HIGHLIGHTED TOPIC | Analogs of Microgravity: Space Research without Leaving the Planet

Effects of isolation and confinement on humans—implications for manned space explorations

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Pagel JI, Choukèr A. Effects of isolation and confinement on humans—implications for manned space explorations. J Appl Physiol 120: 1449–1457, 2016. First published February 11, 2016; doi:10.1152/japplphysiol.00928.2015.—Human psychology and physiology are significantly altered by isolation and confinement. In light of planned exploration class interplanetary missions, the related adverse effects on the human body need to be explored and defined as they have a large impact on a mission’s success. Terrestrial space analogs offer an excellent controlled environment to study some of these stressors during a space mission in isolation without the complex environment of the International Space Station. Participants subjected to these space analog conditions can encounter typical symptoms ranging from neurocognitive changes, fatigue, misaligned circadian rhythm, sleep disorders, altered stress hormone levels, and immune modulatory changes. This review focuses on both the psychological and the physiological responses observed in participants of long-duration spaceflight analog studies, such as Mars500 or Antarctic winter-over. They provide important insight into similarities and differences encountered in each simulated setting. The identification of adverse effects from confinement allows not only the crew to better prepare for but also to design feasible countermeasures that will help support space travelers during exploration class missions in the future.

space analog; stress; psychoneuroendocrinology; circadian rhythm; immunity

IN THE EVOLUTION OF MANKIND, gregarious behavior such as hunting or living together in small groups has been proven advantageous for survival. Sharing of specialized tasks and the division of labor into different professions catering to the individuals’ talents have enabled the development of multifaceted well-functioning modern societies. Isolation and exclusion from a social group as well as confinement have been forms of punishment since the early ages and continue to be the case in societies and prisons all over the world (9). Nevertheless, voluntary long-term confinement as a pair or with a group of people can cause strains on individuals. Differences in nationality, cultural background and character traits may induce severely altered stress levels and tension between the confined subjects, which can result in various disease states.

Historic reports. During the initial winter assignment of the US Amundsen-Scott Station at the South Pole in 1956 under the framework of the International Geophysical Year (IGY), one of the team members developed a severe case of paranoid schizophrenia. This endangered the crew as well as the mission where he had to be sedated and confined for the rest of his stay (1, 53, 55). The arduous weather conditions in Antarctica and the awareness of long-term confinement with a group of mostly strangers can be quite challenging and stressful for the human mind (54). It is difficult to delineate what the exact trigger was for that episode. At the time no provisions had been made to treat such a patient and evacuation was impossible. Stuster wrote in his book Bold Endeavors (53) that the patient was confined to a “special room lined with mattresses (...) to contain the sounds of psychotic ravings.” The condition was clearly severe and long-term sedation was the only option the team had. Based on reports from Nardini et al. in 1962 (31), this unexpected incident has led to routine psychiatric screening as a part of the recruitment process for missions to Antarctica. What remains unknown is whether the individual had predispositions for developing such an episode due to prior mental health or an entirely new manifestation. The individual did display abnormal behavior for a considerable time period before the manifestation of the psychotic episode with signs of disorientation and disruptive behavior. One could also speculate that he felt isolated because he did not “fit” into the team or that many different aspects of the situation reactivated a psychiatric condition he already had. What became clear though is that a 12-mo stay in Antarctica can trigger an acute spell of psychosis, which makes psychiatric screening neces-

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Isolation and Confinement in Space Analog Research

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No psychoneuroendocrine effects observed
High interindividual differences in the behavioral responses
Symptoms of depression
Reduced positive emotion ratings

Psychological effects
Cognitive impairment
Mood alterations (depression)
Tension towards crew members
Sleeping disorder
State of spontaneous fugue
Third quarter phenomenon

Physiological effects
Proinflammatory type 1 CD4+ T helper cell (TH1) pronounced phenotype
Leukocytosis

Increased HRV
Signs of sensory deprivation and monotony (decrease in [alpha]- and [beta]-waves)
Heart rate and HRV significantly disrupted
Sleep quality and sleep-wake periodicity
Impaired neuromuscular performance and circadian heart rate and HRV significantly disrupted

Increased wake parasympathetic activity
Inconsistent immune changes
Increased shedding of the cell adhesion molecule CD62L
Granulocyte-mediated H2O2 production elevated

