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Revisiting the needs for artificial gravity during deep space missions

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ABSTRACT

In the past 15 years, several group studies have identified the need to validate the role of artificial gravity (AG) as countermeasure to physiological deconditioning during long duration space missions. AG during centrifugation can be adjusted by varying the rotation rate of the vehicle or the distance of the habitat relative to the axis or rotation. These AG parameters have an impact on vehicle design and on human activities associated with the mission. Mission designers are presently reviewing the technologies and habitats necessary to maintain optimal health, safety, and performance of the crewmembers for missions to destinations beyond the Earth–Moon system. New health concerns during space flight have now emerged, such as the Vision Impairment and Intracranial Pressure (VIIP) syndrome, which appears to be caused by prolonged cranial fluid shifts that persist in the presence of currently available countermeasures. The notion of AG research therefore needed to be revisited to consider what role, if any, AG should play in these missions. This paper describes the engineering aspects of human spacecraft providing AG, what is known of the effects of AG on humans, and the research needed to answer the questions raised by mission designers.

Contents

1. Introduction

As space agencies plan the next generation of human space exploration missions to destinations beyond the Earth–Moon system, it is incumbent on mission designers to review the technologies and habitats necessary to maintain optimal health, safety, and performance of the crewmembers designated to carry out those missions. The primary hazards leading to health and performance risks during these missions are altered gravity levels, isolation and confinement with altered light–dark cycles, a hostile and closed environment, radiation, and distance from Earth. Altered gravity impacts most of the physiological systems, as shown by orthostatic intolerance, muscle atrophy, sensorimotor performance impairment, bone demineralization, immune deficiencies, back pains, and renal stone formation [1]. Lately, a special focus of concern regards changes in vision acuity in astronauts onboard the

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International Space Station (ISS), which are hypothesized to be caused by weightlessness-induced fluid shifts to the upper body leading to intracranial hypertension [2]. Even though vision disturbances have been reported earlier on the shorter Shuttle flights, these effects are of more concern now because if the hypothesis is confirmed, this risk could be an impediment for future long duration deep space missions. Thus an effective countermeasure against these effects will be required, and if it requires re-establishing gravity-induced hydrostatic gradients, artificial gravity might be the most efficient option [3].

With the end of the ISS era less than a decade away, we must consider now what role, if any, AG should play in future exploration missions. According to NASA's flexible path, the next steps in human spaceflight include flyby and orbital missions to the Moon, Mars and near earth asteroids (NEAs), lunar and Martian landings, and combinations of these scenarios. The year for design decisions to be made for the spacecraft is expected in 2022, and the decision criteria will include whether we can protect the health and performance of astronauts.

Space physiologists, crew surgeons, astronauts, vehicle designers, and mission planners need to review, evaluate, and discuss the issues for incorporating AG technologies into the vehicle design. Commitments by spacecraft designers to spin a vehicle, part of a vehicle, an exercise device within a vehicle, or even just a crewmember will only come following acceptance of a well-argued requirement from the life sciences community. Questions that will need answers are: (a) what evidence do we have to support such a requirement; (b) what design parameters would we levy upon the engineers; and (c) what prescriptions would we recommend to the crewmembers? Research needed to address these questions has a timeframe of less than eight years.

The purpose of this paper is to review the current status of AG research, and to discuss the need for and challenges to implementing AG countermeasures in human exploration missions beyond the Earth–Moon system. The objective is to focus on the research plans for using available facilities to answer the key questions in time to influence the decisions for the next generation of space exploration missions.

2. Artificial gravity concepts

Providing AG on board deep space human exploration vehicles using centrifugation has received surprisingly limited engineering assessment. This is most likely due to a number of factors: (a) the lack of definitive design requirements, especially acceptable AG levels and rotation rates; (b) the perception of high vehicle mass and performance penalties; (c) the perception of complications associated with vehicle spin-up and spin-down, such as antennae and photovoltaic arrays; and (d) the expectation of effective alternative gravity-replacement countermeasures [4].

A number of AG spacecraft concepts have been proposed with a variety of habitat module orientations. Human factor issues associated with each of these concepts have been identified along with mitigation strategies [5,6]. Transfer vehicles equipped with high thrust nuclear thermal rocket (NTR) engines, which use photovoltaic arrays for spacecraft auxiliary power, and "bimodal" NTR (BNTR), which uses the engines to generate the spacecraft's electrical power during the coast phase, are attractive options and are currently under study [7]. Both space transfer vehicle concepts can readily be adapted for AG operation, for example by placing the engines at one end of a structure and the habitat at the other end and rotating the entire structure around its center of mass (Fig. 1).

