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Human physiology adaptation to altered gravity environments

Nandu Goswami [a,b,*], Olivier White [c], Andrew Blaber [d], Joyce Evans [e], Jack J.W.A. van Loon [f], Gilles Clement [g]

[a] Gravitational Physiology and Medicine Research Unit, Otto Loewi Research Center of Vascular Biology, Immunity and Inflammation, Medical University of Graz, Austria
[b] College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates
[c] Université de Bourgogne INSERM-U1093 Cognition, Action, and Sensorimotor Plasticity, Campus Universitaire, Dijon, France
[d] Aerospace Laboratory, Department of Kinesiology, Simon Fraser University, BC, Canada
[e] University of Kentucky, Lexington, KY, USA
[f] Department of Oral and Maxillofacial Surgery/Oral Pathology, Amsterdam University Medical Center Location VUmc, Academic Center for Dentistry Amsterdam (ACTA), Vrije Universiteit Amsterdam, Amsterdam, Netherlands & Life and Physical Science and Life Support Lab, European Space Agency (ESA), Noordwijk, the Netherlands
[g] Neuroscience Laboratory, NASA Johnson Space Center, Houston, TX, USA

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ABSTRACT

Multiple transitions between gravity levels will occur during planetary exploration missions. In reaction to these gravitational transitions, physiological adaptation will be initiated. However, the physiological effects of long-duration exposures to hypogravity and hypergravity are poorly understood. In this review we present an overview of how humans perceive gravity, review sex-based differences in adaptation to changes in gravity, and introduces rather limited evidence currently available related to the effects of partial gravity. The paper then argues that there is a need for more research to better understand the extent and dynamics of physiological adaptation mechanisms during gravity level transitions in spaceflight and proposes a need for artificial gravity (AG) as a multi-system countermeasure and explore the efficacy of AG as countermeasure between short and very long-arm centrifuges. Discussed here are the effects of acute short-arm AG application. The topical review also discusses the usage of chronic AG application via the innovative large-radius *Hypergravity Human Habitat, H^3*, concept.

1. Introduction

As space agencies begin sending humans to again explore the Moon and prepare for a future Mars voyage, astronauts are likely to spend much longer periods in the microgravity environment of transit vehicles and the hypogravity environments of their destinations as during current space missions. Understanding the impacts of prolonged exposures to these altered gravity environments, and examining the effects in different physiological systems in an integrative manner, will become important for maintenance of crew health and mission success [1,2].

By definition, the term "gravity" is specific to the acceleration we have on Earth (~9.81 ms^{-2}), and is expressed in the international system of units (SI) as *g*. "Hypergravity" includes the gravity levels above 1 g. A gravity level lower than 1 g is called "hypogravity" or "partial gravity" or "reduced gravity". The centripetal acceleration generated by a human-rated centrifuge is also expressed in g. This centripetal acceleration can be lower than 1 g. However, when on Earth the resultant of the centripetal acceleration and the gravitational acceleration is always larger than 1 g, i.e. hypergravity. On the Moon or Mars surfaces, where the gravity levels are 0.16 g and 0.38 g, respectively, the resultant of the centripetal acceleration in a centrifuge and the gravitational acceleration can be lower than 1 g. Therefore, hypogravity levels ranging from 0.16 g to 1 g (including Mars gravity) can be generated using a centrifuge on the Moon.

Other terms have been misused over the years. One of them is "microgravity" instead of "free fall" or even better "near weightlessness" while '0 g' does not exist [66]. Another one is "artificial gravity", which technically refers to non-gravitational or non-linear acceleration.

* Corresponding author. Head of research unit "Gravitational Physiology and Medicine" Acting Chair of Physiology, Otto Loewi Research Center, Medical University of Graz, Neue Stiftingtalstraße 6/D.05, A-8010, Graz, Austria.
E-mail address: nandu.goswami@medunigraz.at (N. Goswami).

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However, many authors use the term "artificial gravity" for acceleration levels that are different from 1 g and nearly always use a centrifuge to generate this acceleration. A better term in such conditions would be "centripetal acceleration", which would also include the 1-g value [3].

