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Social Hallmarks of Human Spaceflight

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Abstract

Current frameworks of space medicine treat the social environment of a crew as one hazard among five, grouped as isolation and confinement. Population health research, by contrast, has long described the social environment as a set of distinct conditions that act through separate mechanisms, and aging research has organized them as social hallmarks. In this narrative review, we transpose that approach to human spaceflight and propose eight social hallmarks arranged in two tiers. The first tier adapts five terrestrial conditions to life on board: (1) relative rank and control, (2) minority status within the crew, (3) adverse events during the mission, (4) mission-induced psychological states, and (5) imposed behaviors and sleep. The second tier comprises three conditions without terrestrial counterparts: (6) confinement and loss of privacy, (7) separation from the external social network, and (8) forced autonomy and communication delay. Crew cohesion and the pre-flight life course are proposed as modifiers of all eight. Because housing, food, and medical care are largely equalized on board, the material pathways through which socioeconomic position acts on Earth are attenuated within a crew, whereas psychosocial routes remain. We graded the evidence for each condition at three levels. The grade depended on whether a physiological change had been related to the condition itself (exposure-linked), had been measured only at the start of isolation (co-occurring), or had not been related to the condition in any study eligible for grading (candidate). Mission-induced psychological states and imposed behaviors were exposure-linked, although each rested on a single analog crew of six participants. Confinement and separation from the external network were co-occurring, and the remaining four conditions are candidates supported mainly by terrestrial and animal evidence. Evidence on neuroendocrine axes, latent viral reactivation, the gut microbiome, and autonomic regulation indicates where these conditions may act. Physiological markers and self-report have repeatedly diverged in analog crews, so that both should be measured together. The gap between the social exposures of a crew and their measured physiological consequences therefore remains wide, and ground analogs offer the setting in which individual hallmarks might first be separated.

Categories: Occupational Health, Psychology
Keywords: behavioral health, crew cohesion, human spaceflight, isolation and confinement, latent herpesvirus reactivation, mission design, psychosocial stress, social environment, social hallmarks, spaceflight analogs

Introduction And Background

Current frameworks of space medicine treat the social environment of the crew as a single hazard rather than as a set of distinct conditions. In the taxonomy of the National Aeronautics and Space Administration (NASA), that environment appears once as isolation and confinement, alongside space radiation, altered gravity fields, closed environments, and distance from Earth. These five hazards have been linked to more than 30 documented risks to crew health, among which behavioral health and performance decrements rank within the four highest priorities for a mission to Mars [1]. A similar grouping recurs in the biomedical literature, where reviews of astronaut immunity list isolation and confinement, tight living quarters, and the stress of being away from home side by side with radiation and altered gravity [2]. In terrestrial analogs, ground settings such as chambers, habitats, and polar stations that reproduce features of a mission, isolation and confinement have likewise been examined as one combined exposure [3]. Within this framing, psychological stress is now recognized as a modulator of immune cell biology in flight, although the combined effects of spaceflight stressors remain less understood than their individual effects [4].

By contrast, population health research has described the social environment as a set of distinct conditions that act on disease risk through multiple mechanisms and across multiple organ systems [5]. Socioeconomic position is the most extensively studied of these conditions. Specifically, the theory of fundamental causes holds that it protects health because it confers money, knowledge, prestige, power, and beneficial social connections, so that its association with mortality persists even when the intervening risk factors change [6]. The resulting gradient is not limited to deprivation, as employment grade was inversely associated with angina, electrocardiographic ischemia, and symptoms of chronic bronchitis in a cohort of 10,314 British civil servants [7]. The pattern is not confined to humans, as the social environment ranks among the strongest predictors of morbidity and mortality across social mammals, and experimental work in animals has shown that social conditions causally alter physiology and disease risk [8]. Social connection carries associations of comparable magnitude, and in a meta-analysis of 148 studies, stronger social relationships were associated with a 50% increase in the odds of survival [9].

The biological pathways proposed for these associations include allostatic load, defined as the cumulative physiological cost of repeated or chronic stress responses [10]. A second route is a conserved transcriptional response to adversity, a shared pattern of gene activity in circulating leukocytes in which genes involved in inflammation are upregulated, whereas genes involved in antiviral defense are downregulated [11]. Whether these routes are engaged depends on the character of the stressor, and laboratory evidence indicates that cortisol responses are largest when a stressor is uncontrollable and carries a threat of social evaluation [12].

In aging research, these strands of evidence have been organized under the concept of social hallmarks, defined as a set of interrelated social causes of multiple health outcomes [13]. The five conditions so designated are low lifetime socioeconomic status, adversity in childhood and adulthood, membership in a minority group, adverse health behaviors, and adverse psychological states. In the original analysis, these conditions remained strongly associated with physical and cognitive function and with multimorbidity after a large number of biological measures were taken into account. Hallmark-based frameworks from aging research have recently been applied to the molecular biology of spaceflight [14], although, to our knowledge, not to its social environment. The concept of social hallmarks therefore offers a template for distinguishing social conditions that are often grouped together, although it was formulated for aging populations rather than for small groups living in extreme environments.

In spaceflight, much of the variation captured by these terrestrial hallmarks is reduced by design, because astronauts undergo psychological and psychiatric screening at selection and receive operational support for workload and work-rest scheduling [15]. Food, exercise protocols, and daily schedules on the International Space Station (ISS) are likewise managed by mission operations [16], so that housing, food, and medical care may be considered largely equalized among crew members. Of the resources that socioeconomic position confers on Earth, namely money, knowledge, prestige, power, and beneficial social connections [6], the material ones accordingly differ less within a crew than in terrestrial populations. Differences in pre-flight wealth and health may nonetheless persist through the life course of each crew member. Rank, control, and social connection, by contrast, continue to vary, and the supportive role of the commander has been associated with crew cohesion on the ISS [17]. Consistent with the relevance of perceived rank when material differences are small, subjective social status was more strongly related than objective indicators to heart rate, sleep latency, and cortisol habituation in a sample with a moderately restricted socioeconomic range [18]. At the same time, crews have begun to diversify, as commercial missions now carry private participants with a wider range of ages, wealth, and medical histories alongside career astronauts [19,20].

Analog research on crews has concentrated on team dynamics, cohesion, and performance [21], and the physiological consequences of the individual social conditions of a mission have not been organized within a common framework. In light of this gap, we propose a set of social hallmarks of human spaceflight, organized in two tiers. The first tier adapts the five terrestrial hallmarks to life on board. Low lifetime socioeconomic status becomes relative rank and control, adversity becomes adverse events during the mission, and adverse health behaviors become imposed behaviors, whereas minority membership and adverse psychological states keep their terrestrial meaning within the crew [13]. Of the imposed behaviors, sleep is the best documented in flight [22]. The second tier comprises three conditions with no direct terrestrial counterpart, namely confinement with loss of privacy, separation from the external social network, and forced autonomy imposed by delays in communication with Earth. These conditions derive from the hazards of isolation, confinement, and distance from Earth [1,23]. On this basis, we examine the evidence for each condition, the physiological pathways through which these conditions may act, and the implications for the design of animal and analog studies. We finally discuss the countermeasures that operate on the crew rather than on the individual.