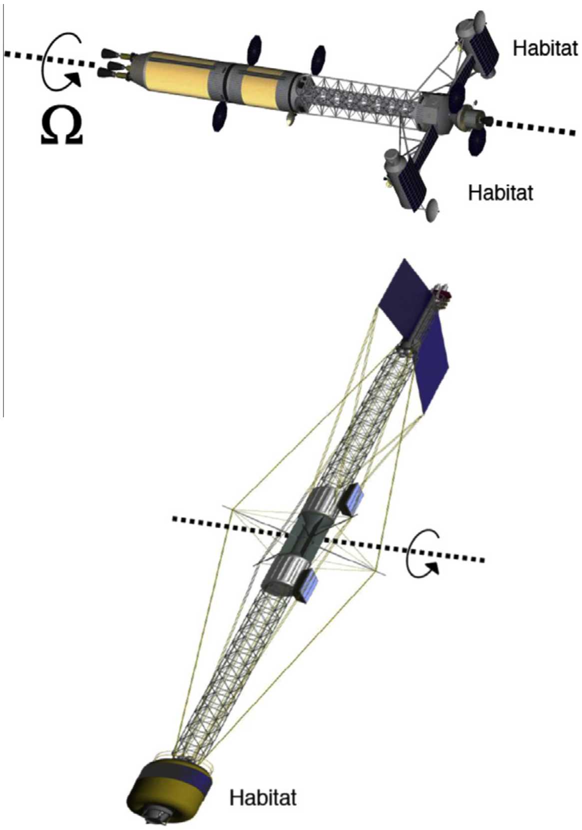

Fig. 1. *Top*. Mars transfer vehicle using conventional nuclear thermal propulsion rocket (NTR) for rotating two habitats along its long axis. The vehicle also utilizes photovoltaic arrays for auxiliary power. *Bottom*. The bimodal BNTR spacecraft configuration – long and linear – is naturally compatible with AG operation. Distance between the habitat and the axis of rotation is 56 m. An AG environment of 1 G can be provided to the crew by rotating the BNTR vehicle about its center of mass at about 4 rpm. Photo courtesy of NASA.

The NTR's high specific impulse of approximately 900 s (100% higher than LOX/LH_2 chemical rockets) is particularly attractive for AG missions because it can more readily accommodate the heavier payload mass and the increased reaction control system propellant required for multiple spin-up/spin-down cycles. Also very important is the fact that NTR can enable shorter transit times (3–6 months) to and from Mars that can help reduce the crew's exposure to galactic cosmic radiation and solar flares. Indeed, the ultimate countermeasure is in fact speed, flying faster and minimizing the weightless cruise time to mitigate the physiologic deficits along with the radiation acquired dose associated with deep space travel [4].

NTR is a proven technology successfully demonstrated in ground tests. This technology is receiving increased attention at NASA through the Nuclear Cryogenic Propulsion Stage (NCPS) project. Ground testing of a NTR engine could occur in the early 2020s, in time to support long duration crewed missions to NEAs, Mars and its moons in the 2028–2033 timeframe. A recent study has tried to understand the implications of and potential solutions for incorporating AG in the design of a vehicle for 18–24 months of round trip and three months stay on Mars using NTR [6]. The habitat would spin at 4 rpm, thus generating 1 G at a radius of 56 m (Fig. 1, left). The trade-off advantages of this design are that it would: (a) reduce the Mars transit time; (b) not require excessive propellants; (c) not require long duration 0 G tests; (d) not require massive de-spun joints; and (e) constitute a good convergence between power system mass and habitat as counterweight [4].

One alternative to spinning the entire vehicle is rotating one vehicle segment only, such as depicted in Kubrick's movie "2001:

A Space Odyssey" where crewmembers exercise in a rotating 6-m radius carrousel inside the much larger spacecraft en route to Jupiter. NASA's advanced spacecraft Nautilus-X (Non-Atmospheric Universal Transport Intended for Lengthy United States Exploration) is based on this concept (Fig. 2). One segment of Nautilus-X is a 6.1-m radius centrifuge that could rotate up to 10 rpm for allowing astronauts to exercise in a 0.7 G environment. The centrifuge includes inflatable structures, like Bigelow Aerospace's modules, that could be tested on the International Space Station [8].

Another AG concept is to expose crewmembers to centrifugal forces while they are exercising. Several designs that use a combination of rotating and cycle ergometer devices have been proposed [9]. For example, the Human Powered Centrifuge is a 1.9-m-radius centrifuge that can carry one or two subjects in the seated supine position with their heads near the centrifuge hub. The configuration allows for one subject to power the centrifuge using a modified cycle mechanism [10]. In the Space Cycle concept, subjects ride opposite one another, one on a bike and one on a platform. As one individual pedals, the cycle and the platform both rotate around a central pole and tilt, thus generating a centrifugal force aligned with the riders' longitudinal body axis in space. The rider on the platform can perform various types of resistance training exercises, such as running on a treadmill or performing squats [11].

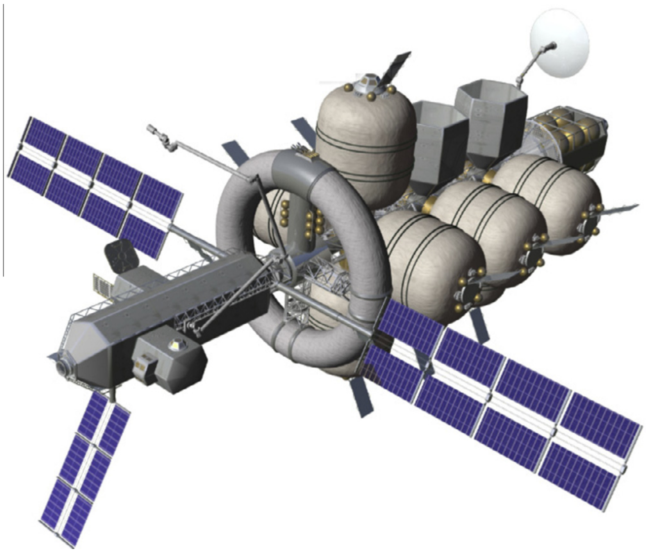

Fig. 2. NAUTILUS-X is a spacecraft that could serve as a reusable vehicle for lunar and deep space missions. It contains a 12.2-m diameter ring centrifuge that provides partial gravity to the crew during long-duration missions. Photo courtesy of NASA.