1.1. The spaceflight environment

Future exploration missions to Moon and Mars will be some of the most difficult and dangerous expeditions in the human history. Space travel will push the limits of human performance further and critically rely on the integrity of physical and mental abilities. Errors and accidents may have debilitating or fatal consequences, leading to loss of crew or equipment, and compromising mission success. In addition to the detrimental physiological effects of microgravity, the space environment can expose the crew to multiple stressors that have the potential to degrade human health and performance. These conditions include - but are not limited to - radiation, noise, hypercapnia, hypoxia, decompression, dietary restrictions, fluid shifts, side effects of certain medications, acute and chronic sleep loss and circadian misalignment related to non-24 h light-dark cycles, acute operational shifts in sleep timing. Additionally, psychological factors related to isolation, confinement, and operational and interpersonal distress could influence team performance and success of spaceflight missions [4]. There is considerable evidence now that any of these conditions can negatively affect physiological functions and present a risk for future human exploration missions [5,6].

Operational performance in microgravity may be impaired by space motion sickness, spatial disorientation, altered sensorimotor control, changes in the musculoskeletal system or decreased cardiorespiratory fitness. In addition, acute effects on spatial cognition and blood pressure regulation mechanisms can be triggered by transitions between gravity levels and persist for some time after as the physiological systems adapt to the new gravito-inertial environment. These changes may impair motor actions, as well as behavior health and performance. While many space studies have demonstrated that humans and animals eventually adapt their sensorimotor function to microgravity and hypergravity, the dynamics of re-adaptation when transitioning back to the 1-g environment or to a new level of gravity (e.g. Moon or Mars) is not fully understood [7]. This lack of knowledge may be partially explained by a methodological barrier; due to operational constraints, it is difficult to collect data on humans immediately upon entry into a new gravitational environment and immediately upon re-entry into Earth gravity. Consequently, current methods of preflight training and post-flight rehabilitation have not been optimized to minimize the functional impacts of these natural adaptive responses during g-transitions or to restore environment-appropriate sensorimotor functions after g-transitions.

Building a percept of the vertical axis, or defining which way is "up" or "down", is critical to cope with a gravitational environment and perform most physical actions. While some sensory organs specifically detect linear and gravitational accelerations acting on our bodies, including the otoliths in the inner ear, there are no dedicated gravity receptors [8]. Multiple sensory cues are used for this purpose [9,10]. Because gravity is sensed through a complex integration of sensory inputs and due to its influence on motor and other physiological systems, understanding how the nervous system adapts to changes in gravity is challenging. However, one major limitation of space research is that the results of studies on the effects of microgravity on physiological functions are often confounded by factors that differ across experiments, such as task-dependency, sample size, and context. Nevertheless, collectively, these studies suggest the existence of a multimodal representation of gravity, in which vestibular, visual, and somatosensory cues play an important role.

Changes in the gravitational environment also have effects on muscle activity and cardiovascular function. Alteration in brain vascular regulations or peripheral hormones could participate in these effects. An integrative approach needs to be employed to address these questions. Studying cardio-postural interaction is one integrative approach that has pointed to vestibular and sensorimotor influences on orthostatic reflex responses to altered gravity [1,11–13]. This research uncovered baroreflex-mediated skeletal muscle activations in the lower legs, which provide muscle-pump responses to decreased blood pressure upon standing. Data from 60-day head-down bed rest studies, which simulate the long-term effects of microgravity on the cardiovascular system, showed a significant reduction in muscle-pump activation, strength, and causal relationship immediately following bed rest, and which persisted up to eight days post-bed rest [14].