Salivary cortisol and urinary catecholamine secretion increased; the endocannabinoid 2-AG decreased
Lymphocytosis with an increase of CD3+ T cells
IFN-γ and TNF-α secretion after stimulation with EBV antigen were altered
Postmission parabolic flight campaign: salivary cortisol levels and urinary excretion of epinephrine were increased compared to preflight and unlike the control group

Elevated 24-h urinary catecholamine excretion
Inflammatory alert state
Elevated hemoglobin and platelets
Increased total body iron stores
Elevated plasma adenosine
Increased oxidative stress

HRV, heart rate variability; PMNL, polymorphonuclear leukocyte; 2-AG, 2-arachidonoylglycerol; EBV, Epstein-Barr Virus.

Laboratory-Based Spaceflight Simulations

The 105- as well as the 520-day studies of the Mars500 program, which was conducted jointly by Roscosmos, the
European (ESA) and the Chinese Space Agencies, were conducted at the refurbished isolation facility located at the Institute of Biomedical Problems (IBMP) in Moscow, Russia. They investigated the effects of long-term confinement in a group of six volunteers during a spaceflight simulation to Mars. Although translation to a real Mars mission is limited (e.g., lack of microgravity or exposure to radiation), this form of space analog research allows an undisturbed view of the effects of confinement on participants.

The factor of duration. The facility was designed as a 550-m³ habitat with four interconnected modules under artificial light (50–300 lux) (61). As a pilot study, Mars105 was conducted before Mars520 from March 31st to July 14th 2009. Mid-term isolation during Mars105 did not affect the participants’ overall health as much as during longer confinement in Mars520, which involved 520 days of confinement from June 3rd 2010 to November 4th 2011. There was no evidence of altered subjective psychological stress level, hypothalamic-pituitary-adrenocortical axis (HPA) (glucocorticoid, catecholamine levels) activity, or changed sleep patterns during Mars105 (16, 51). Autonomic heart rate variability (HRV) showed increased amplitude oscillations at all frequencies and a reduced mean heart rate during the daytime (increased wake parasympathetic activity) in contrast; nighttime observations during sleep (61). Although no acute inflammation or elevated plasma cytokine levels were detected, distinct effectors of innate immunity were found to be inconsistently deregulated. Granulocyte-mediated H2O2 production and shedding of the cell adhesion molecule CD62L were both found to be increased in the volunteers (51). Many studies drew the conclusion that Mars105 did not impose a very strong stress stimulus on participants and the observed effects were therefore limited (16, 51). By contrast, when volunteers were confined for 520 days, the neuroendocrine stress responses were significantly altered. The responses of the endocannabinoid system were partly affected (67) and the level of salivary cortisol and catecholamines as markers for HPA activity were found to be increased during isolation (22, 63, 64, 67). Accordingly, a decrease in cortical activity of α- and β-waves can be correlated with the sensory deprivation and monotony encountered during isolation (22). Physical activity decreased during isolation and resulted in impaired neuromuscular performance mainly in the lower limbs (7). Moreover, the circadian heart rate and HRV were significantly disrupted and circadian misalignment was observed due to the lack of natural daylight (62). A well-balanced day/night cycle, however, with adequate sleep/rest and activity phases properly synchronized to the circadian rhythm is critical for keeping the crew healthy (5, 6, 9). During long-term confinement, the percentage of sleep and rest phases increased and sleep quality and sleep-wake periodicity were disrupted resulting in a decreased performance of participants (5, 6), which was paralleled by reduced positive emotion ratings (67). The influence on the immune system includes a higher percentage of lymphocytes (~50%), an increase of CD3+ T cells with a stable ratio of CD4+ helper T cells/CD8+ cytotoxic T cells and CD19+ B cells (64). IFN-γ and TNF-α secretion after stimulation with Epstein-Barr Virus (EBV) antigen, a measure for adaptive immune response towards viral antigens, was altered (14, 64).

The effect of the individual crew member. Certain crew members are more prone to suffer from disease or psychological strains than others. This can be due to distinct character traits, emotional instability, or a genetic predisposition (36). Interestingly, some of the Mars520 participants showed stronger shifts in the sleep-wake cycle than others. Common genetic variations rendering individuals prone to sleep restriction and sleep cycle disruption have already been suggested. Their use as predictive biomarkers would help to identify vulnerable astronauts before a mission, where one can implement adequate countermeasures such as supported rhythm alignment with the use of an artificial external zeitgeber (19). Moreover, crew members with prior experience in spaceflight mission under difficult circumstances are beneficial in critical situations. An astronaut who stays on the ISS for the first time will find it more difficult to adjust to the conditions and will therefore have a different experience than someone who has been there before and the same is true for confinement in space analogs.