In 2009, a human centrifuge project called AGREE (Artificial GRavity with Ergometric Exercise) was selected to fly on board the ISS as a result of an International Life Science Research Announcement. The objective of AGREE was to test, for the first time, the acceptability and effectiveness of AG generated by short-radius centrifugation as a countermeasure to human deconditioning on orbit [12]. This centrifuge combined with ergometric exercise capability was to be constructed by ESA, launched by JAXA HTV, and placed at the end of the Multi-Purpose Logistics Module (MPLM) (Fig. 3). Unfortunately, AGREE was canceled in 2013 following a stress analysis showing that the ISS nodes would have been structurally compromised by the generated vibration loads.

Yet another concept is that the astronauts produce self-generated artificial gravity. As an example, during the Skylab missions the crew took advantage of the large open compartment to run around the curved circumference. The generated AG level ranged from 0.1 G to 0.2 G and the astronauts felt "no sensation of gravity, just a controlled bounce" (Joe Kerwin, personal communication). In a similar fashion, Valery Polyakov claimed to have used self-generated AG by spinning himself around a rope that was fixed to two points inside Mir. He further claimed that these maneuvers contributed to his ability to walk unassisted upon landing after his 14-month spaceflight (Millard Reschke, personal communication).

3. Current countermeasures augmented by centrifugation

Exercise is currently the dominating gravity-replacement countermeasure during spaceflight, used primarily to maintain muscle and cardiovascular fitness, as well as bone strength. Exercise presumably also benefits other physiological systems such as the sensorimotor system [13]. It has been shown that introduction of systematic resistive exercise on ISS improves muscle and bone strength and that the level of success depends on the intensity and load applied. The most efficient exercise prescription seems to be a combination of aerobic and resistive exercise using a cycle, treadmill, and the Advanced Resistive Exercise Device (ARED) that can apply up to 600-pound loads [14].

During long-duration deep space missions, exercise prescriptions will be required; but will adding AG make it possible to reduce in-flight mass, power and time, and make exercise more efficient? This question has only been studied to a limited extent (only 30 papers have been published to date exploring the effects of exercise combined with AG). There are promising results with

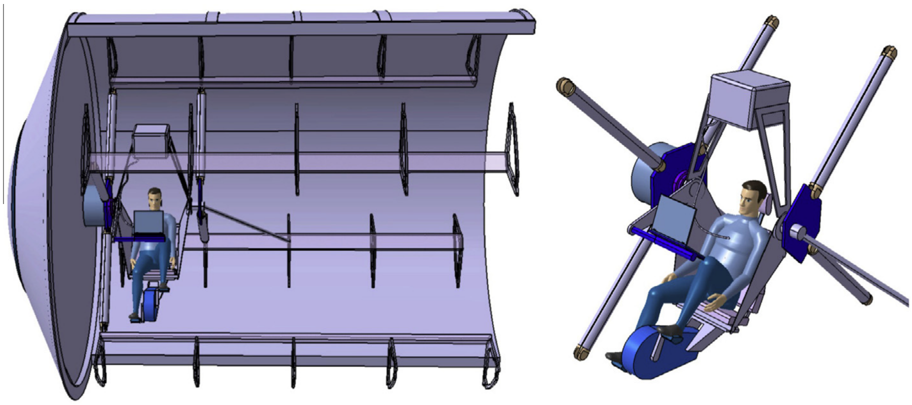

Fig. 3. Schematic drawing of the AGREE human centrifuge combined with a cycle ergometer in the Multi-Purpose Logistics Module of the International Space Station. A 30-rpm rotation generates 1 G at the feet of the crewmember, which would augment the benefits of the exercise activity. Photo courtesy of NASA.

21 days of bed rest and combining AG with shallow squat and heel raise on muscle outcomes [15]. Treadmill exercise coupled with LBNP has also been shown effective as a cardiovascular countermeasure during 56 days of bed rest in female subjects [16].

The current evidence for using exercise as a countermeasure during long-duration space missions in low Earth orbit indicates that astronauts can probably travel to Mars and back with exercise alone as a countermeasure for maintaining adequate muscle and bone strength, muscle performance and sufficient aerobic capacity using a high intensity, low volume exercise training. However, it is likely that adding AG will make the exercise programs more efficient and reduce in-flight resources, including crew time. AG could also prove to be a determining factor for mission success should the exercise equipment fail during the mission [14].

From an astronaut perspective, short-radius centrifuges for intermittent AG exposures during flight may not be preferred over continuous spinning of the entire spacecraft because astronauts generally prefer less complexity in the machines on which they depend. From a habitability standpoint, since spacecrafts are inherently small; the limited volume becomes more usable in weightlessness, an aspect that might be sacrificed for a spacecraft or module that is spun for AG. Human factors represent a nearly even trade because some tasks are easier and some more difficult in weightlessness [17].

An important driver for introducing AG may be as a countermeasure for the Vision Impairment and Intracranial Pressure (VIIP) syndrome. The leading hypothesis is that the weightlessness-induced fluid shift is the precipitating factor inducing impairment in cerebrospinal fluid resorption and central nervous system venous drainage [2]. For the time being, we do not fully understand all ramifications of the VIIP syndrome and whether it has long-term effects on brain function. For this reason, the VIIP syndrome is currently of the highest concern for long duration missions. It is possible that interventions like venous limb occlusion and lower body negative pressure could play a preventive role, and these countermeasures are currently being investigated. However, chronic AG may be the most efficient countermeasure for mitigating the VIIP syndrome and immediate post-landing decrease in performance such as orthostatic intolerance and sensorimotor disabilities [17].

