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Brains in space: Effects of spaceflight on the human brain and behavior, volume II

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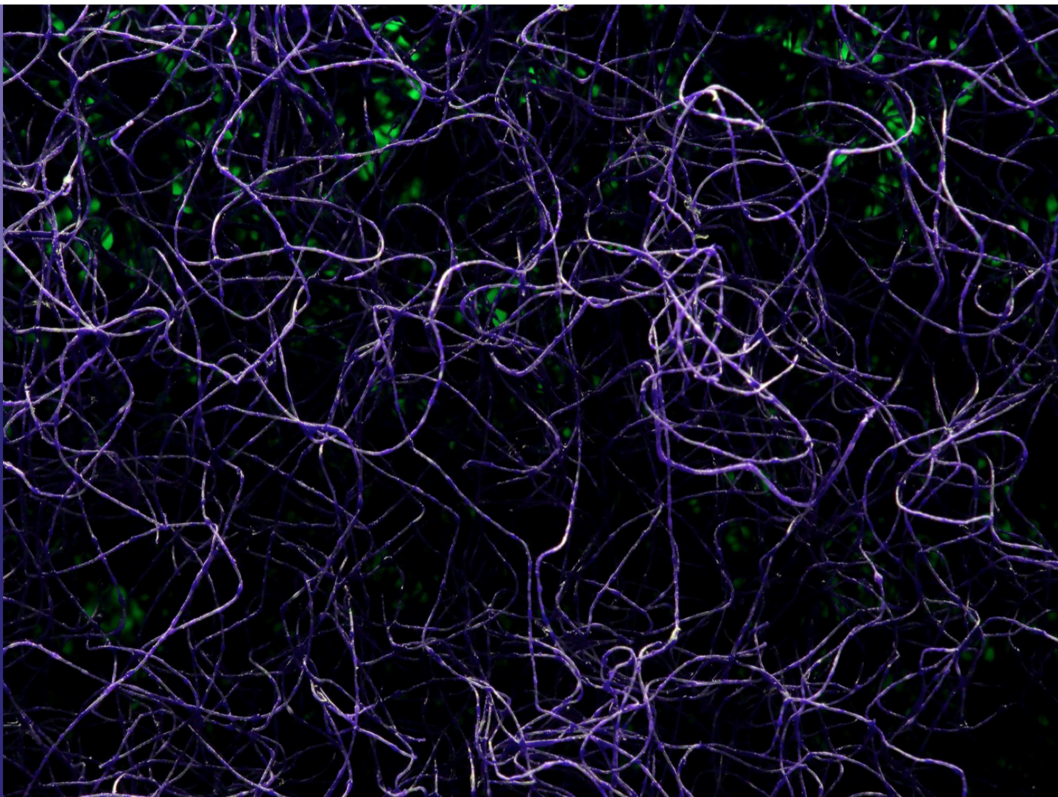
Published in
Frontiers in Neural Circuits
Frontiers in Physiology
Frontiers in Neuroscience
Frontiers in Human Neuroscience



ISSN 1664-8714
ISBN 978-2-8325-4110-4
DOI 10.3389/978-2-8325-4110-4

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Brains in space: Effects of spaceflight on the human brain and behavior, volume II

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Citation
Ricci, R., Goel, R., Roberts, D. R., Tomilovskaya, E. S., Wuyts, F. L., eds. (2023). *Brains in space: Effects of spaceflight on the human brain and behavior, volume II*. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-8325-4110-4

Topic Editor Dr. Donna R. Roberts is an advisory board member for Guerbet and GE Healthcare, and receives research funding from Guerbet. Topic Editor Dr. Rahul Goel is consulting for a private company (all.health). The other Topic Editors declare no competing interests with regard to the Research Topic subject.