1.2. How do we perceive gravity?

Future crewed missions to Moon and Mars will expose astronauts to varying levels of hypogravity. Currently, the physiological effects of exposures to hypogravity levels (i.e. between μ and 1) are poorly understood. During weightlessness, gravity no longer acts as a fundamental reference, and the discrepancy between vestibular, visual, and sensorimotor signals can affect spatial abilities. Similarly, gravity levels higher than Earth's gravity may also affect neurovestibular-controlled performance even if, intuitively, hypergravity could strengthen the gravitational reference. The first three weeks in space and the first two weeks back on Earth present critical adaptation periods that are characterized by impairments in perceptual-motor skills and higher attentional processes [6].

Mirroring the complex effects of changes in gravity levels on behavior, experimental evidence about the neural processing of gravity-related signals for perception and control points to a broad and distributed network including cerebellum, sensorimotor, vestibular, and insular cortices. If one of these nodes is affected by exposure to altered gravity, it is not surprising to observe macroscopic effects on behavior including posture, gaze, functional mobility, and misperceptions of visual orientation, depth, and distance. Emerging evidence highlighted cortical projections of the vestibular system. They include several brain regions involved in spatial navigation, such as the hippocampal and parahippocampal formation, cingulate gyrus and retrosplenial cortex, parietal and medial temporal cortices, and the parietoinsular vestibular cortex and temporoparietal junction. The insula seems to play a key role in the way gravity is processed by the brain. Recent studies suggest that different parts of the insula may process gravity-relevant feedback in simulated or produced actions that involve the body, while external simulation of the environment may exploit other pathways [15].

The absence of dedicated gravity sensory organs and neural structures suggests a distributed processing of gravity cues for perception and action. Ground-based studies have shown that humans use an internal model to dissociate gravitational acceleration (gravity) from inertial acceleration sensed by the otolith organs [16]. Other investigations have addressed the question of an internal representation of gravity through visual information [17,18]. However, its neural basis in the absence of vision remains elusive. Behavioral evidence also points toward the existence of a representation of gravity in somatosensory feedback, likely through an internal model of external forces acting on the limb [19,20]. In addition to visual, vestibular, and internal (prior) information, somatosensory feedback, because of its influence on planning and control, may contribute to perception and the scaling of motor commands. The precise nature and properties of this internal representation during acute transitions between gravity levels is also not fully understood yet. Experiments performed under short-term altered gravity in parabolic flight indicate a rapid but incomplete adaptation. Early access to astronauts (immediately upon entry or after landing) is critical to characterize the dynamics of this adaptation. The next steps to deepen our understanding of the neural basis of adaptation to changes in gravity levels will include techniques to measure brain activity during these periods.

1.3. Sex based differences

At present, the sparseness of gravitational studies in women rules out gender conclusions unless those subjects were oriented to standing, sitting, or lying in Earth gravity. For example, there are no data to answer the serious question of how deconditioned (simulation or spaceflight) women will handle the return from space to a gravity environment [21]. There are many such studies in men but only one, recently conducted, in women [22]. How the hemodynamic and skilled motor systems interact in men and women have only been addressed recently, pointing toward decreased fine motor performances in women only [23].

Responses of men to actual space flight, such as the well documented fluid shift to the upper body, decreased post-flight orthostatic tolerance, decreased central venous pressure, decreased ventricular mass [24], decreased plasma volume [25], decreased aerobic capacity, decreased vagal baroreflex sensitivity, increased sympathetic responsiveness [26] and neuro-ophthalmological changes [27] are supported by a large body of research. It is assumed, but to a large extent unproven, that women's responses to spaceflight are similar to men's although the magnitude of women's responses compared to men's is not so well known. Some sex-based differences in response to actual spaceflight (post-flight versus preflight comparisons) are, however, fairly well accepted: men's post-flight orthostatic tolerance is not as degraded as women's [28,29] and the development of post-flight spaceflight-associated neuro-ocular syndrome is more common in men than women [30].

