Journal of the Australasian Society of Aerospace
Medicine (JASAM) No.14 (2025) 1-18
10.2478/asam-2025-0001

SPACE MEDICINE: CHALLENGES FOR DEEP SPACE EXPLORATION

Gilles Clément, PhD

Director of Research
Honorary Fellow of the Australasian Society of Aerospace Medicine
Université de Caen Normandie, Caen, France

Corresponding author: Gilles Clément
Postal address: Université de Caen Normandie,
Esplanade de la Paix, 1400 Caen, France
Telephone number: +1 (349) 399-7129
Email: gilles.clement@unicaen.fr

ABSTRACT

NASA's Artemis program represents a critical step in humanity's return to the Moon and future crewed missions to Mars. Artemis missions aim to test and develop the systems, habitats, and human performance strategies required for sustained space exploration. These missions vary widely in duration, distance from Earth, and exposure to different environmental stressors, such as radiation and altered gravity, each presenting unique challenges for crew health and performance. Artemis I through VI progressively advance NASA's goals, from uncrewed lunar flybys to crewed landings, the construction of the Gateway station, and the establishment of Artemis Base Camp. These missions serve as platforms to study critical aspects of human spaceflight. Research includes the effects of sleep disruption, cognitive function under stress, manual control in varied gravity, teamwork under communication delays, emergency egress post-landing, immune system vulnerability, and vision changes linked to microgravity. Beyond Artemis, long-duration deep space missions face major challenges including high radiation exposure, psychological and physiological stress from isolation and reduced gravity, limited extra-vehicular activity mobility, and the need for sustainable life support systems. Addressing these requires breakthroughs in radiation protection, artificial gravity, autonomous crew training, and closed-loop ecological systems.

1. SPACE MEDICINE

The challenges of living and working in space mainly revolve around reduced gravity, space radiation, hostile and closed environments, and isolation. Space medicine focuses on gaining an understanding of physiological and psychological tolerance to spaceflight, with the objective to ensure long-term human health and performance for long periods in space. The field of space medicine integrates various disciplines, including radiation health, human factors, space physiology and countermeasures, medical care, and life support. It utilizes diverse research opportunities, such as ground-based simulations like bed rest studies, parabolic flight, polar stations, ongoing investigations on board the International Space Station (ISS), commercial spacecraft, and upcoming missions like Artemis and Mars explorations[1].

The objective on the horizon involves conducting a human expedition to Mars by the 2030s. Given the complexity of this endeavor, a flexible trajectory is imperative—one that adapts and evolves based on insights gleaned from past and ongoing missions. This strategy involves a step-by-step approach, progressively advancing human travel, habitation, and exploration deeper into space. It aims to cultivate capabilities enabling the versatile use of space system components across diverse missions. In this context, new systems and technologies will be tested within the cis-lunar orbit, situated between Earth and the Moon, within the Moon's orbital vicinity, and then on the lunar surface as a preparatory phase before embarking on the journey to Mars.

Shifting the space exploration boundary from Low Earth Orbit (LEO) to deep space represents a monumental endeavor. To put it into perspective, LEO spans roughly 320-2000 km from Earth's surface, whereas the Moon lies approximately 380,000 km away. Like missions on the ISS, astronauts in lunar orbit can return to Earth within a couple of days and receive regular resupply missions. However, Mars, at nearly 55 million km from Earth, presents a vastly different scenario. A round trip to the planet could last up to 3 years amid challenging conditions, rendering resupply missions and swift returns to Earth in case of emergencies nearly impossible.

Medical support strategies for current space missions are structured around the expectation of swift crew evacuation ("stabilize and transport") or immediate real-time medical assistance during emergencies. However, these assumptions are incongruent with the demands of deep space missions. Astronauts must be equipped to independently execute emergency medical procedures, even in scenarios with delayed ground communication. It's crucial for the crews to uphold these competencies throughout the entire mission period. Additionally, they'll need to manage routine as well as unforeseen medical and dental procedures. Addressing this challenge requires research into training methodologies and models to devise effective approaches for initial, proficiency, and just-in-time training, especially concerning in-flight medical conditions.

NASA has developed design reference missions (DRM) for each type of mission along the flexible path to Mars: LEO, deep space sortie, lunar visit or habitation, deep space journey or habitation, and planetary. The DRMs provide a framework to identify capabilities, drivers, and assumptions for each mission type. Although the missions share some of the same human health and performance challenges, each also poses unique challenges. Key factors distinguishing the various DRMs include the mission duration, distance traveled from the Earth, the time it takes to return to Earth in the case of emergency, gravity level, and the radiation environment (Table 1).

Design Reference Mission	Mission Duration	Distance from Earth (in miles)	Earth Return	Gravity Environment	Radiation Environment
Low Earth Orbit (ISS)	6 months	237	less than or equal to 1 day	Microgravity	Low Earth Orbit
Low Earth Orbit (ISS)	1 year	237	less than or equal to 1 day	Microgravity	Low Earth Orbit
Deep Space Sortie	1 month	greater than 237,000	less than 5 days	Microgravity	Deep Space
Lunar Visit or Habitation	1 year	237,000	5 days	1/6 G	Lunar
Deep Space Journey or Near-Earth Asteroid	1 year	237,000 - 33,900,000	weeks to months	Microgravity	Deep Space
Planetary	3 years	33,900,000*	months	Fractional	Deep Space

Table 1. NASA design reference missions for flexible path. Credit NASA.

The hazards associated with deep space human missions encompass:

- **Limited resources:** The spacecraft will be constrained by storage, power, and weight limitations, affecting the availability and type of food, medical supplies, exercise equipment, and other essential resources.
- **Isolation:** Due to crews being millions of kilometers and many months away from Earth, they must anticipate dealing with diverse medical situations, ranging from minor injuries to severe incidents. Isolation from Earth may induce psychological and behavioral challenges among crewmembers, potentially impacting their well-being and performance. Moreover, periodic supply deliveries accessible to ISS crews will not be available in deep space.
- **Confined spacecraft design:** Spacecraft will incorporate closed life-support systems and confined working and living quarters. The ISS offers 500 cubic meters of habitable space, significantly more than the Orion crew capsule NASA is developing for initial missions beyond LEO, which provides only 9 cubic meters of habitable area.
- **Altered gravity:** Prolonged weightlessness in space prompts several physical and physiological changes in astronauts. This includes altered balance and orientation, loss of bone density and muscle strength, and the migration of bodily fluids from the lower extremities to the upper body.
- **Space radiation:** Deep space radiation differs significantly from radiation encountered on Earth. It remains uncertain how prolonged exposure to this radiation will affect the human body. While Earth and, to a lesser extent, LEO are safeguarded by the protective Van Allen Belts, regions containing trapped radiation held in place by Earth's magnetic field, missions beyond LEO lack this shielding.