The effect of available free space. The Simulation of Flight of the International Crew on the Space Station (SFINCSS-99) isolation study was also conducted at the IBMP from July 1999 to April 2000. The first group consisted of four Russian males who were confined for 240 days in a 100-m³ combined working and sleeping room. The second group comprised of four males and spent 110 days in a 200-m³ area with separated dorms for every subject. It was shown, that acute psychic stress, as measured by a self-evaluation questionnaire, did not occur in participants neither during the 110-day nor during the 240-day confinement (7). The innate immune system, however, was consistently activated as measured by enhanced expression of β2-integrins and elevated amounts of circulating granulocytes. Interestingly, the return from confinement back to normal surroundings exerted the strongest immunological changes in the subjects (7). This more pronounced effect on immunity might be due to the restricted free space availability for participants (200/100 vs. 550 m³ during the Mars studies). The restricted space allowed little chance to retreat from the group during tense and stressful situations.

Postoperational long-term effects. Confinement simulation under such high-fidelity conditions is not only a platform to test the effects of spaceflight during the mission but also provides excellent conditions to investigate the effects of environmental re-exposition, such as the return to Earth, when landing on another planet or destination in space (65). Moreover, postmission observation periods can include another evaluation of the physiological system and serve as an acute insult to the organism in testing for persisting effects of such prolonged confinement. Six months after completion of their mission, the Mars520 volunteers were subjected to acute stress during a parabolic flight campaign to compare the stress burden of these previously confined subjects to healthy and unaffected volunteers. After the exposure to 30 parabolas with repeated 1-, 1.8-, and 0-G phases, salivary cortisol levels and urinary excretion of epinephrine were increased compared with preflight (63). Interestingly, compared with the control group, cortisol levels were much higher in the Mars520 group indicating that a chronic stress burden leads to a priming effect with preactivated HPA.

Antarctica, a Testbed for Real Exploration Type Isolation Conditions

Expeditions to reach Antarctica were a heroic endeavor in the 19th century that fascinated people and Roald Amundsen
eventually reached the South Pole on 14 December 1911. Today, the extreme inhospitable environment has not lost its fascination and is host to international research facilities such as the French-Italian Concordia Station at Dome C located 3,233 m above sea level on the Antarctica Plateau. Concordia is one of the inland all year research stations together with the Russian Vostok Station and the US Amundsen-Scott South Pole Station and is situated 1,100 km inland from the coastal-based French research station Dumont D’Urville. Other research facilities situated at the coast include the German Neumayer-III and the British Halley IV research stations.

Psychological strain of an extreme environment. Preselection of suitable expedition volunteers, with regard to psychological and physiological health, is a difficult task (36, 54). Palinkas and Suedfeld (36) defined three critical personal character traits for successful polar missions: task ability, emotional stability, and social compatibility. Although volunteers are thoroughly screened, a 5.2% incidence of Diagnostic and Statistical Manual of Mental Disorders (DSM) IV validated disorders were detected in participants after return with mood disorders being the most common diagnoses (30.2%), followed by adjustment disorders (27.9%), sleep-related disorders (20.9%), and substance-related disorders (9.3%) (33). The 1-yr incidence values of DSM IV classified disorders in the general public of the USA evaluated in the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) were lower: major depressive disorder (1.51%), generalized anxiety disorder (1.12%), bipolar I disorder (0.53%), and drug dependence (0.32%). (20). Nevertheless, the results of the NESARC survey are evidently not directly comparable due to study design, group size, and composition. Being encapsulated with the thought of “nowhere to go,” surrounded by a vast ice covered landscape and spending a winter with a 3-mo lasting complete darkness put full-year inhabitants under extreme psychosocial strain, which has been recognized already during the first winter-over crew in the 1950s (31, 53, 55). Psychological adaptation to this extreme setting is a multifactorial process (32). Typical symptoms that participants of polar expeditions report are fatigue, headaches, gastrointestinal problems, sleeping difficulties, impaired cognition such as a state of spontaneous fugue also called “the Antarctic stare” (35), depressed mood, or tension towards crew members (21, 27, 30).