4. Known effects of centrifugation

4.1. Human studies

Even though there have been proposals to install human AG facilities in space in the US space program, such as a small one-human centrifuge on the Apollo-Lunar Exploration Module, only a very few studies have in fact been conducted in space on AG in humans. On the Gemini-11 mission in 1966, the first and until now only attempt of AG in space was made by rotating the spacecraft connected to an Agena rocket casing using a tether and obtaining 0.15 rpm inducing only 0.0005 G for 4 h in the astronauts. The only other attempts to induce AG in space in astronauts were on Spacelab-1 in 1985 using an ESA-developed linear sled for vestibular experiments obtaining 0.2–1 G for a few seconds, and with rotating chairs on the Space Shuttle obtaining up to 1 G for investigating the vestibular system [3].

On the ground, experiments on intermittent centrifugation in humans have primarily been done in short-radius centrifuges with the test subject being totally passive or performing exercise simultaneously. In these experiments, subjects are typically maintained in −6-deg head-down bed rest [18], or immersed in water [19] for several days, except when being placed on a short-radius centrifuge, generally for 1 h daily with 1–2 G at the heart and 2–3 G at the feet (Table 1). These gravity levels helped to reduce the decrement in orthostatic intolerance and sensorimotor deconditioning after bed rest/immersion. However, the protective effects on muscle and bone changes were inconclusive, mostly due to the limited duration of the bed rest/immersion [15,26,34,40–43]. To our knowledge, no studies have investigated the effects of centrifugation on intracranial pressure to date.

It is reasonable to think that the most effective AG level will be at 1 G all along the crewmembers' longitudinal body axis so that they would be exposed to "normal" gravity loading throughout their trip and arrive on Mars ready to go to work. However, smaller AG levels might also have a mitigating effect, and would require less constraint on the vehicle design. One problem is that the dose–response curve between physiological variables and gravity level is virtually unknown (Fig. 4). We do not know for example, whether the Martian gravity level of 0.38 G is at all protective,

Table 1
Summary of AG level, duration, and frequency used during bed rest (BR) or dry/wet immersion studies in humans. Adapted from [20] and [21].

Study	Days	Intervention	AG level at feet (G)	AG level at heart	Session duration (min)	No. of sessions per day	Daily AG exposure (min)
Shulzhenko et al. [22]	3	Wet immersion + AG	1.6		40	3	120
Vil-Viliams & Shulzenkho [23]	3	Dry immersion + AG	1.6		40	3	120
Vernikos et al. [24]	4	BR + walking	1.0	1.0	15	8, 16	120, 240
Yajima et al. [25]	4	BR + AG		2.0	60	1	60
Iwasaki et al. [26]	4	BR + AG		2.0	30	2	60
Sasaki et al. [27]	4	BR + AG		2.0	30	2	60
Lee et al. [28]	5	BR + running	1.0	1.0	30	1	30
Linnarsson et al. [29]	5	BR + AG		1.0	30, 5	1, 6	30
Mulder et al. [30]	5	BR + walking		1.0	30, 5	1, 6	30
White et al. [31]	13	BR + AG		1.0–4.0	7.5–11.2	4	30–45
Grigoriev et al. [32]	13	Dry immersion + AG	0.6–2.0		60–90	1	60–90
Iwasaki et al. [33]	14	BR + AG + cycling		1.2	30	1	30
Iwase [34]	14	BR + AG + cycling		1.2	30	1	30
Katayama et al. [35]	20	BR + AG + cycling	1.0–5.0	0.3–1.4	40	1	40
Akima et al. [36]	20	BR + AG + cycling	1.0–5.0	0.3–1.4	40	1	40
Young & Paloski [37]	21	BR + AG	2.5	1.0	60	1	60
Vil-Viliams [38]	28	Dry immersion + AG + cycling	0.8–1.6		60–90	1	60–90
Vil-Viliams [39]	28	Dry immersion + AG + cycling		1.2–1.9	120	1	120

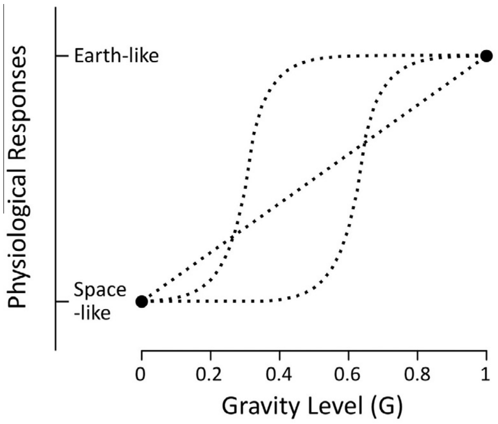

Fig. 4. Hypothetical graded dose–response curves for gravitational levels between 0 G and 1 G.

and what gravity threshold is needed for maintaining musculoskeletal and other functions during long duration weightlessness. To define the physiologically protective gravity threshold of AG is one of the most important requirements for the engineers when developing AG in space.

Generating 1 G inside the entire habitat is possible only with long radius centrifugation (e.g., approximately 60 m at 4 rpm). Shorter radius centrifugation generates AG levels that are different throughout the body; i.e., smaller at the head and larger at the feet. Little is known regarding the implications of this gravity gradient on physiological responses. The presence of this gravity gradient also makes limb movement and changing body positions awkward, which can greatly affect handling materials or moving objects. Based on the observations in the slow rotation room experiments, a minimum radius of 12 m is generally specified to limit the gravity gradient to approximately 15%. This limit was imposed taking into account the human factors consideration of work efficiency [44]. However, recent experiments with subjects lying supine on short-radius centrifuges with gravity gradients of 25% and 50% did not reveal any significant effect on cardiovascular responses [45,46].