Sex-based differences in response to simulations of partial gravity environments come mostly from head-down bed rest and water immersion studies [4,31,32]. For example, the loss of ventricular mass during 60 days of bed rest has been found to be similar in men and women and the Earth-bound tendency of men toward sympathetic dominance and women's tendency toward parasympathetic dominance over heart rate control remained the same after 60 days of bed rest [21]. Men and women use different blood pressure regulation strategies to respond to standing in Earth gravity after being exposed to hypergravity: men start from a lower blood pressure finally reaching their presyncopal endpoint, while women maintain the same blood pressure up to presyncope. In addition, women respond to hypergravity with increased cerebral blood flow while men maintain the same cerebral blood flow in hypergravity than in normal gravity [12,33]. In addition to orthostatic intolerance that is larger in women than men, women show a greater loss of plasma volume, as well as greater loss of sensitivity of baroreflex control of heart rate and vasoconstriction.

It must be remembered, however, that all analogues on Earth only can 'simulate' hypogravity with significant restrictions (shortness in time during parabolic flight, immobilisation in bed rest, different gravitations in short-arm human centrifuge (SAHC)).

1.4. Partial gravity

There is extensive evidence on human physiological adaptation to long-duration exposure to microgravity from studies performed on astronauts and cosmonauts on board Salyut, Skylab, Mir, Space Shuttle, and the International Space Station (ISS), as well as ground-based analogues [7,34,35]. Human physiological adaptation to hypergravity in Earth-based centrifuges has been documented as well, but most studies have used very short-duration exposures [11,12,21,36–39].

Studies on the effects of partial gravity, i.e., between μg and 1 g, on human physiology are very limited [40]. Only fourteen astronauts – from the Apollo missions – have been exposed to lunar gravity (0.16 g), with exposures ranging from 21 to 74 h [1]. These astronauts worked successfully on the lunar surface, but the duration of exposure was too short to evaluate the effects of 0.16 g on their physiological responses to those work environments. Immediately after returning to Earth, these men showed signs of orthostatic intolerance and balance problems that were similar to those seen in their fellow astronauts who stayed in lunar orbit. This on one hand, suggests that lunar gravity does not prevent the anti-gravity muscle atrophy and cardiovascular and vestibular deconditioning that occur during exposure to microgravity. On the other hand, it is plausible that those astronauts who had stayed on the Moon for some days might have trained their cardiovascular system. However, due to the transit time from Moon to the Earth they lost these adaptations, which could have potentially taken place.

Recent studies in parabolic flight where humans are exposed to repeated partial gravity episodes for durations ranging from 30 to 50 s each have shown that acute vascular changes at 0.25 g are similar to those observed in astronauts during spaceflight [27]. These studies also demonstrated that the threshold for the perception of verticality by humans is between 0.16 g and 0.38 g [41,42]. Interestingly, this threshold is much higher than the threshold for the perception of linear acceleration by the vestibular organs, which ranges from 0.005 to 0.02 g depending on the axis of motion [43]. Neurovestibular studies using a human centrifuge on board the Space Shuttle confirmed that the threshold for the perception of verticality by the crew in orbit is higher than 0.22 g [44]. Other studies concluded that postural readjustments, object handling and mechanical tasks such as bolt tightening did not pose significant problems at gravity levels higher than 0.2 g [45,46].

Perhaps as a consequence of this threshold, the Apollo astronauts experienced some balance disorders when they walked in 0.16 g on the lunar surface. A review of the Apollo video footages revealed that 23 falls occurred during the 14 extra-vehicular activities (EVAs). In addition, 11 near falls occurred where astronauts lost their balance but were able to recover prior to hitting the ground [47]. Most falls happened when astronauts got their body's center of gravity too far forward or too far sideways, usually by leaning over when slipping on slopes or stepping on rocks. The astronauts' life support system was contained in a heavy backpack that caused their body's center of mass to be higher than normal, which could have been a contributing factor. Also, although the astronauts perceived their overall weight to be less in 0.16 g than during their training in 1 g, their mass and subsequent momentum were independent of the gravity level, which was not anticipated [48]. Interestingly, most falls happened early on the first EVA, most likely due to the difference in mobility in 0.16 g compared to 1-g training, and toward the end of EVAs as the crew got tired. Adaptation to spatial orientation in partial gravity and learning new locomotion behaviors took place rapidly. One lesson learned, however, was that a fall from a standing position or while "kangaroo-hoping" on the Moon was not as traumatic as on Earth. Many near falls led to remarkably graceful recoveries to a stable position, largely because the event happened so slowly the astronauts had a chance to react, plan, and trigger recovery motor strategies on the way down [49].