Literature search and evidence grading

We searched PubMed for studies conducted in flight or in spaceflight analogs that reported a physiological measure together with a social condition of crew life. The search combined terms for the setting (e.g., spaceflight, astronaut, ISS, Mars-500, and Antarctic station) and the study population with terms for social conditions (e.g., hierarchy, leadership, minority, conflict, cohesion, privacy, crowding, communication delay, and autonomy). These terms were further combined with physiological outcomes, such as cortisol, catecholamines, immune function, herpesvirus reactivation, gene expression, microbiome, heart rate variability, and sleep. This core search covered records from database inception to November 12, 2026, and returned 231 records, whose titles and abstracts were screened for relevance, and its complete string is given in Appendix 1. It was complemented by the same search without the population terms, which also retrieved animal studies; targeted searches that combined the setting terms with terms for each hallmark; and searches of the reference lists of retrieved studies and recent reviews. Of the 113 references cited, 33 were retrieved by the core search. Studies were eligible for grading when they examined crew members during flight or in chamber, habitat, or polar analogs. Studies of single physical stressors without a social component, such as microgravity or radiation alone, were not used for grading and were cited only to document the physiological pathways. Evidence on terrestrial populations and nonhuman primates was not searched systematically and was drawn from landmark studies and reviews of the social determinants of health [5,8,11]. This evidence was used to indicate plausible mechanisms and never to grade a hallmark. The manuscript was checked against the six items of the Scale for the Assessment of Narrative Review Articles (SANRA) [24].

We regard as a social hallmark a condition that arises from the social organization of a mission, namely its command structure, crew composition, operational schedule, habitat, and communication with Earth, and that may act upstream of physiological systems. The two tiers reflect the source of the evidence rather than the importance of a condition, since only the first can draw on terrestrial epidemiology for its mechanisms. Mission-induced psychological states and sleep may also lie on the pathway from other hallmarks to physiology. Because the terrestrial template counts adverse psychological states and health behaviors among the hallmarks [13], we retain both as exposures and treat their position on the causal pathway as an open question. The three conditions of the second tier are separated by the parameter that mission design controls. For confinement, this parameter is the habitable volume and access to privacy; for separation, the frequency of private contact with family and friends; and for forced autonomy, the latency of operational communication and the decision authority delegated to the crew.

The evidence for each hallmark was graded at three levels. A hallmark was considered exposure-linked when at least one study in flight or in analog crews had related a physiological outcome to the social condition itself. Such a study either compared crew members who differed in the condition or related the intensity of the condition to the outcome. For conditions shared by the whole crew, a hallmark was considered co-occurring when physiological change had been measured across the transition at which the condition began, such as the start of isolation. Such a change cannot be separated from other conditions that began at the same time. Candidate hallmarks were those for which no study eligible for grading had related a physiological measure to the condition in crews; therefore, the evidence derived mainly from terrestrial or animal studies. A measurable physiological change was defined as a statistically significant change in an endocrine, immune, autonomic, microbial, or molecular measure or in objectively recorded sleep when sleep was not itself the condition under study. Studies that could be assessed only from an abstract were described but not used for grading. All eight conditions occur in flight or in analogs and can be modified through mission design, and these two features were therefore not used to discriminate between grades. Because the literature combines flight, analog, laboratory, and animal studies of different designs, no formal risk-of-bias tool was applied. The setting and, where reported, the number of participants in the main studies are provided alongside the grade of each hallmark.

Review

Hallmarks adapted from terrestrial social conditions

The five hallmarks of the first tier derive from the conditions described in aging research, redefined for the social structure of a crew [13].

Relative Rank and Control

Among the terrestrial correlates of social position, control over one's own work has shown one of the most consistent links with cardiovascular outcomes. In the Whitehall II cohort, low control at work made the largest contribution to the employment-grade gradient in incident coronary heart disease, whereas height and standard coronary risk factors made smaller contributions [25]. The association also appears cumulative, since low job control assessed on two occasions carried a risk of subsequent coronary events (odds ratio = 1.93; 95% CI = 1.34, 2.77) that employment grade, negative affectivity, and classic risk factors did not explain [26]. Accordingly, a meta-analysis of individual data from 13 European cohorts confirmed an association between job strain and incident coronary heart disease (hazard ratio = 1.23; 95% CI = 1.10, 1.37), which was attenuated but persisted after adjustment for socioeconomic status (hazard ratio = 1.17; 95% CI = 1.05, 1.31) [27].

In nonhuman primates, the physiological cost of a position depends on how the hierarchy is organized, and stressful positions carry adrenocortical, cardiovascular, immunological, and neurobiological consequences [28]. Experimental evidence that rank acts causally comes from female rhesus macaques, in which experimentally assigned low status altered immune cell composition and gene expression and polarized Toll-like receptor 4 signaling toward a proinflammatory response [29]. These effects were causal but largely plastic, a pattern that may be of particular relevance to crews in which rank is assigned by an external authority for the duration of a mission.

On board, rank takes the form of a command structure, and the behavior of the commander has emerged as a recurrent determinant of the group climate. Among 17 ISS crew members who completed weekly mood and group climate questionnaires, cohesion was related to the supportive role of the commander, and negative feelings were displaced toward outside supervisors on all six subscales tested [17]. A comparable displacement of tension and dysphoria from crew members toward mission control personnel had been documented consistently during the Shuttle/Mir program [30]. Analog data separate the two components of the commander's role, since in one crew of the Lunar Palace 1 habitat, leader support, but not leader control, correlated positively with cohesion, expressiveness, and involvement [31]. Control can also be contested within very small teams, and in a two-person polar habitat of 60 days, difficulties over decision authority impaired interpersonal interaction and work performance [32].

Physiological measures have rarely been compared between crew members who differ in command position,

and the evidence on rank therefore derives mainly from terrestrial cohorts and nonhuman primates. Relative rank and control are accordingly graded as a candidate hallmark.

Minority Status Within the Crew

In sexual minority populations, minority stress has been described as a set of processes, including prejudice events, expectations of rejection, and concealment, that operate within a hostile social environment created by stigma and discrimination [33]. In small groups, the corresponding exposure is token status, which laboratory experiments have reproduced by simulating the workplace climate of women in male-dominated occupations [34]. Participants in these experiments occupied the token position and were either socially included or excluded on the basis of gender. Both men and women showed a salivary cortisol response when excluded, whereas those who were included showed no such response, which suggests that exclusion rather than numerical rarity alone drives the physiological reaction.

Within crews, minority status follows national culture, language, and gender, and its effects have been documented mainly through psychosocial measures. During the Shuttle/Mir program, American astronauts scored lowest of all comparison groups on leader support, expressiveness, and independence, and the investigators recommended that future crews include more than one representative of any minority culture [35]. Minority positions can also divide crews. In the Simulation of Flight of International Crew on Space Station 1999 (SFINCSS-99), an international crew that included the only woman evaluated its own group and mission control more negatively than an all-Russian crew [36]. Language barriers and differing attitudes toward gender relations were identified as the main sources of tension between the two crews. The tension escalated to an unplanned closure of the hatch between chambers and to the early departure of one participant.