Several authors have suggested that passive centrifugation on a short-radius centrifuge will not be effective in maintaining skeletal muscle mass and bone density during long exposures to microgravity. Hence, as a complement for passive centrifugation, they have pursued the development of active centrifugation, where the subjects exercise while being centrifuged, as potential multipurpose countermeasures to microgravity. This system has the capacity for studying the effects of centrifugation on muscle mass, bone density, and orthostatic tolerance. Most studies have used AG coupled with cycling, but other types of exercise, such squats or stair stepper, have been evaluated during short-arm centrifugation (Table 2).

AG coupled with cycling has been shown to be effective for many of the cardiovascular parameters, including orthostatic tolerance time and VO_2 max. Although little musculoskeletal data exists for AG, muscle atrophy was prevented in humans with centrifugation for 1 h at 2.5 G at the feet along with calf presses. Squats have been successfully performed in AG training studies without adverse effects from Coriolis forces or motion sickness [51]. Foot forces and EMG activity are comparable when performing high intensity squats during centrifugation and during standing upright [54].

Studies during bed rest and water immersion in humans have focused on centrifugation exposure during one or two daily sessions of 1 h. This regimen is presumably based on the current exercise regimens during long-duration space missions (2 h daily). Very few studies have used multiple daily exposures using exercises or AG, or a combination of AG and exercise. White et al. [31] used 4 daily AG sessions of 7.5 min or 11.2 min during bed rest and showed that this was sufficient to reduce most of the physiological markers associated with orthostatic intolerance. Vernikos et al. [24] used 8–16 daily sessions where the subjects were standing in place or walking during 4-day bed rest, based on the concept that “in general physiological systems respond to signal and intensity changes rather than to the duration of a stimulus” [55]. Recent studies have shown positive effects of AG for a total exposure equal to less than 1% the intervention [30]. Comparison between the effects of one daily 30-min AG session and six daily 5-min AG sessions showed that intermittent centrifugation during a 5-day bed rest had superior effects against orthostatic intolerance and neuroendocrine stress responses compared to continuous centrifugation [29,56]. By contrast, changes in bone markers were more marked after continuous centrifugation [57] and neurovestibular effects were equally reduced by both intermittent and continuous centrifugation [58].

Ground-based experiments on continuous rotation in humans were performed in slow rotation rooms with complete living facilities in which the subjects lived for up to 3 weeks [59,60]. The main purpose was to observe whether the subjects could sustain the rotations from 1 rpm to 10 rpm without experiencing motion sickness, and how they would move and perform daily tasks under the influence of Coriolis forces [61–63]. These experiments demonstrated that humans can adapt to a rotation rate of 3 rpm and that a 14-day period of rotation at this velocity causes no significant changes in general condition or performance. In contrast, no adaptation took place when subjects were rotated at 10 rpm for 12 days, implying that a 10-rpm rotation rate was perhaps close to the upper threshold of endurance.

As a next step, ways of adapting humans to rotation at 10 rpm were investigated through incremental increases in rotation rate over time. Increasing the rotation rate in nine stages of approximately two days each over the course of 16 days mitigated the symptoms of motion sickness and generated fewer balance problems even at 10 rpm [63]. Results also indicated that executing a

Table 2
Summary of AG level, duration and frequency used during studies assessing the effects of exercise combined with centrifugation. Adapted from [21].

Study	Days	Intervention	AG level at feet (G)	AG level at heart (G)	No of sessions per day	Total No of sessions
Iwase et al. [47]	1	AG, AG + cycling		1.2	4	4
Stenger et al. [48]	21	AG, AG + cycling	1.0–2.5		5	105
Evans et al. [49]	21	AG, AG + cycling	1.0–2.5		5	105
Caiozzo et al. [11]	1	AG, AG + cycling	1.0–3.0		4	4
Iwasaki et al. [50]	7	AG		2.0	7	49
Greenleaf et al. [10]	1	AG + cycling	2.2		4	4
Yang et al. [51]	4	AG + squats AG + cycling	1.5–3.0		1	4
Edmonds et al. [52]		AG + stair stepper	0.7–1.3			
Duda [53]		AG + squats	2.0			

series of specific head movements could significantly shorten the time needed to adapt. The higher rotation rate, the more difficult the adaptation, but adaptation to 10 rpm was possible as long as the rate-increase increments were held to 1–2 rpm with a period of 12–24 h at each increment [64]. The time needed for this adaptation might therefore prove to be too long for practical use during spaceflight. However, anti-motion sickness drugs could be used to attenuate motion sickness while the terminal velocity is more rapidly achieved [65].

Periodic stops of 10–15 min were required for re-provisioning during the long-duration slow rotating room runs. Over time, the on-board experimenters who helped in this activity made transitions between the stationary and rotation periods without experiencing motion sickness or disruptions of movement control. They manifested perfect *dual-adaptation* [66], thus indicating that is possible to be simultaneously adapted to rotating and non-rotating environments. Furthermore, there was retention of the adaptation to the slow rotation for several days in all the subjects, which implies that transitions from weightlessness to rotation should be acceptable under certain conditions [67].