The psychosocial effects of the Antarctic environment are noted to be of seasonal nature. The characteristic stare is accompanied with motionlessness and speechlessness, lasting 1 to 90 min, has been reported in the majority of winter-over crew members after the onset of winter and ended shortly before the return of daylight (37). Furthermore, this behavior correlates to reports of depression. Although this is not a proper classified condition according to the DSM IV, the combined state of sleeping disorder, cognition impairment, negative affect, and tension towards crew members is referred to as the winter-over syndrome, which becomes aggravating in the second half of an expedition. This characteristic time course is completely independent of the duration of the expedition and referred to as the third quarter phenomenon (34, 36). The polar triiodothyronine syndrome (T3 syndrome) comprises of subclinical seasonal changes of thyroid gland function including lower levels of the effector hormone T3 (hypothyroidism) and elevated levels of thyreotropin-stimulating hormone (TSH). These changes, although subclinical in nature, significantly correlate with cognitive performance and mood alterations as evidenced by the Profile Of Mood States (POMS) questionnaire (40). Changes in the HPA axis were also detected. Supplements of levothyroxine and exposure to bright light (10,000 lux) during winter had beneficial effects on the observed mood alterations (35, 40). During the early adaptation phase (1 mo) of the Concordia winter-over crew in 2008, cortisol levels and stress questionnaires did not report higher stress levels. However, 24-h urinary catecholamine excretion was significantly increased (13).

Environmental triggers of the immune system. The environmental conditions in spaceflight and the analogs can be described as hypobaric hypoxic. Therefore, decreased mean oxygen saturation levels (85.7 and 88.7%, at 1 wk and 1 mo, respectively) as well as elevated hemoglobin and platelet levels were detected. Plasma adenosine, a measure for hypoxia-related immune alterations, was slightly increased at 1 wk, and accordingly, a leukocyte subpopulation shift towards granulocytes was detected alongside impaired polymorphonuclear leukocyte (PMNL) activation and H2O2 production (13). Innate immune modulations at the mucosal barrier revealed seasonal changes in immunoglobulin (Ig) A and IgM levels, where maximal immune suppression inversely correlated with altered psychosocial stress at a time point after 4 mo (18). Unfortunately, acute stress symptoms or hormone levels were not investigated. In a different study, anti-inflammatory cytokines (IL-10 and IL-1RA) were found to be decreased whereas proinflammatory IFN-γ was elevated (44). The observed immune changes demonstrate a shift towards a proinflammatory type 1 CD4+ T-helper cell (Th1) dominant phenotype and are in line with the previously observed EBV-viral reactivation study (29, 58). Interestingly, body weight supplementation of vitamin D has been shown to reduce the shedding of EBV into saliva (47, 69).

Impairment of cognition. The decline of cognitive performance is one of the key issues during long-term spaceflight. Its decline during spaceflight due to monotony or increased sense of stress could lead to devastating outcomes. Frequently reported symptoms of cognition impairment include memory loss, difficulties concentrating, increased reaction time, and disturbance of vigilance (30, 40). The previously mentioned fugue states and even an increased susceptibility to suggestion belong to the canon of symptoms (3, 36). The dimension of cognitive impairment during Antarctic winter-over is yet to be elucidated. A couple of studies were unable to measure such a decline and this seems to depend on testing format, the composition of crew members, and the course of the mission (1, 28, 40). Abeln et al. (1) for example, used commercially available games to test cognitive tasks such as visuoperceptual speed, reaction time, arithmetics, and object recall. However, likely due to a training effect, no alterations in cognition were detectable. Other studies showed that the motivation of subject was key to good performance values (12). Due to inconsistent use of testing formats and variable subject composition as well as limited study size, it is difficult to compare study results and to detect discrete changes.