Comparable dynamics have been observed in polar stations, where Antarctic winter-over crews from five nations showed culture-specific trajectories of mood and social support, and an individualistic cultural orientation was associated with both lower social support and lower negative mood [37]. Such divisions have also been measured directly, as wearable proximity sensors over a 10-month winter at Concordia station recorded social interactions that became increasingly clustered within national groups, alongside a progressive increase in loneliness and conflict [38].

Physiological measures in mixed-gender crews have so far compared men with women rather than minority with majority members. Among 10 women and 16 men studied during three one-year expeditions at the Neumayer III station, cortisol concentrations were higher in women than in men during winter, although psychological stress did not increase in either sex [39]. A sex difference of this kind does not isolate the effect of minority position, and minority status within the crew therefore remains a candidate hallmark.

Adverse Events During the Mission

Interpersonal conflict is the most consistently documented adverse event in long-duration missions and their analogs. A systematic review of 72 analog sources found that every team had reported at least one conflict by 40% of mission completion or by day 90 [21]. In the 520-day Mars-500 simulation, conflicts with mission control were reported five times more often than conflicts among crew members [40]. Conflict was concentrated in a few individuals, since the two crew members with the highest ratings of stress and physical exhaustion accounted for 85% of perceived conflicts. One of these two, moreover, developed persistent sleep-onset insomnia, with chronic partial sleep deprivation and frequent lapses in behavioral alertness. Tension within crews also arises from divergent motivational goals because perceived incongruence in seven of eight personal values predicted interpersonal tension among 12 astronauts during four- to seven-month ISS missions [41].

Physiological data on conflict within crews are scarce. During a 34-week chamber confinement with resident and visiting crews of mixed nationality, occasional peaks of urinary epinephrine appeared to coincide with changes in group dynamics, and norepinephrine excretion was reported to correlate with social events [42]. In the Mars-105 chamber study, six men lived for 105 days under high autonomy and restricted external communication. Critical statements in the daily reports of five participants were related to weekly urinary testosterone, and the correlation reached statistical significance in one participant (correlation coefficient, 0.66; $p < 0.05$) [43]. Prolonged confinement may also change the response to a later acute stressor because Mars-500 participants showed higher cortisol peaks than matched controls during a parabolic flight performed after the mission [44]. Consistent with this human observation, rats exposed to social isolation combined with simulated space radiation showed greater freezing, greater stress-induced hyperthermia, and altered post-stress sleep after an unexpected fear-conditioning challenge [45]. As the only statistically tested association within a crew concerned critical statements rather than conflict events and was confined to a single participant, adverse events during the mission are graded as a candidate hallmark.

Mission-Induced Psychological States

Psychological states during isolation and confinement appear to change in stages rather than linearly.

Across three 8-12-month missions in the Hawai'i Space Exploration Analog and Simulation (HI-SEAS), metabolite profiling of hair and urine was combined with wearable and self-report data [46]. This approach identified an initial phase of high stress hormone levels followed by a phase of declining dopamine and serotonin. A phase of disrupted individual and team dynamics then emerged after roughly six months, before a final period of asynchronous coping. In the Mars-500 crew, mood appeared to change in stages similar to the third-quarter phenomenon, although this pattern was not statistically significant, and mood scores correlated with changes in plasma serotonin, dopamine, and norepinephrine [47]. Individual trajectories nonetheless varied widely, and one Mars-500 crew member reported depressive symptoms in 93% of mission weeks [40]. In a 10-day confinement of 10 young adults, the participants whose mood changed toward the end of confinement also showed changes in granulocytes, natural killer cells, and CD69 expression, whereas those without mood changes showed less marked immune changes [48]. With physiological measures related to the psychological state itself in the Mars-500 crew, mission-induced psychological states are graded as exposure-linked, on the basis of a single crew of six men.

Imposed Behaviors and Sleep

Sleep is the most extensively documented of the behaviors governed by mission operations because operations frequently require work during the biological night and sleep during the biological day [49]. Actigraphy in 64 astronauts on 80 shuttle missions and 21 astronauts on 13 ISS missions showed about six hours of sleep per night in flight, with similarly short sleep during a training interval three months before launch [22]. Pharmacological compensation was common, as sleep-promoting drugs were taken by 78% of shuttle crew members on 52% of nights and by 75% of ISS crew members. Circadian timing accounts for part of this deficit, as sleep on the ISS lasted 6.4 hours when sleep episodes fell at an appropriate circadian phase and 5.4 hours when they did not [49]. Use of sleep-promoting medication followed the same contrast, at 11% of appropriately timed sleep episodes compared with 24% of those timed adversely.

Short sleep in flight has measurable consequences, as durations below six hours were associated with slower psychomotor responses, higher stress, and higher workload among 24 astronauts on six-month ISS missions [50]. In the Mars-105 study, higher urinary cortisol, even within the normal range, was associated with shorter sleep, more arousals, and shorter rapid eye movement latency [51]. Imposed sleep loss also acts on autonomic regulation. In the four-month confinement of the Scientific International Research in Unique Terrestrial Station program (SIRIUS-19), a night of complete sleep deprivation produced the most pronounced nocturnal autonomic activation among six participants, whereas moderate sleep fragmentation had smaller effects [52]. In a one-week lunar-habitat analog, likewise, reductions in sleep duration and quality correlated with increases in reactive oxygen species [53].

A second behavior shaped by the mission environment is physical activity. Over 520 days of Mars-500 confinement, actigraphy documented progressive hypokinesis, longer sleep and rest times, and decreasing light exposure, and most crew members showed disturbances of sleep quality, vigilance, or sleep-wake timing [54]. Because these behaviors are set by operations, they are also open to redesign. In a 45-day mission in the Human Exploration Research Analog (HERA) with scheduled sleep restriction, a dynamic lighting schedule reduced circadian drift and the proportion of sleep episodes at an adverse circadian phase [55].

Since autonomic measures have been related to imposed sleep loss within a six-person analog crew, imposed behaviors and sleep are graded as exposure-linked.

Hallmarks specific to spaceflight

The three hallmarks of the second tier arise from the physical and communicative separation of the crew from Earth, which the NASA taxonomy places under the hazards of isolation and confinement and of distance from Earth [1].

Confinement and Loss of Privacy

Confinement and isolation are usually grouped under one hazard, although behavioral data indicate that they may act in opposite directions. A video-ethological comparison of the 507-day Tara polar drift and the 520-day Mars-500 simulation found more stress-related behaviors under confinement, such as collateral acts and time spent in personal actions [56]. Isolation, by contrast, was associated with more visual interaction among crew members. Proximity data point in the same direction, as close-range interactions recorded by wearable sensors over a 10-month winter at Concordia were positively associated with conflict and paranoid thoughts and negatively associated with individual performance [38]. On this basis, the investigators proposed that close confinement, rather than isolation alone, may trigger interpersonal strain.