4.2. Animal studies

The use of animals both on ground and in space should play an important role in facilitating the development of a human AG countermeasure and be part of a translational science based approach. AG in space can be also be beneficial for more fundamental animal research for understanding, e.g., vestibular system adaptation to transitions between gravity levels. Rodents immediately sense exposure to a novel, non-1 G environment and adaptive mechanisms in physiological functions are quickly initiated. In the short term, compensation is likely confined to the peripheral sensory receptors, the brain or both. For longer exposure, structural modifications of the end organ may also result. How these functional and structural changes within the otolith organs affect performance and neurovestibular perception, particularly following transitions between gravity levels, are yet to be determined, but clearly pose severe challenges to long-duration missions. Artificial gravity tools on the ISS used either intermittently or on a continuous basis are essential and can directly address these challenges [68].

The first animals to be centrifuged in space were flown on the 20-day Cosmos-782 mission in 1975, when fish and turtles housed in containers were centrifuged at 1 G. The center of the containers was placed at 37.5 cm from the center of a platform rotating at 52 rpm. After the flight, the physiology and behavior of the centrifuged animals was indistinguishable from their 1-G ground controls [69]. More extensive investigations were executed using rats that were centrifuged during the 19-day mission of Cosmos-936 in 1977. The rats were kept in individual cages and were not restrained. Their cages were placed in a centrifuge with a radius of 32 cm. An artificial gravity level of 1 G was obtained by spinning the centrifuge at 53.5 rpm [70]. Results revealed that in-flight centrifugation had a protective effect on the myocardium and the musculoskeletal system, as compared to the animals that were exposed to microgravity and not centrifuged [71]. However, there were some adverse effects of the in-flight centrifugation that were noted in the visual, vestibular, and motor coordination functions, such as equilibrium, righting reflexes, and orientation disorders. These deficits may have been the result of the high rotation rate of the centrifuge and the large magnitude of the gravity gradient [72].

Other experiments with rodents in flight centrifuges showed that for AG levels above 0.28 G the effects were like 1 G, and that for AG levels below 0.28 G the responses of the animals were not different from those of the in-flight 0-G control animals [73]. In the U.S., a series of experiments involved rotating four rats on sub-orbital rockets during a 5-min period of free fall. The rocket was rotated about its longitudinal axis using a special motor at a rate of 45 rpm. The rotation created a variable AG from 0.3 G to 1.5 G along the boxes that housed the rats. The movements of the rats were recorded on film and showed than one rat stayed in a position where the artificial gravity level was about 0.4 G, whereas the other three settled down where the artificial gravity level was 1 G [74].

Small radius high rotation-rate centrifuges have been flown in the Spacelab of the Space Shuttle and in the Skylab, Salyut, and Mir space stations to conduct experiments on bacteria, cells, and other biological specimens. Results indicate that microgravity effects, especially at the cellular level, may be eliminated by artificial gravity (see [75] for a review). The original plans to install a 2.5-m-radius centrifuge on the ISS to carry up to eight modules for rodents, fish, and eggs were canceled in 2005. This variable gravity animal centrifuge would not only have provided a 1-G control for the 0-G experiments, but would also have allowed exploring the entire range from 0.01 G to 1 G for a variety of species. Such a device would have afforded the opportunity to examine the adequacy of various levels of artificial gravity in protecting rodents during spaceflight.

An experiment using centrifugation as artificial gravity is currently being performed with fruit flies on board the ISS. JAXA has launched a mice habitat in 2015 and will soon conduct the first investigation for 30 days in 12 mice with six of them being subjected to AG centrifugation of 1 G in space. NASA is also developing a rodent habitat equipped with a centrifuge for investigating AG in rats on board the ISS.

In the meantime, ground-based models are used to simulate the effects of weightlessness in animals. The hind limb suspension is used to simulate fluid shift and hind limb immobilization [76]. The animal retains some mobility with its front limbs; the bar to which the tail is attached can swivel 360 deg. This model has become a widely used spaceflight analog since it allows chronic unloading of the hind limbs in semi-ambulatory rodents. About 25% of the studies published focus on bone or calcium metabolism and often the suspension model is used as a precursor experiment modality to study the effects of musculoskeletal disuse. In recent studies, rats were exposed to a single bout of hind limb suspension for 28–56 days and tracked for 84 days after return to weight bearing. Proximal femur mass and density of the rat exhibited similar loss and recovery trends as those reported for ISS crewmembers [78].

Recent studies in mice using partial weight-bearing activity have shown proportional declines in bone mass to partial gravity. The authors used a partial weight suspension system, in which a two-point harness is used to offload an adjustable amount of body weight while maintaining quadrupedal locomotion (Fig. 5). Skeletally mature female mice were exposed to partial weight bearing at 20%, 40%, 70%, or 100% of body weight for 21 days. It was found that total body and hind limb bone mineral density, calf muscle mass, trabecular bone volume of the distal femur, and cortical area of the femur mid shaft were all linearly related to the degree of unloading [77].