New strategies for the evaluation of neurocognitive performance. New research increasingly focuses on advanced imaging techniques to quantify neurocognitive alterations and the brain’s ability to quickly adapt to altered stimuli (neuropsychology) in confined situations such as long-term spaceflight.
Advanced magnet resonance imaging (MRI) techniques such as diffusion tensor imaging (DTI) (15) allow for the visualization of diffusion changes in target neurofiber tracts, which enables direct measurement of the distinct changes due to neuroplasticity (11). With the use of DTI and whole brain voxel-based analysis, it has been shown that patients suffering from bipolar I disorder exhibit distinct white matter changes compared with healthy controls (4). Studies using DTI in space and Antarctic winter-over crews are still ongoing (17, 26, 60) and the results of these studies are highly anticipated. Functional MRI (fMRI) comprises of MRI imaging and a simultaneous functional performance of the test subject. The participant investigated is first examined in a resting state and then asked to mentally visualize activities (e.g., imagining running, walking, etc.). Recently published data examining a single astronaut before and after a 6-mo flight in space revealed alterations in vestibular and motor-related regions. The observed dysfunctions were clinically correlated with vestibular ataxia and reduced motor control abilities. Interestingly, these dysfunctions likely originate from the cortex, rather than from deconditioned gravity sensing organs as previously suggested (59). The application of these MRI methods will greatly advance our knowledge on the neurocognitive effects in terrestrial analog and spaceflight studies. The immune modulatory changes together with the severe psychosocial stress render Antarctica as one of the most interesting space analogs available. Aside from all the predominant negative effects, it is worth mentioning that many volunteers return with positive memories of their expedition to Antarctica. A stay at Antarctica for a short time or for winter-over is for many a once in a lifetime challenge and adventure, not to mention a worthwhile undertaking.

Short-Term Confinement in Underwater Habitats: Bridging Science to Operational Needs

Human beings can experience isolation and confinement not only in prepared laboratory settings or specialized research facilities, they encounter it everyday. A naval expedition or sailing trip where one is confined to a vessel with others and exposed to the force of nature, very closely resembles an interplanetary mission (53). The vastness of the ocean does provide some sensory input (daylight, animals, colors) but when diving, these sensory inputs are eradicated. Saturation divers live and work in underwater-pressurized habitats. The nature of this remote and extreme environment makes underwater habitats an excellent facility for space analog research. The Aquarius Reef Base is an underwater sea laboratory currently owned by the Florida International University (FIU) and located in the Florida Keys National Marine Sanctuary at an operating depth of 47 ft and operating pressure of 2.5 Atos. NASA Extreme Environment Mission Operations (NEEMO) trains astronauts in this unique underwater setting during 10–14 space analog missions. Astronauts are subjected to isolation and confinement in an extreme environment based station, daily 5- to 9-h dives simulating extra vehicular activity (EVA), and circadian-rhythm misalignment due to a lack of natural synchronizers (10, 50).

In a pilot study investigating six male astronauts in the context of innate immune alterations before, during, and after hyperbaric hyperoxia, no psychoneuroendocrine changes were detected. Blood analysis revealed leukocytosis, granulocytosis, monocytes, and lymphocytopenia during the dive, whereas proinflammatory cytokines such as IL-2, IL-6, IL-8, TNF-α, and IFN-γ remained unchanged. An increased expression of the adhesion molecule CD11b and shedding of CD62L on PMNLs were also detected. Moreover, PMNLs related H₂O₂ production exhibited an increased sensitivity to adenosine (50). These results illustrate an inflammatory high alert state with increased sensitivity towards possible stimuli. Similar systemic proinflammatory states and increased oxidative stress were also observed after a short dive (56). Well-known inflammatory markers of red blood cell metabolism, the total body iron stores (serum ferritin) (46) and toxic labile iron forms (non-transferrin-bound iron), were increased in the participants (2, 8). Blood homocysteine levels went up while the activity of superoxide dismutase (SOD) deteriorated, suggesting oxidative stress during the dive (68).

Although NEEMO is a very special setting with hyperbaric hyperoxic conditions, it shows that even a 14-day exposure to such a harsh environment can cause changes in immunity and antioxidant levels in the body. The long-term effects remain unknown, since a prolonged observation was not a part of the protocol. Clearly as human beings, we are not adapted to these living conditions but these would be the conditions on other planets such as Mars. Even if we were to build an artificial habitat with tolerable atmospheric conditions, we have to be aware of the fact that our body will still react to the non-Earth environments. Correspondingly, our immune system will most likely encounter altered and more virulent strains of Earth pathogens or perhaps completely novel foreign pathogens in space. This means astronauts are faced with adverse conditions with an impaired immune response, making medical support and optimizations all the more important in spaceflight.