The notion of privacy, understood as the desired level of personal space, has framed confinement research since the early chamber studies. In one such study, crowding during a 14-day stay of four men and two women in a 50 m^3 chamber was accompanied by mood and sleep disturbances [57]. Privacy can now be quantified, and a validated habitability questionnaire administered to 19 HERA crew members rated privacy,

comfort, and convenience significantly lower in the habitat than in private hotel rooms [58]. Evidence from terrestrial populations suggests that chronic crowding may amplify the effect of acute social stressors, since daily social hassles predicted psychological symptoms only among residents of crowded homes [59].

Physiological changes have also been documented during prolonged confinement with unchanged gravity. Over the 520 days of Mars-500, salivary cortisol was elevated, lymphocyte counts increased, and ex vivo responses to a simulated viral infection were heightened and poorly controlled [60]. In the same crew, the intima-media thickness of the common carotid and femoral arteries increased by 14% to 28% during confinement and returned to baseline within six months [61]. When two four-man groups were confined for 240 and 110 days in modules of 100 and 200 m^3, respectively, only the group in the smaller module showed a depressed diurnal rhythm of cortisol and increased urinary norepinephrine [62]. These changes were measured at the start of confinement, and the only contrast between habitats of different volume also differed in the duration of confinement, so that confinement and loss of privacy are graded as a co-occurring hallmark.

Separation From the External Social Network

On Earth, the diversity of social ties has been linked to host defense against infection under conditions that resemble confinement. Among 276 volunteers inoculated with rhinovirus and kept in quarantine, susceptibility to colds decreased in a dose-response manner with the diversity of social ties [63]. The gradient was steep, as the adjusted relative risk was 4.2 for participants with one to three types of ties compared with those with six or more. Perceived isolation, in turn, heightens vigilance for social threat and has been associated with lower sleep quality and with higher morbidity and mortality [64].

Analog campaigns show a measurable erosion of these ties, and across five such campaigns involving 64 crew members with restricted communication, perceived social support declined over time for every source [65]. The decline was steeper for the public, the organization, and family and friends than for fellow crew members. Importantly, only support from fellow crew members was related to the stress levels reported in the evening. For a Mars mission, two-way communication with family and mission control may take up to 44 minutes, a condition termed the Earth-disconnect phenomenon and proposed as a source of emotional distress and impaired performance [23]. Separation from family is already addressed operationally on the ISS through a Family Support Office and psychological services provided for crew members and their families before, during, and after flight [15].

Separation from the external network begins at the same transition as confinement, and the physiological changes recorded during the 520 days of Mars-500 [60,61] therefore apply to both conditions without distinguishing between them. Separation is accordingly graded as a co-occurring hallmark, whereas the support that crews receive from their external network has so far been measured only by self-report.

Forced Autonomy and Communication Delay

Autonomy is protective on Earth when it confers control, and low decision latitude, including little freedom to set one's own schedule, has been associated with a higher risk of cardiovascular disease and death [66]. At the neural level, passivity is the default response to prolonged aversive events, whereas the detection of control engages the medial prefrontal cortex and inhibits the stress response of the dorsal raphe nucleus [67]. In deep space, however, crews will be required to function with less guidance and support from Earth [68], so that the autonomy imposed by communication delay may combine elements of control with elements of deprivation.

Communication delay has been introduced experimentally on the ISS, where three crew members and 18 mission support personnel performed 10 tasks, four of which carried a 50-second one-way delay [69]. That study established the feasibility of using the ISS to assess the behavioral effects of delay, and the crew judged the question an important one. Behavioral effects have since been quantified in a three-year multi-site NASA analog, in which one-way delays of 60 and 180 seconds lengthened time on task, and information networks predicted team performance only when communication occurred with a delay [70]. The SIRIUS experiments, in addition, confirmed a progressive detachment of the crew from mission control, first described in Mars-500, in which a simulated landing halfway through isolation reversed only temporarily [71]. On the ground side of the link, mission controllers working with a 20-minute one-way delay during a 21-day analog left more tasks incomplete and reported a higher workload, although their reported stress did not change [72]. Physiological correlates of delay come mainly from outside crews, as a large time delay in a laboratory lunar teleoperation task increased perceived workload and decreased heart rate variability [73]. Within an analog crew, the only hormonal data come from the final five weeks of Mars-105, when audio contact with mission control was restricted to four sessions a day and written messages arrived with a 30-minute delay [43]. In that period, estradiol excretion fell in almost all participants, whereas testosterone increased in two and decreased in three, without a statistical comparison between periods. Because these changes were neither tested statistically nor separated from the third month of confinement, forced autonomy is graded as a candidate hallmark.

Table *1* summarizes the grade of each hallmark together with the setting, design, and sample size of the studies on which it rests.

Hallmark	Main evidence in flight or analogs (setting, participants)	Physiological evidence and its link to the condition	Modification through mission design	Grade
Relative rank and control	ISS, 17 crew members [17]; Shuttle/Mir [30]; Lunar Palace 1 [31]	Not compared across command positions in crews; terrestrial cohorts and nonhuman primates [25,29]	Supportive role of the commander [17]; countermeasures for displaced tension proposed but not tested [30]	Candidate
Minority status within the crew	Shuttle/Mir [35]; SFINCSS-99 [36]; Concordia, wearable sensors [38]	Sex differences in winter cortisol, 10 women and 16 men [39]; minority position not measured	More than one representative of each minority culture [35]	Candidate
Adverse events during the mission	Analog systematic review, 72 sources [21]; Mars-500, 6 men [40]; ISS, 12 astronauts [41]	Catecholamines and social events, 34-week chamber study (abstract only) [42]; testosterone and critical statements, significant in 1 of 5 participants, Mars-105 [43]	Pre-mission conflict resolution training [74]	Candidate
Mission-induced psychological states	HI-SEAS, three missions [46]; Mars-500, 6 men [47]; 10-day confinement, 10 adults [48]	Plasma monoamines correlated with mood, Mars-500 [47]; immune changes with mood change (abstract only) [48]	In-flight monitoring and psychological support [15]	Exposure-linked
Imposed behaviors and sleep	Shuttle and ISS actigraphy, 85 astronauts [22]; ISS [49]; Mars-500 [54]	Autonomic activation with imposed sleep deprivation, SIRIUS-19, 6 participants [52]; urinary cortisol related to sleep, Mars-105 [51]	Dynamic lighting and scheduling [55]	Exposure-linked
Confinement and loss of privacy	Mars-500 and Tara [56]; Concordia [38]; HERA, 19 crew members [58]; chamber, 6 participants [57]	Salivary cortisol, immune responses, and intima-media thickness across the start of isolation, with absence of sunlight as an alternative explanation, Mars-500 [60,61]; module volume confounded by duration (abstract only) [62]	Habitat size and layout [58]	Co-occurring
Separation from the external social network	Five analog campaigns, 64 crew members [65]; ISS [15]	Changes across the start of isolation shared with confinement, Mars-500 [60,61]; perceived support by self-report only [65]	Family support services, communication with Earth [15,23]	Co-occurring
Forced autonomy and communication delay	ISS, 3 crew members [69]; NASA analog [70]; SIRIUS [71]	Heart rate variability in a laboratory teleoperation task [73]; gonadal hormones during restricted communication, 5 participants, not tested statistically, Mars-105 [43]	Communication protocols [75]	Candidate

TABLE 1: Evidence grades for the social hallmarks of human spaceflight

Exposure-linked, physiological outcome related to the condition itself in flight or analog crews; co-occurring, physiological change measured across the transition at which a condition shared by the crew began; candidate, no physiological measure related to the condition in a study eligible for grading. Studies assessed only from an abstract were not used for grading.