1.5. Artificial gravity

Minimizing the deleterious physiological effects of prolonged microgravity exposure during the outgoing transit phase of a deep space exploration mission, or partial gravity on the Moon and Mars surfaces, will be key to ensuring that a healthy productive crew is available to carry out the surface exploration objectives as well as to endure the return transit phase [1,2]. Taking along gravity in the form of sustained inertial acceleration generated by centrifugation has long been proposed as an integrated countermeasure [50]. In particular, artificial gravity may prevent fluid shifts and decreased blood volume associated with microgravity. But it is also ethically required to provide functional gravity as part of a spacecraft life support system to keep crew healthy and safe [51].

It is important to emphasize that an integral part in the maintenance of the mental, social and physiological health of the astronauts is space station design. Indeed, every space agency should go beyond arguments of flight costs, complexity and logistical challenges to address the most important question in this regard: What is the price of safety and health? It is highly unethical and mission threatening to withhold gravity from astronauts. No stones should be left unturned by space agencies when it comes to meeting the necessary gravity requirements for the health and safety of astronauts. A recommendation of this review is that it is an ethical requirement to provide functional gravity as part of a spacecraft life support system to ensure crew healthy and safe [51].

Many engineering approaches have been proposed to generate this artificial gravity, including very large structures spinning about their central axis, spinning modules joined by a tether, and on-board short-radius human centrifuges ("a spin in the gym"). Each approach has its technical problems, including limitations in structural mass, tether performance, and reliability; abort capabilities for interplanetary spacecraft because of a limited number of spin/de-spin cycles; mishaps that might require EVA repair; interference with astronomical observations; and motion sickness. Although solutions have been identified for most of these issues [52–54], artificial gravity, even not short radii centrifuges, have yet been implemented in space missions. Nevertheless, treadmill exercise using bungees to pull down the body, resistive exercise instruments and lower body negative pressure have been used to artificially load the musculoskeletal and cardiovascular systems in microgravity [55,56]. These stimulations are applied for short and intermittent durations, however, and do not address all the physiological systems in the same manner that centrifugation would.

One of the overarching questions regarding adaptation of the physiological systems to artificial gravity generated by centrifugation are what levels of angular velocity humans can tolerate before getting dizzy and having difficulty during locomotion and manipulating objects, and what minimal gravity level and duration (as well as frequency) are needed to mitigate altered gravity physiological deconditioning and related pathologies. Several investigations have been performed to look at the protective effects of centrifugation-induced artificial gravity on physiological deconditioning associated with head-down bed rest [22,57]. Interestingly, 6-degree head down bed rest is itself an artificial gravity environment in which the subjects are exposed to −0.1 g along their longitudinal axis (Fig. 1).

During prolonged head-down bed rest, exposure to 1 g at the subject heart level during supine centrifugation in a short-arm centrifuge for 30 min. per day seems to be efficient for mitigating some bone loss [58]. Short-radius centrifugation coupled exercises, such as cycling, squats or stair stepper, has also been shown to be an effective countermeasure for many negative cardiovascular consequences of hypogravity, including orthostatic tolerance time and maximal aerobic capacity [59]. Nevertheless, subjects in bed rest on Earth are still exposed to the Earth's gravitational acceleration, which could confound these effects. The effectiveness of short-radius centrifugation, as well as long radius centrifugation (see later), during head-down bed rest needs therefore to be validated during physiological deconditioning in space in both male and female crewmembers.