The environmental factors encountered in space affect every organ system, yet their impact on astronaut health and performance differs widely in terms of severity and duration. These effects span from severe consequences to gradual declines, short-term adjustments, or even benign impacts with minimal repercussions on health and performance. The research methodology for each physiological condition or organ system encompasses documenting the adapted state, suggesting revisions to crew health standards if medically unsatisfactory, identifying physiological mechanisms if needed, and formulating appropriate countermeasures.

The adapted state, known as “space normal,” defines the new baseline for physiological conditions in space. Establishing this standard rigorously involves considering multiple factors such as pre-existing clinical conditions, previous countermeasures, space radiation, atmospheric elements (pressure, temperature, composition), auditory and lighting conditions, and the level of gravity. Once a definitive definition of space normal is determined, space agencies can decide whether adaptation to space conditions should be permitted, and to what extent. This decision might involve adaptation followed by treatment before or after returning to Earth, adaptation with ongoing monitoring and countermeasures based on specific declines, or no provision for adaptation at all.

2. HUMANS IN SPACE

Human space exploration commenced on April 12, 1961, with Yuri Gagarin orbiting the Earth aboard the Vostok-1 spacecraft. Since then, 650 individuals have surpassed the 100 km altitude threshold (considered as the onset of space, by the International Federation of Astronautics). This equates to an average of about 10 flights per year. These spacefarers are referred to as astronauts, cosmonauts (in Russian), or taïkonauts (specific to Chinese astronauts). Several among these individuals have undertaken multiple missions. As of May 2025, the total count of person-flights—signifying crewmembers flying one mission, irrespective of its duration or their multiple flight experiences—stood at 1,413. Among these, 852 flights (60%) occurred during Space Shuttle missions, which ranged from 5 to 17 days in duration. The remaining 561 person-flights were conducted during extended missions aboard space stations such as Skylab, Salyut, Mir, Tiangong, and the ISS[2].

The Apollo Program demonstrated humans’ capability to effectively function in space and on the lunar surface. Astronauts performed critical tasks like deploying equipment, collecting samples, conducting drills, and navigating vehicles within strict timelines. Despite missions being shorter than two weeks, these astronauts demonstrated the viability of lunar travel, conducted valuable scientific research, and safely returned to Earth. Six out of eleven Apollo missions successfully landed on the Moon, with 12 astronauts spending a total of 12.5 days on its surface.
The explosion of an oxygen tank during the Apollo-13 mission emphasized human adaptability in managing on-orbit emergencies, preventing a potential disaster.

It is both intriguing and disheartening to note the male-dominated nature of human space exploration. Specifically, female crewmembers account for a mere 16% of individuals who have ventured into space—precisely 104 in number. While humans have collectively spent over 175 years in space, the combined duration of all female crewmembers’ flights is approximately 22 years. In the broader perspective of a human lifespan, the involvement of women in spaceflight is still in its early stages. However, distinctions in adjusting to spaceflight exist among male and female astronauts[3]. For example, post-spaceflight, the occurrence of orthostatic intolerance—difficulty standing without fainting—is more common in female astronauts compared to males. This gender disparity might be linked to decreased leg vascular compliance, as shown in bed-rest studies, a simulated condition akin to spaceflight on Earth. Also, female subjects tend to be more susceptible to radiation-induced cancer compared to male counterparts. Consequently, permissible radiation exposure levels are lower for women astronauts than for men.

The accomplishments of programs like Mir, Skylab, and ISS have provided valuable insights into extended space missions. Evidence of bone loss, muscle decline, cardiovascular issues, vestibular and sensorimotor changes, and the stress of isolation and confinement has surfaced. These concerns intensify during longer missions While the seven individuals who spent over a year in space showed no significant physiological or psychological issues, it’s crucial to acknowledge that the absence of reported problems doesn’t guarantee there were none. Some issues might not have been openly discussed or acknowledged. A series of planned one-year missions on the ISS aims to gather extensive data, shedding more light on the long-term impacts of spaceflight on human health[1].