ISS: International Space Station; SFINCSS-99: Simulation of Flight of International Crew on Space Station 1999; HI-SEAS: Hawai'i Space Exploration Analog and Simulation; SIRIUS-19: Scientific International Research in Unique Terrestrial Station 2019; HERA: Human Exploration Research Analog; NASA: National Aeronautics and Space Administration.

Modifiers: crew cohesion and pre-flight life course

Team dynamics in isolated, confined, and extreme settings emerge from a closed system in which food,

exercise, sleep and work rhythms, and habitat design act on neurobiological substrates [76]. Within such a system, crew cohesion may function less as an exposure than as a group property that modifies the effect of the other hallmarks. In a systematic review of 72 analog sources, team members in longer missions generally spent less social time together [21]. In the same review, the relationship between cohesion and performance appeared to differ from that observed in other teams that live and work together. Stress can also strengthen cohesion, as the crew of a 14-day chamber study under crowded conditions became more cohesive and came to share more common values [57], and cohesion increased toward the end of the SIRIUS experiments [71]. The role of cohesion as a modifier of physiological responses is therefore proposed here as a hypothesis to be tested.

Each crew member also brings to the mission a personal history that may condition the response to these exposures. A systematic review of 73 studies identified emotional stability, hardiness, task-oriented coping, past experience, a low need for social support, and adequate sleep among the attributes linked to adaptability in isolated, confined, and extreme environments [68]. Flight experience may also modify the biological response to the mission. Among eight ISS crew members studied before, during, and after a six-month mission, those on their first flight had lower salivary secretory immunoglobulin A but higher alpha-amylase, lysozyme, and LL-37 compared with veterans [77]. The pre-mission period itself carries psychosocial stressors that may affect behavioral health before launch [78], and the pre-isolation phase proved particularly stressful for chamber participants with little previous isolation experience [57]. In female rhesus macaques, likewise, the effect of current social status on immune gene expression depended on social history [79]. For a subset of genes, animals that had fallen in rank were more strongly affected than those that had risen. These data suggest that the life course of crew members before flight, including their flight experience and prior position in social hierarchies, may shape the biological response to the social conditions of the mission.

Commercial missions add a further source of variation because private participants differ from career astronauts in selection, training, flight experience, and position on board. ISS visiting missions now pair a career-astronaut commander with private participants aged 33 to 71 years, a civilian cohort whose documented comorbidities include treated coronary artery disease, paroxysmal atrial fibrillation, and type 2 diabetes mellitus [20]. The first all-civilian orbital crew showed physiological and stress responses across several systems during a three-day mission, most of which returned to baseline after landing [80]. In two commercial ISS missions of 10 and 21 days, gut and oral microbiomes remained stable, whereas skin communities shifted transiently and cytokine transcripts indicated immune activation [81]. These differences suggest that rank, minority status, and the pre-flight life course may take a different form in commercial crews than in professional ones.

Physiological pathways

The eight hallmarks may act through a limited number of physiological systems (Figure *1*), several of which correspond to the routes proposed for social conditions on Earth, such as allostatic load and the conserved transcriptional response to adversity [10,11]. Ground analogs reproduce part of the physiological and psychological stress response of spaceflight, and their findings have been interpreted within a framework of acute and chronic stress [82].

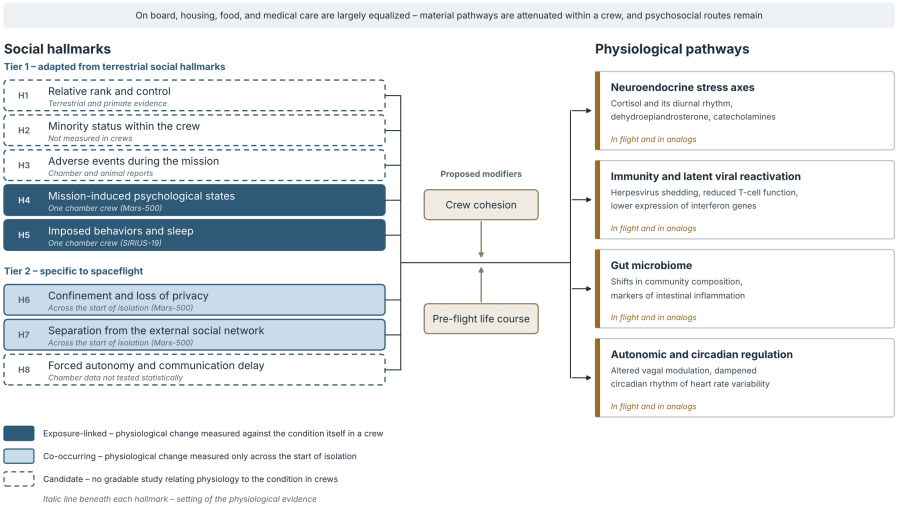


FIGURE 1: Social hallmarks of human spaceflight and the pathways through which they may act

The first tier (H1 to H5) includes five conditions adapted from the terrestrial social hallmarks, and the second tier (H6 to H8) includes three conditions specific to spaceflight. The box style indicates the evidence grade of each hallmark, namely exposure-linked (filled), co-occurring (shaded), or candidate (dashed border). Crew cohesion and the pre-flight life course are proposed as modifiers of all eight conditions. The italic line beneath each hallmark indicates the setting of its physiological evidence. All four physiological pathways on the right have been measured both in flight and in analogs, although rarely against a defined social exposure.

Image credit: Piercarlo Minoretti (created with Claude Code).

Neuroendocrine Stress Axes

Activation of both the hypothalamic-pituitary-adrenal axis and the sympathetic-adrenal-medullary axis has been documented in flight, as indicated by increased levels of cortisol, dehydroepiandrosterone, epinephrine, and norepinephrine [83]. Among 23 astronauts on ISS missions of up to 180 days, the diurnal trajectory of salivary cortisol changed significantly during flight compared with before flight ($p = 0.010$) [84]. By contrast, plasma cortisol and dehydroepiandrosterone measured in the same astronauts did not differ significantly across the phases before, during, and after flight, although cortisol levels were lower at the mid-flight and late-flight time points. Because uncontrollability and social-evaluative threat amplify the cortisol response [12], hallmarks that combine the two, such as a subordinate position in the command structure or a token position within the crew, may place the greatest demand on this axis.