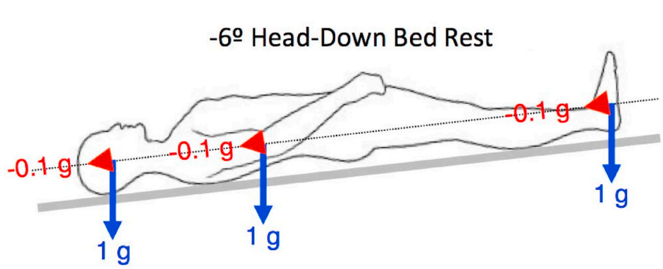

Fig. 1. Head-down (−6°) bed rest is a ground-based artificial gravity environment generating −0.1 g along the subject longitudinal axis. g can be described as two orthogonal vectors on the body: az and ax. g is the hypotenus. The angle between az and horizontal is 6°, and g is 90°. Therefore, the angle between az and g is 84°. az = g•cos(84°) = 0.1 g. In this case it is head down, so in body reference this is −0.1 g.

1.6. Future research

Future crewed missions to Moon and Mars will expose astronauts to microgravity, hypergravity, and hypogravity. Research on board the ISS during the past 20 years of continuous human presence in space has increased our knowledge of the physiological effects of long-term exposure to near weightlessness and readaptation to Earth's gravity. However, the physiological effects of long-duration exposures to hypogravity and hypergravity especially on integrative physiology and systems, are poorly understood. Most research is focused on small pieces and do not evaluate their interactions and consequences onto other related subsystems. Gravitational acceleration can still be used as a fundamental reference for orientation on Mars surface (but not on the Moon surface) and for cardiovascular regulation, but its salience is presumably reduced compared to Earth's gravity. This may induce more discrepancy between vestibular, visual, and sensorimotor signals, which can affect spatial abilities and movements. Similarly, gravity levels higher than Earth's gravity may also affect human performance even if, intuitively, hypergravity should strengthen the gravitational imprint.

Characterizing the gravitational dose response curve system by system should be considered a priority, over a range of at least μg to 1 g for a full understanding of spaceflight gravitational physiology and adaptation. However, this is only the first step before considering possible interaction effects across physiological systems. These studies should also include levels higher than 1 g, which perhaps are greater for countermeasures purposes. "Gravity doping" (sudden acute exposure to small bout of hypergravity) might be more effective than a longer exposure to 1 g or partial gravity. Also, artificial gravity, especially with intermittent exposure of about 30 min to 1 hour a day, in itself will presumably not be enough to ensure full fitness. Even with short-arm artificial gravity, exercise capabilities will be needed for maintaining bone, muscle, and aerobic fitness.

Data regarding large radius chronic artificial gravity is even far less available compared to the short-arm systems mentioned before. The concept of very large radius centrifugation was already postulated by the Russian space pioneer Konstantin Tsiolkovsky in 1903. Many others have since worked on large rotating spacecraft for the application of chronic acceleration but such a system has never materialized [60,61]. Although there are challenges, from a technological perspective realizing an in-flight rotating station is very well feasible and does not have to be that much more expensive as a regular static space craft [62]. The current focus in research is on short arm centrifuges. Main reason being that such in-flight centrifuges should fit into the hull diameter of spacecraft which are in the range of 3–4.5 m. However, rotating in such a limited space results in very large body gravity gradients when rotating (Fig. 2).

For example, pressure differences within the cardiovascular system are directly related to such gravity gradients. In these short arm centrifuges the subjects are places with their heads in or very near the center of rotation. In such a configuration e.g. the vestibular otoconia do not generate significant afferent signals to the central nervous system while there are more and more indications that the peripheral vestibular organs are involved in regulating various body functions like arterial pressure, body temperature, and muscle and bone metabolism; all functions that are altered under microgravity conditions [63]. In contrast, a large-radius centrifuge would accelerate or stimulate the vestibular system to the same value as the remaining parts of the body while there is a more physiological pressure and force distribution within the body in large diameter systems. Long radius chronic artificial gravity also does not require specific episodes of countermeasure training per day. Currently crew spend about 1.5–2 h a day, 5 days a week trying to work against the microgravity pathologies while they are not even fully counteracting these effects [64].