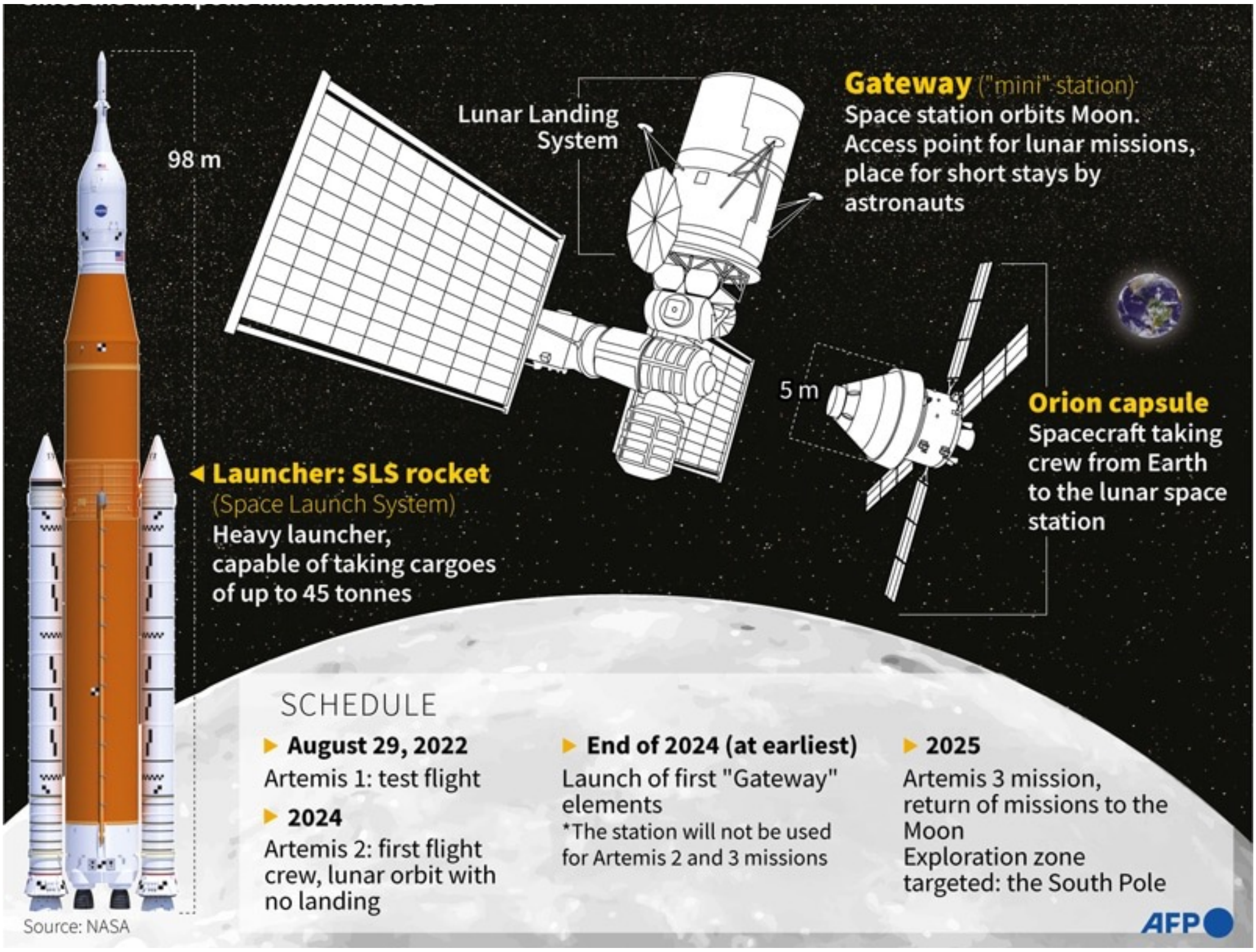

Figure 1. Components of the Artemis program to return to the Moon. Image credit AFP.

3. PLANS TO RETURN TO THE MOON

In the wake of the Apollo program, the 21st-century lunar initiative known as Artemis aims to put humans back on the moon's surface as early as 2025. During the Artemis missions, the Space Launch System (SLS) will launch Orion, a capsule built to sustain a team of four individuals in deep space for up to 21 days (Figure 1). As Orion itself cannot land on the Moon surface, NASA plans to transfer the crew from Orion to a modified version of SpaceX's Starship spacecraft while in lunar orbit for the lunar landing attempt during Artemis III. The Starship, currently undergoing testing by SpaceX, will then transport the astronauts to and from the lunar surface. Upon returning to Earth, the capsule-shaped Orion will utilize its heat shields to endure the scorching reentry through Earth's atmosphere, followed by the deployment of parachutes for a splashdown in the Pacific Ocean.

3.1. ARTEMIS DESIGN REFERENCE MISSIONS

The inaugural mission, named Artemis I, marked the first uncrewed flight test around the moon before returning to Earth in the Pacific Ocean 25 days later. Artemis II, anticipated no earlier than November 2024, represents the program's inaugural crewed flight. This 11-day mission will involve a crew of four flying past the Moon aboard Orion and then making their journey back to Earth.

Artemis III, scheduled for launch no earlier than 2026, is the mission intended to return individuals to the lunar surface. In this expedition, comprising a crew of four astronauts, the initial phase mirrors Artemis II. However, upon reaching the Moon orbit, Orion will dock with a SpaceX Starship stationed there. Subsequently, two members of the crew will use Starship to land near the lunar south pole, embarking on approximately 6.5 days of exploration and research. Following their mission, Starship will transport the crew back to lunar orbit, where they will rejoin Orion and commence the return journey to Earth. Total duration of the mission should be 28-34 days.

Unlike the Apollo missions that targeted the Moon equatorial region, Artemis III aims to touch down near the Moon's south pole. NASA has unveiled at least 10 potential landing sites showcasing diverse geologic features that have not been previously explored. They boast flat terrains, ensuring a safe landing, and receive continuous sunlight for approximately 6.5 days, enabling astronauts to spend nearly a week on the surface. However, these areas also experience periods of shadow, thus the exact landing spot for Artemis III will hinge on the mission's launch timing. Areas with permanently shadowed regions, where lunar rock and dust (regolith) contain traces of water, have piqued NASA's interest among the targeted landing sites. Extracting water ice from the lunar regolith could significantly ease the establishment of a sustained human presence, akin to an Antarctica-style research station.

Currently, NASA is strategizing multiple missions to the Moon surface. Preparations for Artemis IV are underway, involving the construction of the Gateway space station intended to orbit the Moon. This station is envisioned to serve as a base for forthcoming excursions of 14 to 16 days to the lunar surface. Artemis IV, anticipated to commence no earlier than 2027, is planned to conclude the assembly of the Gateway in lunar orbit.

A surface habitat will be designed to accommodate four crew members on the lunar surface. This habitat will serve as the anchor for Artemis Base Camp. Unpressurized rovers will facilitate astronauts' movement around the site and a pressurized rover will enable extended journeys away from the base camp. These elements, in conjunction with essential infrastructure such as communication systems, power sources, radiation protection, and waste disposal and storage plans, will form a sustained capability on the Moon for Artemis V and VI fully integrated missions lasting 30 to 60 days. They will also serve as a platform for testing systems essential for human missions venturing farther into the solar system[4].

3.2. SLEEP STUDIES

The extent of sleep deprivation and disruptions to the body's natural sleep-wake cycle might differ during long-term space missions beyond Earth's orbit compared to stays aboard the ISS, where frequent shifting between time zones and multiple sunrises and sunsets within 24 hours occur. Many of the circadian rhythm challenges observed in current missions appear linked to the specifics of orbital operations and may not have the same prominence in extended, exploration-based missions.

During the Artemis missions, various factors such as deep space radiation, noise, schedule, carbon dioxide levels, stress, among others, impact astronauts' sleep, affecting both its quantity and quality, potentially diminishing their performance. Monitoring the astronauts' activity and sleep patterns is crucial to understand the metadata essential for interpreting health and performance impacts. Throughout the mission, crewmembers will be equipped with actigraphy devices (Figure 2). Actigraphy is a very cost-effective and convenient tool for activity-based monitoring. These devices, in conjunction with sleep-wake logs, will continuously assess the sleep-wake cycle. However, relying solely on actigraphy may not adequately gauge sleep quality or offer a comprehensive assessment of total sleep duration. For instance, agitated sleep might register as wakefulness, while a relaxed waking state, such as deep relaxation or meditation, could be misconstrued as sleep. Future missions, utilizing the Gateway, aim to implement more effective methods, leveraging advanced technology like ambulatory EEG, for a more nuanced analysis of sleep-wake patterns.

Figure 2. NASA Astronaut Scott Kelly utilized an actiwatch device to monitor his movements, tracking his sleep-wake cycles. Image credit NASA.

3.3. COGNITIVE STUDIES

Research will explore cognitive domains particularly susceptible to stress-induced impacts, including those related to sleep deprivation. This encompasses judgment, decision-making, abstract thinking, the ability to shift cognitive focus, devising innovative solutions for new challenges, and various executive functions. Sleep loss or medication doesn't solely lead to cognitive alterations; it can also affect perceptual-motor behavior, impacting reaction time and motor coordination, ultimately influencing both individual and collective performance5.