Immune Function and Latent Viral Reactivation

Reactivation of latent herpesviruses is the most consistently documented immune consequence of flight, with one or more herpesviruses shed in saliva or urine by 53% of shuttle astronauts and 61% of ISS astronauts [83]. Viral shedding did not abate as missions lengthened, and varicella-zoster virus and cytomegalovirus continued to be shed for up to 30 days after return from the ISS. Compared with short shuttle missions, ISS missions were associated with greater frequency, duration, and amplitude of Epstein-Barr virus, varicella-zoster virus, and cytomegalovirus reactivation [84]. The release of stress hormones, in combination with reduced cell-mediated immunity, has been proposed as the mechanism underlying viral reactivation in astronauts [83]. Consistent with that mechanism, reduced T-cell function, cytokine imbalance, and increased stress hormones preceded the first laboratory-confirmed case of zoster on board the ISS [85].

Immune dysregulation is not confined to flight, as a systematic review of 140 studies found it consistently across isolated, confined, and extreme environments, with the most pronounced changes in space missions and Antarctic stations [86]. In that review, space simulation units such as Mars-500 produced changes similar to those of actual missions, whereas gravity simulation studies such as bed rest produced fewer immune alterations. These observations suggest that features of the mission environment other than altered gravity may account for part of the immune phenotype of flight.

Over one year at Concordia station, 14 crew members exhibited a two-step pattern of immune adaptation, in which moderately sensitized responses gave way after three to four months to markedly raised cytokine responses to *ex vivo* stimulation [87]. Blood RNA sequencing in eight men studied before, during, and after a 12-month stay at the same station predicted inactivation of interferon signaling, owing to downregulation of

14 genes involved in antiviral immunity [88]. Among these genes, *IFIT3* remained downregulated after return, as did pathways of chemotaxis and leukocyte recruitment. This antiviral profile resembles one arm of the conserved transcriptional response to adversity, which social isolation, social threat, and low or unstable social status evoke in human leukocytes [11]. Leukocytes of chronically lonely adults, for example, showed reduced expression of type I interferon genes together with underexpression of genes bearing glucocorticoid response elements, and this shift was not attributable to differences in circulating cortisol [89]. In female rhesus macaques, experimentally manipulated dominance rank altered chromatin accessibility in immune cells, and its effects on gene expression were less pronounced after *in vitro* glucocorticoid treatment, a pattern interpreted as glucocorticoid resistance driven by social stress [90]. These data suggest that the immune effect of social conditions may depend on leukocyte sensitivity to glucocorticoids as well as on hormone concentrations, so that cortisol measurements alone might not capture it.

Gut Microbiome

Changes in the gut microbiome have been documented both in flight and during prolonged confinement. In the NASA Twins Study, the gut microbiota of the flight subject changed during a one-year ISS mission and returned to near preflight levels within six months [91]. Plasma metabolomics in 52 ISS astronauts, likewise, indicated increased gut microbial protein fermentation during flight [92]. A reanalysis of fecal samples from the six Mars-500 crew members identified 32 sequence variants whose abundance changed over 520 days of isolation, including depletion of species associated with resistant starch degradation, anti-inflammatory activity, and insulin sensitivity [93]. These changes accompanied losses of strength and lean body mass and increases in fasting plasma glucose, calprotectin, and neutrophil levels characteristic of intestinal inflammation. In addition, the same analysis identified 49 bacterial species shared between crew members and their habitat. In Antarctic isolated, confined, and extreme settings, the type of accommodation emerged as a predictor of microbial alterations in a meta-regression of seven studies [94]. Social contact can itself move microbes between individuals, and in wild baboons, rates of social interaction predicted gut microbiome composition after diet, kinship, and shared environment were controlled for [95]. Close and prolonged contact within a crew might therefore act on the microbiome both through the stress response and through the exchange of microbes among crew members and their surroundings.

Autonomic and Circadian Regulation

Cardiac autonomic regulation changes both in flight and in prolonged isolation. Among 10 astronauts recorded before, during, and after long-duration ISS missions, total heart rate variability increased in flight, and its component with a period of about 90 minutes became about three times larger than on Earth [96]. Monthly recordings of heart rate variability in 25 crew members over winter at the Neumayer III station showed a gradual reduction in vagal modulation [97]. The sympathovagal balance shifted progressively toward sympathetic predominance, which reached statistical significance in the final trimester of the expedition and was more pronounced in women. At the Belgrano II station, parasympathetic regulation decreased during wakefulness and increased during sleep as isolation lengthened, whereas parasympathetic activity during sleep fell during the polar night [98]. Similarly, in the Mars-500 crew, circadian rhythms of heart rate variability were dampened during confinement, with a reduced amplitude of the rest-activity pattern of parasympathetic function [99]. The investigators related this reduction to lower daylight exposure and changes in mood. Sleep loss imposed by operations may also act through this pathway because a night of complete sleep deprivation, but not moderate sleep fragmentation, markedly affected nocturnal autonomic regulation in an isolated crew [52].

Strength of the Pathway Evidence

Direct measurements in flight are now available for all four pathways [83,91,96], although most data on the gut microbiome and autonomic regulation still derive from chamber and polar analogs [93,97,99]. Physiological data linked to a defined social exposure within the crew remain scarce, and they consist mainly of correlations between mood and plasma monoamines in a single Mars-500 crew [47] and autonomic and endocrine correlates of sleep loss [51,52]. In most other studies, physiological changes were measured against mission phase rather than against a defined social exposure [84,87]. To our knowledge, the conserved transcriptional response to adversity has not been measured in astronauts or in analog crews, although interferon-related gene expression has been profiled during a polar winter-over [88]. Ground analogs offer lower cost and easier access than flight platforms [82], and they might therefore provide the setting in which the effects of individual hallmarks can first be separated from that of the shared environment.

Implications for study design

Animal models of spaceflight have rarely treated social conditions as an experimental variable, although most hindlimb unloading studies, the standard ground model of musculoskeletal disuse and cephalad fluid shift, are performed in singly housed animals. In a 30-day unloading study of female mice, musculoskeletal deficits were similar in singly and socially housed animals, whereas the reduction in the percentage of CD4+ T cells occurred only in singly housed mice [100]. A three-day unloading study, similarly, attributed the markers of stress observed in the hippocampus and amygdala to social isolation rather than to unloading

[101]. When simulated galactic cosmic radiation was combined with different housing conditions in mice, radiation drove early changes in circulating immune cells, whereas housing drove later changes [102]. These findings suggest that the housing of animals may act as an uncontrolled social exposure, which could either amplify or mask the effects attributed to altered gravity and radiation.