In another study, skeletally mature female mice were subjected to 16% (i.e., simulated lunar gravity) or 33% (i.e., simulated Martian gravity) weight bearing for 21 days. Earth gravity and tail-suspended mice (simulated microgravity) served as controls to compare the effects of simulated lunar and Martian gravity to both Earth gravity and microgravity. Animals experiencing 33% weight bearing exhibited fewer deficits in femoral neck mechanical strength than those experiencing 16% weight bearing and the tail-suspended mice. This result suggests that Martian gravity is not sufficient to protect against bone loss. However, it might

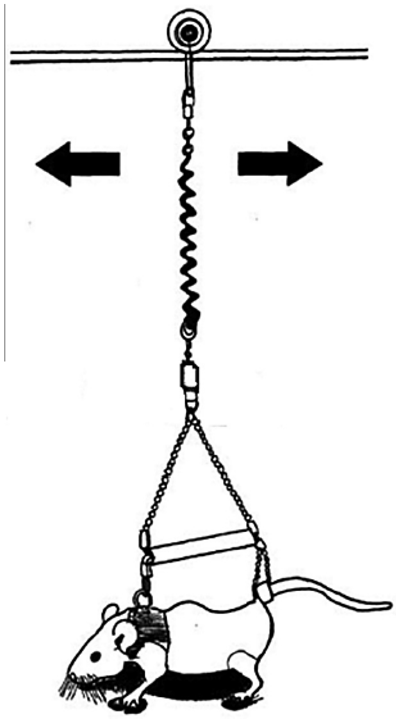

Fig. 5. A harness connected to a spring enables long-duration exposure of mice to partial loading while maintaining quadrupedal locomotion. Loading conditions corresponding to 16% and 38% weight bearing simulate the effects of lunar and Martian gravity, respectively, on bone and muscle atrophy. Adapted from [77].

mitigate muscle atrophy, as indicated by the absence of reduction in soleus mass in mice subjected to 33% weight bearing [79].

5. Research plan

Based on NASA's flexible path for future manned deep space missions, design requirements for AG will be sought circa 2022. Regarding the physiological requirements for AG, the following scenarios are considered: (a) centrifugation inside the space vehicle (intermittently, autonomously and/or human powered; radius less than 2.5 m); (b) centrifugation of part of the vehicle (continuously or intermittently; radius between 3 m and 15 m); or (c) spinning the whole vehicle (continuously; radius 60 m or greater).

To help inform the final decision whether to conduct short- or long-radius centrifugations in space and whether whole or only part of the space vehicle should be spun, it is important to know the limitations of AG in humans. For intermittent, short-radius centrifugation the question that needs to be addressed is: what are the acceptable and/or optimal ranges for radius and rotation rate of an onboard centrifuge to avoid unacceptable crew health and performance consequences? To address this question, research should determine (a) what the physiological consequences are of AG generated by short-radius centrifugation; (b) what the physiological limits are for rotation rate, gravity gradient, and duration of AG exposure; and (c) what frequency of AG exposure is optimal for intermittent applications [80].

For continuous, long-radius centrifugation, the question that needs to be addressed is: what are the acceptable and/or optimal ranges for radius and rotation rate of a rotating transit vehicle to avoid unacceptable crew health and performance consequences? To address this question, research should determine (a) what the physiological consequences are of AG generated by long-radius centrifugation; (b) what the physiological limits are for rotation rate; and (c) what the acceptable ranges of Coriolis forces and cross-coupled angular accelerations are to avoid spatial disorientation and motion sickness when moving inside the rotating vehicle.

The AG Study Group of the Human Research Program at NASA has identified some areas in which more research is needed to provide answers to the above questions. First, more gravity level values along Gz within the range from 0 G to 1 G must be tested to reasonably identify the threshold, optimal stimulus–response, and saturation for the effects of centrifugation on cardiovascular, sensorimotor, and musculoskeletal functions. Also, we do not know if increasing the intensity of the AG stimulus actually reduces the time of exposure needed. Consequently, the effects of gravity levels higher than 1 G on physiological functions definitely need to be further investigated. In the absence of a space-based human rated centrifuge, these tests would include intermittent centrifugation during deconditioning interventions such as bed rest [18,80], wet/dry immersion in humans [19] and tail suspension or partial unloading in animals [76,77].

Centrifugation could also be replaced by head-up tilt in humans within the range of 0–90 deg. For example, during a 22.3-deg head-up tilt there is a 0.38 G force exerted along the body longitudinal axis. Subjects could also be partly immersed in water so that the hydrostatic gradient and body unloading is equivalent to Moon or Mars gravity [81]. Measurements of cardiovascular and sensorimotor responses after bed rest in this position would provide evidence of the effects of Mars gravity on physiological functions. The recovery of deconditioning of these functions in crewmembers following six months in weightlessness could also be obtained by placing ISS crewmembers returning from the ISS in a 22.3-deg head-up tilt for several hours.

To study the effects of AG on musculoskeletal system, ambulatory subjects could be exposed to intermittent centrifugation, say 2–3 times per week, for a period >3 months. Centrifugation could be coupled with squats or other exercises. Measurements of the antigravity muscles and weight-bearing bones and biological markers would be taken before and after training. Comparison with control groups without centrifugation, and possibly with or without exercise, would help determine the benefits of centrifugation training on muscle and bone.

Short-radius centrifugation generating Gz centrifugal force from head to foot could potentially be a countermeasure against VIIP by counteracting the headward fluid shift, reducing vascular and lymphatic congestion, allowing outflow of cerebrospinal fluid, and reducing intracranial pressure. The effects of centrifugation on vision changes and intracranial pressure would be investigated when subjects are exposed to AG levels of >1 Gz at the head. Subjects will include healthy individuals and terrestrial populations with elevated intracranial pressure and vision issues.

The maximum rotation rate of a centrifuge or spinning spacecraft is limited by the Coriolis (linear) and cross-coupled (angular) accelerations encountered when walking, moving the head, or when moving the objects within the rotating environment. At body motion or centrifuge rotation rates that are of low magnitude, the effects of the Coriolis force are negligible. However, in a centrifuge rotating at several rpm, there can be disconcerting effects. Simple limb movements become complex, eye-head movements are altered, and nausea can occur [82]. These effects could be assessed comparing the effects of head, arm, and leg movements in various postures (e.g., supine, on-side) for increased rotation rates of centrifugation. It is also very easy in relatively short radius rotating devices to have a servo-controlled platform so that the test bed can be tilted to keep it in alignment with the changing gravitoinertial force vector associated with rotation at constant velocity.