The NASA Cognition test battery will be employed to assess a wide range of cognitive abilities among the Artemis astronauts, encompassing skills from sensorimotor speed to abstract reasoning. This battery comprises 10 standardized clinical cognition tests, each sensitive to distinct neurological conditions. It has been previously administered aboard the ISS, consistently yielding reliable scores across repeated tests, serving as a credible gauge for different cognitive processing stages (Figure 3). Specifically, the Psychomotor Vigilance Test gauges levels of sleepiness, correlating with significant operational performance and acting as a predictive factor for overall performance.

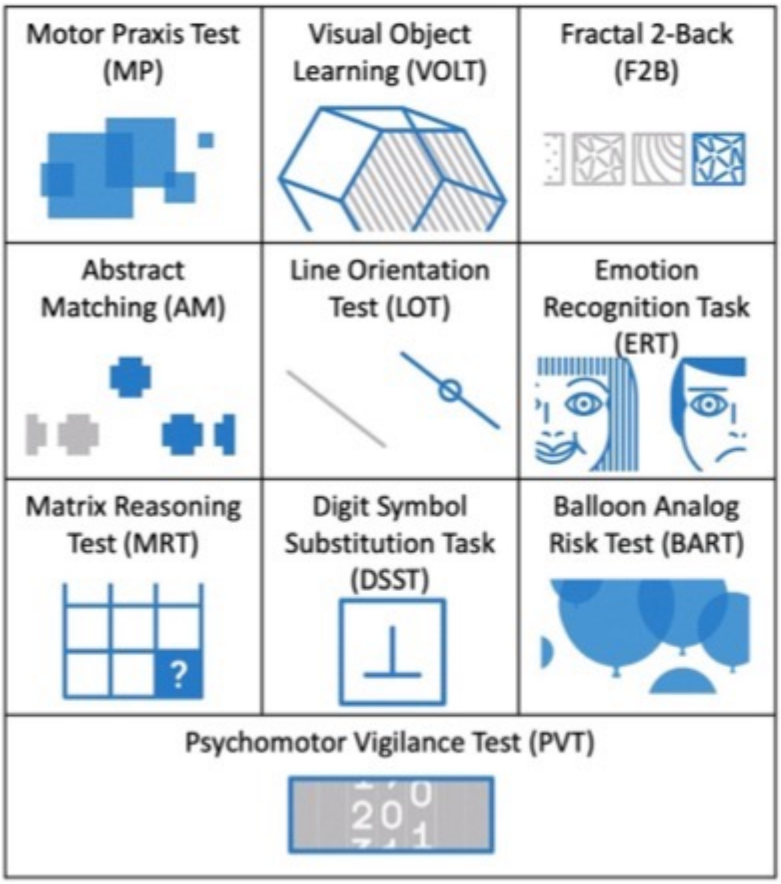

Figure 3. The Cognition battery consists of 10 tests assessing a broad range of cognitive domains that are highly relevant for the conditions of spaceflight. Adapted from 6.

3.4. PILOTING SKILLS

The supervision and manual control exerted by astronauts during vehicle docking and landing, alongside the needs for reduced gravity and post-landing extravehicular activities, stand as critical elements. Missions to the Moon are anticipated to encompass multiple gravity transitions (1 g to 0 g, 0 g to 1.6 g, 1.6 g to 0 g, and 0 g to 1 g) and intricate docking procedures, as well as more elaborate spacewalks compared to LEO missions. Transitions between gravity levels have the potential to impact fine motor tasks and spatial orientation, leading to potential changes in manual control and spatial cognition Consequently, challenges associated with sensorimotor adaptation might pose greater risks during these expansive exploration missions[7].

Figure 4. NASA astronauts Christina Koch is at the robotics workstation controlling the Canadarm2 robotic arm to support an extra-vehicular activity. Image credit NASA.

The Robotics On-Board Trainer (ROBoT) is NASA's platform for training astronauts to perform docking and grappling maneuvers using the robotic arm on the ISS (Figure 4). It is regularly used by crewmembers during spaceflight for refresher training. The operational ROBoT system, however, does not record data. Thus, a research version of ROBoT, called ROBoT-r, was developed so that operationally relevant data could be mined to provide feedback to crewmembers. The ROBoT-r simulation replicates a challenging spaceflight maneuver that involves grappling an approaching spacecraft. To successfully execute this task, participants need to extend the robotic arm toward the incoming spacecraft, align the end effector precisely with a designated target on the approaching vessel, and secure the target by grappling a pin. This maneuver necessitates various cognitive skills, including situation analysis, planning, decision-making, object orientation, mental rotation, visual processing, fine motor control, and visual-motor integration[8]. Astronaut performance on ROBOT-r will be assessed throughout the Artemis missions. The metrics obtained from ROBoT-r will be analyzed in connection with the previously mentioned sleep loss and psychomotor vigilance task.

3.5. CREW AND TEAM PERFORMANCE STUDIES

Reduced gravity, stress, isolation, confinement, and deep space radiation potentially impact situational awareness, workload fatigue, as well as individual and team performance. The Artemis trajectory into deep space will lead to longer exposures compared to the durations experienced in Apollo missions.

The communication delay between ISS crewmembers and ground support personnel is currently 0.25 seconds in one direction. However, this one-way delay will extend to approximately 1.25 seconds during Moon missions and to 4 to 24 minutes during Mars missions, depending on the mission phase. Additionally, periods of communication blackout or whiteout, lasting up to 2 weeks, can occur during solar conjunctions. Consequently, Artemis crews will need to function with significantly higher autonomy compared to ISS crews.

There is a recognized need for additional countermeasures, particularly in team communication training. Incident analyses indicate that inadequate ground-crew communication can cause frustration and impact performance negatively. Ground operators sometimes struggle to convey task duration information accurately, leading to discrepancies in perception between those setting timelines and those executing tasks, fostering frustration (Figure 5). Without task-specific procedures and effective communication training, especially in distributed teams, essential communication functions might be impaired.
During Artemis, experiments will focus on gathering task-related data like keystrokes, response times, and errors by the crew, as well as recording audio-video interactions between the Artemis crew and Mission Control for future analysis.

Figure 5. Flight directors Gerry Griffin, Glynn Lunney, Milt Windler, and Chris Kraft at NASA Mission Control Center during the Apollo 10 mission in May 1969. Image credit NASA.

3.6. EGRESS CAPABILITIES

The current evidence strongly suggests that reducing or eliminating linear acceleration inputs to the vestibular otolith receptors triggers extensive reorganization of sensorimotor systems, impacting the control of crucial body segments like eye movements, posture, and limb control[9]. Sensorimotor integration plays a pivotal role in posture and movement control, essential for activities like locomotion and tool use. When exposed to altered gravitational environments, sensory signals from the vestibular system, especially those originating from the otolith organs, undergo changes. These alterations significantly affect visual and spatial orientation, impacting mobility during spaceflight and upon return to Earth. Such disturbances are more common during longer missions, and complete recovery may take weeks or, in some cases, months. Issues like disorientation, impaired visual clarity, and instability while standing can greatly affect the performance of sensorimotor tasks, including spacecraft piloting or emergency egress[10].