Human analogs add a level of organization that animal models do not reproduce because crew members share their exposures and may differ systematically from one crew to another. Among 20 adults studied weekly during five four-person HERA missions of 45 days, DNA integrity, radiation-induced DNA damage, and DNA repair differed between missions beyond what interindividual variability could explain [103]. Analyses that treat crew members as independent observations might therefore misattribute crew effects to individual responses. Variation between crews is also growing, as commercial missions have widened crew composition, and the Space Omics and Medical Atlas now holds clinical and multi-omic profiles from the Inspiration4, Axiom, and Polaris crews [104]. Some molecular responses were consistent across these missions, whereas others were specific to individual missions. Because commercial crews differ in composition, rank structure, and flight experience [20], repositories of this kind may allow the social characteristics of a crew to be examined as covariates of mission-specific responses.

Testing the Framework

The framework yields a central question for each hallmark, namely whether a defined social exposure predicts a physiological outcome within a crew beyond the effect of mission phase shared by all its members. Each hallmark can be assigned a measurable exposure, and some of these exposures are already recorded in analogs, such as close-range interactions captured by wearable proximity sensors [38] and one-way communication delays set by the mission protocol [70]. Examples of exposures, outcomes, and designs for each hallmark are listed in Table *2*.

Hallmark	Exposure measure	Physiological outcome	Design
Relative rank and control	Command position and delegated decision authority	Diurnal cortisol rhythm and leukocyte gene expression	Within-crew comparison across positions
Minority status within the crew	Token or balanced composition by nationality, language, or gender	Cortisol response to social-evaluative events	Comparison of crews of different compositions
Adverse events during the mission	Logged interpersonal conflicts and critical incidents	Catecholamines and cortisol before and after each event	Event-related sampling within crews
Mission-induced psychological states	Repeated validated scales of mood and stress	Hair cortisol, plasma monoamines, and immune cell subsets	Within-person longitudinal models
Imposed behaviors and sleep	Work and sleep scheduled at an adverse circadian phase	Actigraphy and nocturnal heart rate variability	Crossover of schedules between campaigns
Confinement and loss of privacy	Habitable volume per person, access to private space, and proximity data	Salivary cortisol, immune responses, and gut microbiota	Campaigns differing only in habitat layout
Separation from the external social network	Frequency and duration of private contact with family	Antiviral gene expression and latent herpesvirus shedding	Campaigns with different contact schedules
Forced autonomy and communication delay	One-way latency and decision authority delegated to the crew	Heart rate variability and catecholamines	Campaigns with and without delay

TABLE 2: Examples of measurable exposures, physiological outcomes, and designs for testing each social hallmark

Outcomes can be chosen among measures already obtained in flight, such as salivary cortisol, latent herpesvirus shedding, the gut microbiota, and heart rate variability [84,91,96]. Self-report alone is unlikely to suffice because physiological stress markers and self-reported state have repeatedly diverged in analog crews. In the four-month SIRIUS-19 confinement, hair cortisol nearly doubled early in the mission (from 31.8 to 62.3 pg/mg), whereas psychometric measures of affect remained positive and stable [105]. Similarly, at the Neumayer III and Concordia stations, endocannabinoids and catecholamines changed over 11 months of deployment without significant changes in psychometric stress scores [106]. Physiological and self-reported measures should therefore be collected together, so that a change in one without the other can be interpreted rather than missed.

Several designs could separate individual hallmarks from the shared environment. Within-crew

comparisons, which contrast members who differ in exposure while living in the same habitat, would control for mission phase. Repeated analog campaigns in which a single parameter is varied between otherwise similar missions would allow the exposure to be manipulated, as has been done for lighting in HERA [55]. Multilevel models with crew members nested within crews would separate individual from crew-level effects, which differed beyond interindividual variability in the HERA study of DNA integrity [103]. In animal studies, housing could be specified and reported as an experimental factor rather than left as a background condition [100,102].

Crew-level countermeasures

Most countermeasures proposed for spaceflight, such as nutritional supplementation, exercise, and pharmacological agents, operate on the individual crew member [107], whereas the conditions considered here are properties of the crew and the habitat. Operational evidence indicates that changes at this level can modify physiology because immunity, stress, and latent herpesvirus reactivation all improved across 12 years of ISS construction and operations [16]. The improvement began around 2012 and coincided with a higher frequency of cargo delivery and resupply, more personal communication, better exercise equipment and protocols, greater food quality and variety, nutritional supplementation, and schedule management. Since these changes were introduced together, their separate contributions cannot be estimated, although the investigators attributed the physiological improvement to operational measures and biomedical countermeasures on board.

Crew composition is the earliest point at which the social environment can be shaped, as it is fixed before launch. A review of team-behavior studies indicated that cohesion arises more readily when crew members resemble one another [74]. In that analysis, deep-level variables such as personality and personal values affected compatibility more than surface variables such as age, nationality, or gender. The same review identified pre-mission conflict resolution training as a further determinant of group cohesion.

The habitat offers a second level of intervention, and the introduction of plants acts on confinement and on the absence of natural stimuli at the same time [108]. Among 27 long-duration ISS astronauts who took part in crop growth experiments, the tasks were rated as enjoyable, engaging, meaningful, and stimulating, with the strongest effects reported for consuming the crops and voluntary viewing of the plants [109]. More broadly, a systematic review of 124 studies reported that greenery in confined settings such as hospitals, eldercare facilities, and space habitats reduced stress and improved mood [108].

Virtual reality has been evaluated as a substitute for natural stimuli where plants cannot be accommodated. Across the Canadian Forces Station Alert and two HI-SEAS expeditions of 8 and 12 months, 43 participants broadly considered natural scene virtual reality restorative, although its perceived usefulness varied considerably between individuals [110]. After long periods of isolation, dynamic and familiar scenes, including scenes containing people, were also appealing, which suggests that the intervention may act on separation from the external network as well as on confinement. Preferences vary, however, and among 25 overwintering crew members at the Amundsen-Scott South Pole Station, longer nature scenes were preferred overall, with interindividual variation that led the investigators to recommend an individualized approach [111].

Food is managed by mission operations and therefore acts as a countermeasure at the level of the crew [16]. Over four 45-day HERA missions, 16 subjects received either the standard spaceflight diet or a diet with greater quantity and variety of fruits, vegetables, fish, and other foods rich in flavonoids and omega-3 fatty acids [112]. Subjects on the experimental diet had lower cortisol and lower cholesterol levels compared with subjects on the standard one. They also showed better cognitive speed, accuracy, and attention, as well as a more stable microbiome and metatranscriptome.

Communication protocols address the delay that imposes autonomy on the crew, and they have been tested in the laboratory as well as in analogs. Among 24 three-person teams collaborating by voice or text on simulated failures of a life support system, media-specific protocols reduced threats to common ground and information splitting, although instances of miscommunication did not decrease [75]. In the analog simulations of the same work, compliance with the protocols was high, and they maintained perceived communication effectiveness between the crews and mission control under time delay at a level comparable with that observed without delay.