As with the current ground-based short-arm centrifuges, future attention should also be paid to explore the potential of large-radius chronic artificial gravity. This could be a rotating device with a

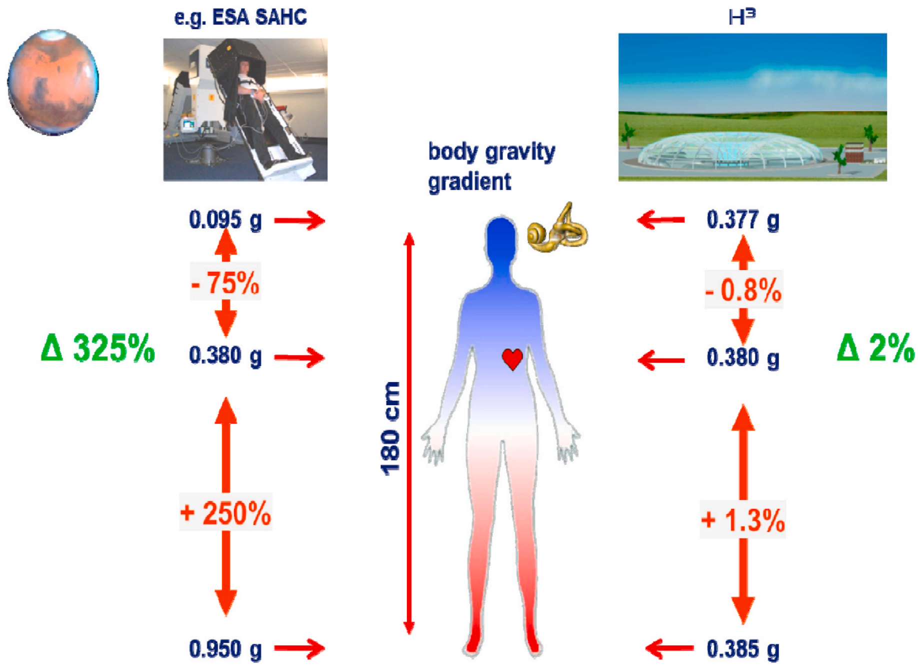

Fig. 2. Overview of body gravity gradients in a short-arm (2 m radius, Short Arms Human Centrifuge (SAHC) of the European Space Agency (ESA)) versus a long-arm (100 m radius, Human Hypergravity Habitat (H^3) concept centrifuge [3]) both set to generate Mars gravity (0.38 g) at heart level. The total body gradient is more than 300% in the short arm centrifuge while only a few percent in the long arm system. Also, in the long arm system the vestibular system perceives a comparable stimulus as the lower part of the body, a stimulus lacking in a short arm centrifuge.

diameter of some 150 m, where subjects could live and be exposed to moderate levels of hyper-g for weeks or months, the *Human Hypergravity Habitat*, H^3, concept [3]. Applying such chronic hypergravity provides the opportunity to explore the impact of gravity on human physiology. We have a wealth of data regarding the human physiology under long duration microgravity conditions but we hardly know anything about chronic hypergravity. With such a system one could explore the impact of very long duration rotation to human physiology and behavior, address specific flight requirements, explore the Reduced Gravity Paradigm or identify minimum gravity thresholds [65]. Most of the pathologies seen in crew members after long duration spaceflight are similar to processes seen in our ageing population. If microgravity simulates and/or stimulates ageing related phenomena, what would hypergravity do? Could we make use of a moderate hypergravity environment to learn and maybe counteract some of the obesity and ageing-related processes.

Finally, multiple transitions between gravity levels will occur during planetary exploration missions, i.e. during insertion into microgravity, and then from microgravity to hypogravity, back to microgravity, and finally hypergravity during re-entry into the Earth's atmosphere. In reaction to these gravitational transitions, physiological adaptation will be initiated. However, these periods are also the most critical phases of the mission for the crew. Therefore, more research is needed to better understand the extent and dynamic of physiological adaptation mechanisms during these gravity level transitions. The way these fundamental and practical research questions are addressed can bring new insights into what shapes our lives on Earth well beyond the mere space science field.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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