Analog Environment for Future Space Exploration

The evolution of human kind is still ongoing. On our journey to another planet we would have to rely on the sharing of responsibilities among crew members similar to the early ages when we transformed from hunter-gatherers into ancient civilized societies. The extensive program of cosmonaut and astronaut training allows these candidates to experience some aspects of space travel in a relatively secure setting on Earth. Evidently, an intensive and exhaustive training for astronauts is crucial for the success of a mission but can only be as good as the scientific foundations it is based on. Program designers and scientists have to define what risks and dangers astronauts might encounter and to better prepare them: future manned exploration to the moon, asteroids, and Mars can be best practiced when the facilities appropriately simulate outer space conditions. This will become increasingly more critical since when the Earth bound analogs will be a function of the mission scopes, mission length, and overall boundary/budgetary estimates of such future exploration class missions. The selection of an analog mission scenario must meet two criteria: it must be a high-fidelity simulation that enables in-depth exploration of spaceflight-related stressors on a large number of subjects and be representative of the missions anticipated in the next 10–25 yr. In the post-ISS era, several vehicles and missions are in the planning and preplanning stages, ranging from free flyers in various Earth (or even lunar) orbits or beyond. These projects include the Chinese Space Station (CSS), “landing”-.
docking scenarios on asteroids, expeditions to the moon, or prolonged presence as a stepping stone for future Mars missions. The aim is for these plans to be realized by 2050. These conditions and scopes are highly variable, and the analogs must address the effects of various group sizes, gender composition, and limited living space in the spacecraft vs. more spacious habitats at the lunar or planetary destination. Also, the effect of life support systems (regeneration, green houses) must be considered alongside the effects of the atmospheres. The latter is generally speaking a hypobaric and hypoxic condition to facilitate extra-habitat/vehicular activities but imposes fire hazards and technical constraints (57).

Depending on the scopes and in particular, the confinement facilities, high-fidelity mid- to long-term simulations with variable crew sizes of three and more crew members can be accommodated, for example, in Russia. The Human Exploration Research Analog (HERA) facility and NEEMO will support research especially on operational issues, crew composition, and day to day life in habitats. When environmental or additional life support systems are to be tested with measurements on human organ homeostasis, the newly built and recently operational envihab facility (25) or the Olympic sport center in Planica (48) are favorable candidates. When a non-artificial habitat is to be tested, Antarctica seems to serve as the

Table 2. Space analog characteristics

<table>
<thead>
<tr>
<th>Mars500 Facility</th>
<th>Envihab</th>
<th>PlanHab</th>
<th>NEEMO</th>
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<tbody>
<tr>
<td>Normobaric normoxia</td>
<td>Adjustable: normobaric/hypobaric normoxia/hypoxia</td>
<td>Adjustable: normobaric normoxia/hypoxia</td>
<td>Hypobaric hypoxia</td>
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<td>Confinement</td>
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<td>Isolation</td>
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<td>Group psychology</td>
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<td>Group psychology</td>
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<tr>
<td>Circadian rhythm alterations</td>
<td>Environmental changes (pressure, (O_2) and (CO_2) content, temperature, light)</td>
<td>Environmental changes (hypoxic conditions)</td>
<td>Extreme environment</td>
</tr>
<tr>
<td>Sleep disruption</td>
<td>Circadian rhythm alterations</td>
<td>High altitude (3,000–3,500 m)</td>
<td>Access to the sea</td>
</tr>
<tr>
<td>Simulated docking/landing maneuvers</td>
<td>Combination with bedrest possible</td>
<td>Winter-over expeditions</td>
<td>Rescue possibility</td>
</tr>
<tr>
<td></td>
<td>Sleep disruption</td>
<td>Access only during Nov-Feb</td>
<td>3-mo period of darkness</td>
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<tr>
<td></td>
<td>Combination with bedrest possible</td>
<td>Limited rescue</td>
<td>Simulated docking/landing maneuvers</td>
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<td></td>
<td>Hypergravity studies (short-arm centrifuge)</td>
<td>3-mo period of darkness</td>
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<td>Microgravity</td>
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<td>Radiation</td>
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<td>Real docking/landing maneuvers</td>
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<td>Real docking/landing maneuvers</td>
<td>Real docking/landing maneuvers</td>
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<tr>
<td>Hostile environment</td>
<td>Difficulty of evacuation</td>
<td>Difficulty of evacuation</td>
<td>Difficulty of evacuation</td>
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<td>Mostly complete camera surveillance of the team at all times</td>
<td>Not directly integrated into a clinical facility</td>
<td>Only short-term (&lt;4 wk) projects</td>
<td>Hypobaric hypoxia as exploration mission relevant “confounder”</td>
</tr>
<tr>
<td>Not directly integrated into a clinical facility</td>
<td>Not directly integrated into a clinical facility</td>
<td>Limited on-site research laboratory facilities</td>
<td>Hyperbaric hyperoxia as a confounder</td>
</tr>
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Review