Figure 6. Astronauts rehearse egress from Orion after splashdown. Image credit NASA.

Orion is engineered for a parachute-assisted water landing. However, this landing method presents potential challenges. The vehicle's integrity might be compromised upon landing, and rough sea conditions could render it unstable or uninhabitable for an extended duration. Astronauts might need to swiftly evacuate Orion upon landing, even before re-adjusting to Earth's gravity, a task that can be demanding. Exiting Orion in an open-sea scenario entails dealing with the vehicle's motion in the waves, climbing a ladder for the exit, descending from the vehicle, and managing Earth's gravity-induced roll and pitch movements (Figure 6). Without comprehensive training and effective design, a prompt, safe, and successful egress under these circumstances might be unlikely for the astronauts. Additionally, if Orion were to land on uneven terrain on land, it could potentially tumble and end up inverted, potentially compromising the vehicle's integrity. This situation would require immediate and rapid evacuation by astronauts accustomed to microgravity conditions. The emergency egress might become the primary task upon their re-entry to a gravitational field, emphasizing the need for studies to assess their capabilities immediately post-return.

Even standard vehicle egress procedures following extended missions often require assistance. During the Artemis missions, studies will evaluate astronauts' orientation and mobility capabilities before and immediately after lunar missions. Additionally, there will be efforts to devise training programs, human-centered designs, and automated assistance systems to aid rapid emergency evacuation from Orion-type vehicles, whether on land or in water.

3.7. IMMUNE SYSTEM STUDIES

Recently, it has been discovered that certain aspects of adaptive immunity experience dysregulation during a six-month orbital spaceflight, persisting throughout the duration of the mission. This dysregulation involves altered leukocyte distribution, reduced T-cell function, and disrupted cytokine profiles. These immune changes directly trigger the chronic reactivation of latent herpes viruses in astronauts. Additionally, some crewmembers experience potential adverse medical events related to immune dysregulation, such as unusual allergic symptoms, hypersensitivity reactions, and various infections. Although these occurrences haven't raised significant concerns during missions on the ISS, they serve as important baseline data, suggesting an elevated clinical risk for crewmembers during deep-space exploration missions. Efforts to validate analogs, like studies conducted during Antarctica's winter-over, are ongoing to help understand the flight phenomenon and assess possible countermeasures in a terrestrial setting similar to space conditions.

During Artemis missions, factors like increased radiation, stress, circadian misalignment, altered gravity, and limited healthcare options could exacerbate immune dysregulation during such missions. The combined impact of this factors might interact additively or synergistically, influencing the physiological and neuroendocrine systems of crewmembers. This could involve changes in stress hormones, anti-microbial proteins, cytokines, as well as potential effects on viral DNA and viral reactivation. Compact booklets containing specialized pages will be utilized for the collection of "dry" saliva and blood.

3.8. OCULAR CHANGES STUDIES

Astronauts on extended ISS missions have reported various levels of alterations in eye structure and reduced visual performance. These symptoms include changes in optic disc appearance, flattening of the eyeball, choroidal folds, cotton wool spots, heightened nerve fiber layers, and reduced near vision. Among astronauts tested, a 60% incidence of these symptoms has been observed, with the most severe clinically significant cases accounting for 15%[11]. Despite extensive research conducted aboard the ISS and in analogs like head-down bed rest, various contributing factors to these ocular changes have been identified without a conclusive cause. These alterations in the eyes appear to stem from extended shifts in cranial fluid, potentially exerting elevated pressures on the optic nerve. As these ocular changes seem to correlate with the duration of exposure to microgravity, they may not pose a concern for the initial Artemis missions. Nevertheless, the implications of prolonged fluid shifts on neurological functions might become more apparent during future one-year missions.

Experts in ophthalmology, neurosurgery, neurophysiology, and cardiology have provided recommendations regarding pre-flight, in-flight, and post-flight procedures, emphasizing research areas in detection, monitoring, treatment, imaging, susceptibility, computer modeling, and analog usage. Leading hypotheses will be further investigated during the Artemis program.

4. OUTSTANDING CHALLENGES FOR LONG-DURATION DEEP SPACE MISSIONS

The primary objective for human exploration continues to be Mars, as it stands as one of the few known locations in our solar system where life might have previously existed. Understanding the Red Planet could unveil significant insights into Earth's history and future, potentially addressing the question of life beyond our planet.

NASA's current plan is to send astronauts to Mars by the late 2030s or early 2040s. Achieving this goal poses substantial challenges. Even with adequate funding and technological advancements, the round-trip travel time is estimated to remain around 500 days due to the considerable distance between Earth and Mars. The astronauts will reach Mars after enduring months in microgravity, and they will encounter a substantial path to recovery, particularly to operate in 0.38 g. Four crew members would embark on the extended expedition, with two landing on the surface. The first mission will include having the crews live in a pressurized rover on the Mars surface. Approximately 25 tons of supplies and equipment would be pre-positioned for the crew during a preceding robotic mission. Among these supplies, there would be a crew ascent vehicle, fully fueled and prepared for the astronauts' departure from Mars and their return to orbit around the planet.

Space agencies encounter significant hurdles in ensuring crew safety during human missions to Mars or deep space. A major obstacle hindering the timely development of solutions is the uncertainty surrounding the specifications—mass, volume, and weight—of vehicles and habitats required for deep space. Essentially, researchers are striving to devise remedies for an environment they don't yet fully comprehend. Additionally, despite advancements in understanding the effects of radiation and other space conditions on the human body and gaining more knowledge about these vehicles and habitats, achieving countermeasures to lower risks for deep space travelers to meet LEO mission standards may prove unfeasible. Consequently, astronauts embarking on initial voyages into deep space might need to acknowledge a higher level of risk compared to those involved in ISS missions.

In the next decade, space life scientists aim to develop and bring most risks associated with a human mission to Mars to an acceptable level. Progress in risk reduction will be evaluated by assessing whether health and performance effects during and after the mission can be minimized to meet the health and performance standards defined by the space agencies. At this point, the majority of risks related to missions lasting up to a year on the ISS are reduced to an acceptable level. However, several risks concerning a three-year planetary mission, such as a journey to Mars, still remain unaddressed. These specific challenges are outlined below.

