of non-government space travelers, there promises to be more opportunities for basic nervous system research in spaceflight environments on a wider range of demographics [7]. This research can be directly translatable to the fields of neurology and oncology [11] and flight countermeasures/technologies might translate to ground-based patient populations. Overall, the broad field of neuroscience stands to benefit greatly from continued spaceflight research and the advancement of fundamental insights in the process of neuroplasticity.

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