Countermeasures acting on the crew or the habitat therefore exist for confinement, imposed behaviors, separation from the external network, and communication delay. The evidence for these countermeasures differs in strength, as only the diet study and the operational package on the ISS reported physiological endpoints [16,112], whereas the evidence for plants, virtual reality, and communication protocols rests mainly on ratings, self-report, or performance [75,109,110]. For relative rank and minority status, the available measures are confined to crew composition and pre-mission conflict-resolution training, which have been discussed as determinants of cohesion [74] but, to our knowledge, not evaluated against a physiological outcome. The framework proposed here might indicate which components of the operational package to test separately against stress and immune endpoints.

Limitations

Limitations of the Evidence

The physiological evidence for most of the eight conditions comes from ground analogs rather than flight, and analog studies have enrolled small, predominantly male samples. The Mars-500 and Mars-105 chamber studies included six men each [40,51], and the HERA study of DNA damage enrolled 20 participants across five missions [103]. Three confinement studies, on catecholamines and group dynamics, on mood and immune status, and on habitat volume, could be assessed only from their abstracts [42,48,62], and they were described but not used for grading. The hormonal data of the Mars-105 study were analyzed in five of the six crew members, and the investigators described their results as preliminary [43]. In Mars-500, the correlations between mood and plasma monoamines were computed across repeated measurements in six men, so that they may partly reflect changes shared by the whole crew over the mission [47]. In analog environments, the social conditions are not separable from the physical ones. Concordia station lies at an altitude of 3,232 m, so that hypoxia accompanies isolation and confinement there [87], and the polar night adds prolonged darkness to overwintering [98]. The vascular changes recorded during Mars-500 were attributed by the investigators either to the stress of the confined environment or to the absence of sunlight [61], which is a physical rather than a social factor. The systematic review of immune parameters in isolated, confined, and extreme environments, in turn, attributed the observed dysregulation to low antigen diversity and extreme conditions [86].

Some observations run against the mechanisms proposed here. In the Mars-500 crew, 520 days in a shared confined habitat did not affect the resilience of the individual gut microbiota [113]. A reanalysis of the same mission, by contrast, found bacterial species shared between crew members and their habitat [93]. The divergence between physiological markers and self-report was interpreted by the original investigators as an adaptation phase [105] or as an effect of the extreme environment, including hypoxia at Concordia [106], rather than as unreported strain. In the HERA diet study, no immune effects were detected, although no illness or infection occurred during those missions, so the benefits of the diet may not have become apparent [112]. The terrestrial evidence that motivates the first tier also carries its own qualifications. In the meta-analysis of 13 European cohorts, the population attributable risk for job strain was 3.4%, considerably smaller than that of standard risk factors such as smoking [27]. Associations of this kind derive from populations with a wide range of material circumstances, whereas crews are selected, trained, and supported by the same operational services [15,16]. Rodent housing conditions, likewise, represent isolation or group living rather than the graded social positions that arise on board [100]. Analog participants are volunteers who operate without the formal command hierarchy of an actual mission, so that findings on rank and control may not transfer to flight. Most studies reported statistical significance in small samples without estimates of clinical relevance, and the grades proposed here therefore indicate the presence of evidence rather than the size of an effect.

Limitations of the Framework

The framework rests on choices that other investigators might make differently. Mission-induced psychological states and sleep may act as both exposures and mediators, and their retention as hallmarks follows the terrestrial template [13] rather than a demonstrated causal order. The sleep deprivation that supports the grade of imposed behaviors was scheduled by the analog protocol, which in a chamber mission stands in for mission operations. The three hallmarks of the second tier are defined by parameters that mission design can vary separately, although in most missions, confinement, separation, and communication delay change together, and their effects have not been separated in practice so far. The grades depend on thresholds defined here, such as the requirement of a statistically significant change, and they describe the current state of the evidence rather than a fixed property of each condition. Crew cohesion has been related to team performance in analogs [21], but, to our knowledge, it has not been tested as a moderator of a physiological response, and no study has measured a physiological outcome against minority position within a crew.

Conclusions

The social environment of a crew comprises several distinct conditions rather than one hazard, and treating them separately makes their physiological consequences open to study. We have organized eight such conditions in two tiers, the first adapted from the social hallmarks described in aging research and the second arising from the separation of a crew from Earth. Because housing, food, and medical care are largely equalized on board, the material pathways that carry socioeconomic position on Earth are attenuated within a crew, and psychosocial routes may become the main channels through which the social environment acts. When graded against the requirement that physiological change be related to the condition itself, only mission-induced psychological states and imposed behaviors met that standard, and each did so in a single analog crew of six participants. Confinement and separation from the external network showed physiological change only at the start of isolation, and the remaining four conditions are candidates. The gap is therefore wide because physiological outcomes have rarely been measured against a defined social exposure within a crew, and most studies compare mission phases instead. Ground analogs, where exposures can be manipulated and crews studied as units rather than as collections of individuals, offer the setting in

which that comparison can first be made. Work of this kind would indicate which components of the operational package now used on the ISS deserve separate testing. It would also place the social environment of exploration crews on the same evidentiary footing as radiation and altered gravity.

Appendices

Appendix 1

PubMed Search String

(spaceflight[tiab] OR "space flight"[tiab] OR "Space Flight"[mh] OR astronaut*[tiab] OR Astronauts[mh] OR "International Space Station"[tiab] OR "isolated and confined"[tiab] OR "isolated, confined"[tiab] OR "Mars-500"[tiab] OR Mars500[tiab] OR "Mars-105"[tiab] OR "HI-SEAS"[tiab] OR "Human Exploration Research Analog"[tiab] OR "SIRIUS-19"[tiab] OR "SIRIUS-21"[tiab] OR "Concordia station"[tiab] OR Neumayer[tiab] OR "space analog"[tiab] OR "space analogue"[tiab] OR "Antarctic station"[tiab]) AND (crew*[tiab] OR astronaut*[tiab] OR participant*[tiab] OR expeditioner*[tiab] OR volunteer*[tiab] OR Humans[mh]) AND ("social"[tiab] OR interpersonal[tiab] OR cohesion[tiab] OR leadership[tiab] OR commander[tiab] OR hierarchy[tiab] OR "social status"[tiab] OR minority[tiab] OR multicultural[tiab] OR "cultural"[tiab] OR conflict[tiab] OR conflicts[tiab] OR privacy[tiab] OR crowding[tiab] OR confinement[tiab] OR "communication delay"[tiab] OR "time delay"[tiab] OR autonomy[tiab] OR loneliness[tiab] OR "crew composition"[tiab]) AND (cortisol[tiab] OR catecholamine*[tiab] OR immune[tiab] OR cytokine*[tiab] OR herpesvirus*[tiab] OR "viral reactivation"[tiab] OR "gene expression"[tiab] OR microbiome[tiab] OR microbiota[tiab] OR "heart rate variability"[tiab] OR autonomic[tiab] OR sleep[tiab] OR "oxidative stress"[tiab] OR hormone*[tiab] OR physiological[tiab]).

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

Concept and design: Piercarlo Minoretti

Acquisition, analysis, or interpretation of data: Piercarlo Minoretti

Drafting of the manuscript: Piercarlo Minoretti

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Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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