4.1. SPACE RADIATION

The ISS operates within the protective magnetosphere, shielding its occupants from radiation exposure levels comparable to those encountered in deep space. Deep space radiation consists of high-energy ions, such as Galactic Cosmic Rays (GCR), and solar particles of lower mass and energy. Consequently, a Mars mission is expected to entail significantly higher radiation doses (~0.66 Gray for the shortest round-trip case; ~ 1 Gray for a 3-year mission) than on the lunar surface (~0.42 Gray per year), and on board the ISS (~0.2 Gray per year). Limited studies have examined dose-rate effects or combinations of particles resembling the GCR environment, making the determination of threshold doses challenging. Establishing long-term biological systems on the Moon or Mars would enable the exploration of prolonged exposure effects to combined protons and high-charged particles in tandem with reduced gravity. These colonies could encompass diverse biological systems, from brain tissue cultures to plants and small animals, including vertebrates. Assessment could include evaluations for genetic changes, tumor development, and potential reductions in lifespan[12].

Mission factors influencing space radiation include orbital inclination, spacecraft altitude, solar cycle, shielding effectiveness, mission duration, radiation types, potential of synergistic effects, and individual characteristics astronaut characteristics (Table 2).

Orbital inclination	• Spacecraft that travel closer to Earth's poles experience higher levels of radiation
Altitude above Earth	• Higher altitudes, more exposure as the magnetic field is weaker and less protective
Solar cycle	• Solar Particle Events (SPE), and influence on Galactic Cosmic Radiation (GCR) flux
Shielding	• Amount and type, creation of secondary radiation
Length of exposure	• Long duration exposure to low level versus single rapid exposure to large amount of radiation
Type(s) of radiation	• Effects of GCR vs. other ionizing radiation exposure
Synergistic effects	• ncluding microgravity, immune dysregulation
Individual characteristics	• Age, gender, etc

Table 2. Mission factors influencing space radiation.

The risks associated with space radiation are classified into categories such as cancer, late and early effects on the Central Nervous System (CNS), acute radiation sickness, and degenerative risks, encompassing conditions like circulatory diseases and eye cataracts. Each of the identified sites—lung, breast, colon, stomach, esophagus, blood system (leukemias), liver, bladder, skin, and brain—exhibits distinct mechanisms in cancer induction. To minimize uncertainty, precise risk estimations for each tissue type are essential. Genetic and epigenetic factors play a role in varying radiation sensitivities, and delving into these aspects will aid in crafting dedicated cancer models tailored to each tissue type.

Concerns about CNS risks from GCR arise from the potential tissue damage caused by individual high-energy nuclei components traversing, evident from the light-flash phenomenon observed in the Apollo missions. Additionally, patients undergoing brain tumor treatment and experiencing improved survival rates have shown persistent CNS changes long after gamma-ray treatment, hinting at potential risks during large Solar Particle Events (SPE). Animal studies on behavior and performance suggest possible adverse changes during prolonged GCR exposures. Presently, NASA lacks a projection model for these CNS risks. Establishing potential thresholds and understanding how to extrapolate these thresholds to individual astronauts are pivotal milestones in the long-term research agenda.

Mission operations, monitoring, and storm shelter provisions are in place to mitigate the risk of significant SPE exposure for crew members. Nevertheless, in the event of an unavoidable large SPE exposure, various acute radiation syndromes may be a concern, such as radiation sickness. Prodromal symptoms, including nausea, vomiting, diarrhea, and fatigue, can manifest within 4 to 24 hours post-exposure for sub-lethal doses, with the onset time linked inversely to the dose received. There is also a valid concern about potential immune system compromise due to high skin doses from an SPE or other in-flight factors, although the likelihood of acute death from blood-forming system failure is minimal. A key research focus is exploring the role of the immune system in acute risks. Approaches for countermeasures in acute scenarios, studied using animal and cell culture models, are anticipated to differ from those for cancer and other radiation risks. Long-term research will consider fertility, sterility, and hereditary risks arising from space radiation.

The key takeaway is that the space radiation environment is intricate and vastly dissimilar from Earth. Biological impacts could be severe, yet our understanding remains limited. Various factors complicate the prediction of outcomes, making mission planning and crew selection extremely challenging. Finally, there isn't a singular "magic bullet" countermeasure available.

4.2. HUMAN FACTORS

For extended exploration missions, crews will need to address unforeseen challenges, seize unexpected opportunities, and adapt behaviors and procedures as situations arise. To accomplish this, apart from task-specific training, comprehensive knowledge of spacecraft systems and overall operations will be essential, along with broader training across crew members. Another critical consideration for long-duration missions is the necessity for enhanced education beyond specific skill training to handle unforeseen situations amid extended communication delays. Addressing gaps in training strategies is also crucial to tackle potential social, medical, and psychological issues during these missions. Some key considerations include managing disparities between space expectations and actual conditions, replacing task-focused training with skill-based approaches for greater crew adaptability, selecting appropriate training methods (classroom vs. computer-based), empowering crews to self-develop training, and establishing strategies for teaching and sustaining problem-solving and decision-making skills throughout extended space missions.

Future research in preparation for long-duration exploration missions includes examining signs of disorders in analog environments, establishing effective psychotherapeutic practices without immediate communication, standardizing research measures, and assessing environmental effects on cognition and behavior. Additionally, it entails developing optimal methods for team selection, composition, and communication skills training, alongside employing discreet monitoring technologies to identify team performance decline, all underpinned by longitudinal designs.

Studying the interplay among behavior, health, and performance is crucial. For example, understanding how sleep deprivation impacts team dynamics and task completion, as well as evaluating the effects of sleep aids on task performance, are vital. There's also a need for extensive exploration into the effects of space radiation on cognition and increased collaboration with clinical pharmacology groups. Furthermore, investigating leadership dynamics and the significance of diverse thinking within teams warrants deeper evaluation.

Finally, extended-duration missions are also expected to heighten challenges linked to familial concerns, consequently impacting interactions between crew members and their families. These interactions are equally anticipated to influence crew morale, behavioral well-being, and overall performance.

4.3. REDUCED GRAVITY

On Earth, gravity significantly influences spatial orientation and movement, with the vestibular, proprioceptive, and haptic receptors particularly responsive to gravitational cues. In space, the absence of gravity initially forces astronauts to rely solely on their vision, leading to misperceptions of orientation, misinterpretation of visual information, and experiencing illusions related to visual reorientation. Over time, they adapt to the microgravity environment, developing new strategies for navigating and interacting with their surroundings.

In microgravity, the familiar terrestrial ways of moving that heavily rely on gravity are gradually replaced by alternative modes of body movement that don't rely on gravitational forces. Astronauts become adept at navigating accurately and precisely in a virtually gravity-free environment. However, this transition affects their previous terrestrial movement patterns and motor skills. Multiple studies have documented degraded balance control, increased gaze instability during movement, limited head movement, and greater variability in the step cycle[13]. While astronauts regain balance control swiftly within the first twelve hours post-flight, it may take weeks for it to fully return to pre-flight levels[7]. Additionally, the locomotion capabilities of astronauts during the initial moments of entry into reduced gravity have not yet been studied.