Because the design for a future interplanetary spacecraft would include the preferred option of rotating either the entire vehicle or a device within a vehicle, it would be useful early on to determine what force levels and rotation rates humans can adapt to in time to inform the design of that spacecraft by HRP's self-imposed deadline of 2022. Stone et al. [83] laid out a number of situations that humans would have to adapt to in any rotating environment and they came up with a number of theoretical limits to rotation rates and radii for vehicles. Their assumptions have largely been taken at face value as correct. However, it is very important to confirm whether or not their predictions hold true. Also, inside a rotating vehicle, the artificial gravity level is constantly being distorted as the astronauts move about within the spacecraft, except when they move along an axis that is parallel to the axis of rotation. As mentioned above, Coriolis forces act on the limbs during movements and after-effects occur when rotation stops. Only a few studies have taken into account the cognitive aspects of centrifugation (e.g., prediction, memory, dual-task); therefore, more research is needed in this area.

The critical AG research path that will enable an answer by 2022 to the concerns raised by the deep-space mission designers includes several parallel tracks. Specimens will include cell cultures (e.g., from bone, muscle, heart and brain tissues), animals (mice and rodents), and humans. For ground-based research, the AG models will include immobilization, parabolic flight with various partial gravity levels, body-out immersion, head-up tilt, short- and long-radius centrifugation, as well as slow rotating rooms. These AG models will be applied for durations ranging from seconds to months depending on the main research objective (Table 3).

The AG prescription will recommend how much, how long, and how often the application of centrifugal force is necessary to maintain human health and performance at an acceptable functional level on a planetary surface. As a minimum, crewmembers should maintain their ability to perform critical mission tasks immediately after landing on Mars or Earth, such as seat egress, ladder climb, jump down, recovery from fall, and walk. Therefore performance metrics need to be assessed before and after the use of AG models.

Although the above ground-based studies described have the potential for determining a sound AG prescription (rotation rate, duration, frequency), its validation can only be performed in space. As mentioned above, rotating vessels and centrifuge are available on board the ISS for cell culture and animal research. However, no human-rated centrifuges that have been built specifically to counteract cardiovascular and musculoskeletal deconditioning have flown in space to date. Given the time constraints of this project, it is most likely that a full validation using an ISS-based human rated centrifuge won't be feasible. Nevertheless, questions such as what the impacts are of centrifugation inside a space vehicle on the vibration level, motion sickness, or crew time could be answered using a simple, lightweight on-board centrifuge. Any positive results from this space centrifuge would also provide the impetus for further ground-based research.

Table 3
AG ground-based research approach.

Species	AG	Duration	Objectives
Cells	Centrifugation	Hours	G-dose–response curve
Rodents	Tail suspension	Days	G-dose–response curve
Rodents	Centrifugation	Weeks	G-dose–response curve
Humans	Parabolic flight	Seconds	G-dose–response curve
Humans	Body out immersion	Minutes	G-dose–response curve
Humans	Short-radius centrifugation	Minutes	Cross-coupled/Coriolis effects
Humans	Short-radius vs. long-radius centrifugation	Minutes	G-gradient
Humans	Head-up tilt	Hours	Physiological G-dose–response curve
Humans	Bed rest or dry/wet immersion and short-radius centrifugation	Weeks	AG rotation rate, duration, frequency
Humans	Ambulatory and short-radius centrifugation	Months	AG rotation rate, duration, frequency
Humans	Slow rotating room	Days	Cross-coupled/Coriolis effects, human factors, dual adaptation, spin-down effects
Humans	Long-radius centrifugation	Months	G-dose–response curve, cross-coupled/Coriolis effects, human factors, dual adaptation, spin-down effects

6. Conclusions

Many "recommendations for AG research" reports have been written between 1999 and today, including the excellent white paper based on the discussions at the International Workshop on Research and Operational Considerations for Artificial Gravity Countermeasures from last year [84]. But they are just reports. It is time to take action. So, how should we prioritize the research? We have a 0-G platform (the International Space Station) and multiple ground-based venues with which to develop the answers. ISS studies might focus on a proposed rodent centrifuge facility that would allow us to establish the long-term effects of hypo-gravity exposure, or possibly a human short-radius centrifuge equipped with an exercise device that would allow us to test specific AG exercise prescriptions. Ground-based facilities would allow us to examine various short-radius exposure paradigms in subjects deconditioned by bed rest or dry/wet immersion, medium- and long-radius live-aboard paradigms to investigate long-term effects of rotation on behavior and performance, and small animal centrifuges to investigate the mechanisms of the physiological adaptive responses.

In the review of existing studies assessing the effects of centrifugation, many confounding variables arose from the protocols themselves. Differences were observed in intervention duration, subject selection criteria, daily nutritional content and supplements (if any), fluid intake, and conventional countermeasures, etc. Standardizing the deconditioning protocols should be the first step in future AG research since it would allow for more compatible assessments across various studies. This standardization could be achieved by establishing a minimal set of standard measures, primarily before and after AG, but also during AG, focusing on medical events, countermeasure validation, and subject acceptance and comfort. Also, the biomedical measurements should be specifically designed for comparison of gravity level, gravity gradient, and exposure duration.

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