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most hostile and mission relevant environment at either hypoxic (e.g., the French/Italian Concordia, the US Amundsen-Scott South Pole, or the Russian Vostok Station) or normoxic conditions (e.g., at the British Halley VI or Neumayer III).

Already to date, given the broad portfolio of space analogs available for research, scientists have been gathering data from very unique and interesting environmental settings on Earth. However, each and every analog has its own characteristics, which have been described in this review (see Table 2).

**Space Analogs as Training Facilities**

Analog studies provide valuable insight for two parties, on the one hand to the scientific community by extending our knowledge in the field, on the other hand to cosmonauts and astronauts as they gain experience while taking part in mission simulations. As such, complete mission simulations are highly valuable tools. The ESA CAVES program (Cooperative Adventure for Valuing and Exercising human behavior and performance Skills) is a training opportunity where astronauts participate in a cave exploration with the goal of encountering new life forms and to train teamwork skills (49). The nature of the strange and uncommon environments inhabited by often novel organisms surviving off of elements like manganese or sulfur, without light and in a potentially life-threatening setting, offers a training scenario for space missions (8, 49). Similarly to the effects observed during the Mars confinement studies, the reunion with daylight after leaving the darkness and seclusion of the cave is a highly emotional experience for participants. With regard to an expedition to Mars, extraterrestrial caves are being discussed as a possible first natural form of habitat on Mars (8). Expanding this approach of priming the crew to space-like conditions and especially to prolonged confinement and isolation, a “mission” to Antarctica before Mars can certainly be worthwhile preparation.

**Coping Strategies and Countermeasures in Space Analogs**

Current strategies to ameliorate the effects of isolation and confinement in space or Antarctica involve first and foremost the careful selection of candidates for group compatibility, social skills, as well as psychological and physical health (31). Once mission bound, maintenance of crew health is a better strategy than therapy. Providing good nutrition and dietary supplements can prevent disease. This could involve previously mentioned levothyroxine (35) or vitamin D (69) supplements. Furthermore, physical exercise was found to be beneficial for a balanced mood in Antarctica (1) and during Mars500 (42). Sleeping disorders and disruption of the circadian cycle can be reduced at least in part with the use of an artificial zeitgeber, e.g., 10,000 lux bright white light (35). Core social coping strategies involve team-building exercises, team activities, or entertainment and access to communication such as “support from home.” Current research stations in Antarctica are capable of providing access to the Internet or telephone. Social bonding between fellow crew members especially for long-term confinement missions is best achieved before the mission, if possible. Training in space analog facilities can be a platform to achieve this goal.

**Conclusion and Outlook**

Isolation and confinement can put the human body under a large amount of psycho-neuroendocrine duress, which results in measurable pathophysiological symptoms. Terrestrial space analogs offer a very good setting for scientists to study these effects and to provide international space agencies with the information they need to select, prepare, and protect astronauts in short spaceflight and, in particular, long-term exploration class missions. Experiments in analog environments offer unique conditions to explore the nature of human adaptation and to allow high fidelity investigations in a clinical context. As such, standardized conditions of confinement (e.g., MARS500, envihab, PlanHab, and other in the US and in China) can be advantageous in their application as a metabolic chamber for nutritional and metabolic studies (38, 66) or as a hypoxic environment for disease studies in human organs.

Despite the scientific advancements thus far, exploration class interplanetary missions are a bold endeavor not for the faint of heart. They require not only brave and experienced crew members but also a huge amount of resources including further technical developments, medical scientific research, and strong psychological support. These investments into further investigations will not only be required for safe manned space exploration but will no doubt serve to benefit life on Earth.

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**AUTHOR CONTRIBUTIONS**

J.-I.P. drafted manuscript; J.-I.P. and A.C. edited and revised manuscript; J.-I.P. and A.C. approved final version of manuscript.

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