Extensive research has focused on understanding human reactions to extended exposure to microgravity during and after orbital space missions. However, there's a significant knowledge gap regarding the physiological responses to prolonged exposure to reduced gravity. Prior insight into the potential impacts of these effects on crew health, safety, or performance during such missions could inform the implementation of suitable countermeasures from the outset.

The impact of lunar or Martian gravity on human sensorimotor, cardiovascular, musculoskeletal, immune systems, behavior, overall health, and performance remains uncertain. Space agencies are orchestrating reduced gravity missions during brief intervals aboard aircraft during parabolic flight campaigns. These studies aim to delineate the connection between gravitational levels and acute physiological reactions in various bodily systems such as cardiovascular, cerebrovascular, ocular, muscular, and sensorimotor systems. In a comprehensive approach, three 5-day campaigns have been planned, maintaining an integrated design where a consistent group of subjects (n=12) undergoes multiple experimental protocols. This design facilitates the assessment of responses across multiple bodily systems in partial gravity. Each flight encompasses 10 parabolic maneuvers, exploring reduced gravity levels between 0 g and 1 g.

Figure 7. The NASA Active Response Gravity Offload System (ARGOS) simulates reduced gravity by applying a consistent force offload using an overhead hoist system and horizontal movement via a rail and trolley setup. Image credit NASA.

Suspension techniques are employed to replicate partial gravity conditions during studies on locomotion and training exercises. These overhead suspension systems often rely on cables, springs, and air-bearing rails to reduce or eliminate the subject's weight. NASA utilizes the Active Response Gravity Offload System (ARGOS) for astronaut training and to assess their performance in simulated partial gravity and microgravity environments This system employs a spring-offset system to investigate body movements in simulated partial gravity as low as 0.05 g (Figure 7).

Research on aboard the ISS measures the impact of Martian gravity (0.38 g) by centrifuging cell cultures and animals. The animal studies employ the JAXA ISS mice centrifuge. Previous investigations using a partial weight-bearing suspension on mice for 21 days revealed that simulated Martian gravity doesn't completely prevent bone loss experienced in weightlessness but does alleviate the decrease in soleus mass[14]. The ISS study aims to examine if the same outcomes are observed during centrifugation to replicate Martian gravity in space. The findings from this study will assist in determining the necessity of countermeasures to address muscle and bone loss while on the Martian surface.

4.4. EXTRA-VEHICULAR ACTIVITY

Extra-Vehicular Activity (EVA) pertains to working outside a spacecraft or planetary outpost.
EVA performance requires establishing a micro-environment that mirrors the life support, nutrition, hydration, waste management, and consumables functions of a space vehicle. This setup aims to enable crewmembers to operate as closely as possible to how they would function in a 1-g shirt-sleeved environment.

Past imitations in suit design, particularly regarding joint mobility, have resulted in injuries, compromised physiological performance, and incomplete mission objectives. Astronauts trained for the Apollo missions using a Lunar Landing Training Vehicle that didn't simulate the vestibular effects of 0.16 g. Before their missions, the only exposure they had to 0.16 g vestibular stimulation was during limited parabolic flight training. Upon walking onto the lunar surface, astronauts mentioned feeling slightly unsteady initially but reported that their coordination improved progressively during the first few hours of their exploration. They moved more slowly during lunar EVAs than they did on Earth. However, the challenging lunar terrain, coupled with restricted mobility and limited visibility caused by their suits, led to frequent instances of falls and near-falls. Across the six Apollo missions to the Moon, 12 crew members conducted 14 EVAs totaling 78 hours. Throughout these 14 EVAs, there were 23 instances of falls and 11 incidents where falls were prevented[15].

On the lunar surface, lunar dust poses a pervasive threat. Comprised of crushed rock, it can damage lunar landers and spacesuits. This dust, if it infiltrates the habitat, poses a contamination hazard to the cabin's environmental control system. During excursions to the lunar surface, significant quantities of dust were gathered on astronauts' spacesuits. As astronauts transitioned in and out of the lunar module, the dust infiltrated mechanisms, disrupted instruments, led to radiator overheating, and even caused damage to their spacesuits. The new Artemis lunar suit or Extra-vehicular ctivity Mobility Unit (xEMU) is currently being developed. The xEMU suit will allow for more range of motion and flexibility (Figure 8). Features of the suit will include high-definition video cameras and a light band mounted to the visor of the helmet. The light band will afford astronauts better visibility as they work in the permanently shadowed regions of the lunar south pole.

Figure 8. Left: Suit of one Apollo crewmember covered with lunar dust from the waist down. Right: Prototype of the Artemis extra-vehicular activity mobility unit. Image credit NASA.

4.5. ARTIFICIAL GRAVITY

Artificial Gravity (AG) emulates the gravitational force within a manned spacecraft through steady rotation or linear acceleration of the entire craft or its components[16]. This simulation, compensating for the absence of natural gravitational cues and loading in space, holds promise in counteracting the physiological deconditioning typically linked with extended weightlessness. Its aim is to prevent the onset of adaptive responses caused by reduced gravity.

Previous attempts to counter physiological deconditioning have involved targeted solutions, like lower body negative pressure and fluid loading for cardiovascular health, and exercise for muscle and bone strength. While these methods have reduced the risk of physiological deconditioning, they come with significant drawbacks in terms of crew time and equipment usage. AG, however, offers the advantage of replicating Earth-like gravity, affecting all physiological systems. AG can be achieved through continuous rotation of the spacecraft or via an intermittent short-radius centrifuge used by crewmembers (Figure 9). Decisions regarding the most effective rotation rate, radius, duration, and frequency of AG exposure to counter microgravity-induced physiological deconditioning are crucial in early exploration program planning.

Figure 9. Short-arm human centrifuge utilized on board Spacelab in 1998 to study the effects of artificial gravity on the vestibular system of astronauts. Image credit NASA.

Yet, the potential downsides of intermittent or continuous rotation need consideration. The Coriolis and cross-coupled angular accelerations resulting from head and body motion in a rotating environment can lead to motion sickness, disorientation, and falls. Studies in slowly rotating rooms have indicated additional effects like apathy, fatigue, and cognitive impairment among inhabitants[17,18]. Hence, AG research necessitates an inclusive approach encompassing physiological, behavioral, and human factor aspects. Despite limited human trials with AG in space and the absence of human-rated AG systems on the ISS, a comprehensive research program is imperative to establish the prerequisites and limitations of rotating humans in space before considering AG implementation on a Mars mission.

Understanding how gravity influences fundamental physiological processes is crucial for comprehending spaceflight physiology and devising effective countermeasures. The initial step involves establishing a dose-response relationship between gravity levels and physiological changes, ranging from 0 g to 1 g. Subsequently, identifying the gravity threshold where physiological responses most closely resemble Earth's gravity is essential. This examination will delineate the operational range of AG levels most likely to counteract these effects. While some dose-response curves exist for certain biochemical systems in animals, most human physiological systems lack such data. The objective is to measure various dependent variables across physiological systems affected by microgravity at different gravity levels (0 g to 1 g) to ascertain the gravity thresholds for these variables[19].

The primary aim of AG research is to provide crucial insights to managers and mission planners regarding the specific AG needs, their associated costs, and benefits for various mission scenarios. The adjustment of AG via centrifugation involves modifying the rotation rate of the spacecraft/centrifuge or adjusting the distance of the habitat/crewmember relative to the rotation axis. These AG variables significantly influence both vehicle design and operational considerations. Key questions that demand answers include: (a) What evidence substantiates the necessity of AG within a spacecraft for extended missions? (b) What design specifications should be imposed on engineers as a result? (c) What recommendations, in terms of gravity level, duration, and frequency, should be provided to crewmembers? Moreover, recommendations for complementary countermeasures to safeguard the health and performance of long-duration crewmembers must be outlined. Addressing these inquiries is crucial before finalizing the spacecraft and mission design[20].

The research into AG extends beyond species and spans various systems. AG involves an integrative approach encompassing biological, physiological, behavioral, and human factors. It's a multidisciplinary endeavor involving space physiologists, crew surgeons, astronauts, vehicle designers, and mission planners who must collectively assess and discuss integrating AG technologies into vehicle design. The commitment from spacecraft designers to adopt AG will depend on the acceptance of a well-substantiated requirement from the aerospace medicine community[21].

4.6. CLOSED LIFE SUPPORT SYSTEM

There are two primary methods used in designing life support systems: open loop and closed loop. The open loop approach involves bringing all life support resources from Earth and discarding them once converted into a non-useful form. Open loop technologies have been widely used in human spaceflight due to their simplicity and high reliability. However, a significant drawback of open loop systems is that their resource demands increase proportionally with longer missions and larger crew sizes. For example, a four-person crew over a three-year period would consume 2.7 metric tons of food, 3.6 tons of oxygen, and 129.5 tons of water, exclusive of packaging.

The alternative approach in life support system design involves bringing an initial resource supply from Earth and then processing non-useful waste products to reclaim useful resources. These systems, termed "closed loop," recycle materials within the system without their removal once introduced. Closed loop systems offer the advantage of transporting processing hardware and initial resources to orbit only once, with minimal subsequent resupply of expendables. However, these systems have drawbacks such as lower technology maturity and increased power and thermal requirements. Nonetheless, for longer missions or situations where resupply isn't feasible (e.g., a voyage to Mars), closed loop technologies become the most cost-effective solution at a certain point.

A closed ecological life support system represents the pinnacle of closed-loop systems, employing either physical-chemical or biological (also known as bioregenerative) methods, or a hybrid of both. The most efficient closed-loop and bioregenerative systems will incorporate both flora and fauna to manage air, water, waste, and food processing However, these systems extend far beyond the concept of a mere "greenhouse in space." They must function as multi-species ecosystems operating within a confined environment. Replicating Earth's functionalities in the absence of its vast buffers, such as oceans, atmosphere, and landmasses, poses an extraordinary challenge. Various experiments, including the Biosphere-2 project, have been conducted in pursuit of this goal, yielding limited success.

Advanced life support systems in deep space missions are expected to depend on plants, serving as food sources and aiding in air and water purification (Figure 10). Space-grown plants offer a potential food source that can improve astronaut nutrition and foster greater self-sufficiency for future missions. Additionally, these plants serve as a link to Earth, evoking the sensations of sight, touch, taste, and scent that reconnect astronauts with life on their home planet, contributing positively to their mental well-being. Nevertheless, this strategy has several downsides. Introducing both plants and humans into a confined environment heightens the risk of unintended, potentially hazardous microbial contamination. Microbes exhibit resilience, adaptability to harsh conditions, and the capacity to colonize surfaces with ample nutrients and moisture.

The challenges faced in long-duration interplanetary missions involve designing closed life support systems that possess specific characteristics: (a) Closed-loop: materials are not required to be added, except for energy, for the system to operate; (b) Bio-regenerative: biological recycling is prioritized over physical or chemical means for all processes; (c) Non-polluting: the system generates no toxic byproducts; (d) Self-sustaining: it operates autonomously and productively over extended periods, solely using available internal resources; (e) Intensive: it yields high production rates with diverse crops; (f) Pathogen-free: it relies solely on beneficial bacteria[22].

Until comprehensive understanding of closed ecological life support systems under spaceflight conditions is achieved, the most viable approach for life support systems involves a hybrid model, blending physical-chemical and bioregenerative methods. Designing and assessing such systems draws expertise from diverse disciplines, encompassing mechanical, electrical, and thermal engineering, life sciences, material sciences, physics, chemistry, and agriculture. Various factors come into play, including mission duration, system mass, reliability, maintainability, power and thermal requirements, and the extent of interactions with other systems and subsystems. Similar to space biology, physiology, and medicine, research on life support systems stands as a crucial field in preparing for human missions to Mars.

Figure 10. NASA astronaut Mike Hopkins collects leaf samples from plants growing on the ISS. Image credit NASA.

5. CONCLUSION

The future of space life sciences holds significant promise and challenges. Researchers aim to delve deeper into understanding the effects of space travel on the human body, seeking solutions for extended space missions and improving astronaut health and performance. Key areas of focus include:

- **Health Optimization:** Exploring countermeasures against the physiological effects of space travel like bone density loss, muscle atrophy, cardiovascular issues, and vestibular alterations. Researchers are working to develop personalized interventions and preventive strategies.
- **Radiation Exposure:** Addressing the impact of space radiation on the human body during long-duration missions. Efforts are being made to devise shielding techniques and understand the potential health risks associated with prolonged exposure to cosmic radiation.
- P**sychological Well-being:** Enhancing mental health support and identifying strategies to combat isolation, confinement, and stress factors during extended space missions. Understanding crew dynamics and providing psychological support remain crucial.
- **Human Adaptation:** Investigating how the human body adapts to long-term space environments and gravitational variations. Studying these adaptations aids in designing spacecraft, habitats, and life support systems that optimize human health and performance.
- **Advanced Technologies:** Leveraging innovative technologies such as artificial intelligence, advanced sensors, and robotics to improve health monitoring, diagnose medical conditions, and streamline life support systems in space.
- **Terrestrial Applications:** Translating knowledge gained from space life sciences research to benefit healthcare on Earth, potentially contributing to advancements in medicine, rehabilitation, and understanding human physiology in different environmental conditions

Overall, the future of space life sciences involves an integrated approach, leveraging technological advancements and interdisciplinary collaborations to protect human health and performance in the challenging environments of space exploration.

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