Table of contents

frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 17 March 2023
DOI 10.3389/fphys.2023.1141078

OPEN ACCESS

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SPECIALTY SECTION
This article was submitted to
Environmental, Aviation and
Space Physiology,
a section of the journal
Frontiers in Physiology

RECEIVED 09 January 2023
ACCEPTED 03 March 2023
PUBLISHED 17 March 2023

CITATION
Kuldavletova O, Navarro Morales DC,
Quarck G, Denise P and Clément G
(2023), Spaceflight alters reaction time
and duration judgment of astronauts.
Front. Physiol. 14:1141078.
doi: 10.3389/fphys.2023.1141078

Spaceflight alters reaction time and duration judgment of astronauts

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We report a study on astronauts aimed at characterizing duration judgment before, during, and after long-duration stays on board the International Space Station. Ten astronauts and a control group of 15 healthy (non-astronaut) participants performed a duration reproduction task and a duration production task using a visual target duration ranging from 2 to 38 s. Participants also performed a reaction time test for assessing attention. Compared to control participants and preflight responses, the astronauts' reaction time increased during spaceflight. Also, during spaceflight, time intervals were under-produced while counting aloud and under-reproduced when there was a concurrent reading task. We hypothesize that time perception during spaceflight is altered by two mechanisms: (a) an acceleration of the internal clock through the changes in vestibular inputs in microgravity, and (b) difficulties in attention and working memory when a concurrent reading task is present. Prolonged isolation in confined areas, weightlessness, stress related to workload, and high-performance expectations could account for these cognitive impairments.

KEYWORDS

duration judgment, internal clock, memory, spaceflight, time perception

Introduction

During long-duration spaceflight, astronauts have reported periods of temporary cognitive impairment, which they often describe as "space fog", a "sensory saturation", or a "task distraction at work". This cognitive impairment is characterized by poor concentration, increased errors, altered time awareness, motor slowing, and difficulty with multi-tasking, which results in diminished ability to perform the tasks for which astronauts have been trained (Kanas and Manzey, 2008). Spaceflight might affect these functions through direct microgravity effects or through stress effects associated with sleep loss, physical fatigue due to workload, over-extended tasking, excessive noise, or the emotional burdens of adapting to the novel, hostile environment.

The control of vehicles and other complex systems places high demands on cognitive and psychomotor functions and could therefore be impaired by the conditions of spaceflight. More specifically, spatial and temporal abilities are particularly important when moving or controlling a vehicle. Previous research suggests that spatial abilities, such as an object's distance and depth, are underestimated when subjects are in microgravity during parabolic (Clément et al., 2008) and orbital (Clément et al., 2013) flight and in patients with vestibular disorders (Clément et al., 2009). The interpretation of these underestimations is that the adaptive changes in the processing of gravitational information by the neuro-vestibular system alter the construction of spatial maps (Clément et al., 2015; Stahn et al., 2020). In contrast, the temporal abilities have received very little attention during spaceflight. Some previous studies reported underestimates of time durations in weightlessness, suggesting a time-compression effect for spaceflight (Albery and Repperger, 1992; Clément, 2018). When astronauts were asked to perform periodic arms movements with the same rhythm as a metronome and continue after the metronome had been switched off, the variability of inter-response intervals significantly increased during spaceflight (Semjen et al., 1998a; 1998b). During time production tasks, some astronauts overestimated a 2-s interval during a short-duration space flight (Ratino et al., 1988), whereas other astronauts underproduced a 1-min interval, and underestimated intervals in the range of hours during long-duration spaceflight compared to preflight baseline (Navarro Morales et al., 2023).

This study aimed to further evaluate the effects of long-duration spaceflight on time perception. Four prospective temporal tasks were used: two time-interval production tasks (while counting aloud or reading digits), and two time-interval reproduction tasks (reproducing the duration of a visual stimulus while counting aloud or reading digits). Because it is known that attention plays a critical role in time perception (Zakay and Block, 1996), a reaction time task was also used to assess the subject's attention level during these tests.

Methods

Participants

Ten healthy crewmembers (9 male, 1 female; age $M = 44.1$, SD = 4.6) who flew on the International Space Station (ISS) participated in this study. All crewmembers passed a United States Air Force Class III medical examination and had no known history of vestibular or oculomotor abnormalities. 15 healthy subjects (6 females, 9 males; age $M = 43.2$, SD = 18.8) participated in a control study in the laboratory.

The test procedures were approved by the European Space Agency Medical Board and the NASA Johnson Space Center Institutional Review Board and were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All subjects provided written informed consent before participating in the study.

Experimental protocol

Literature data from ground-based studies indicate that time perception may be altered by how the subject counts time (Carlson and Feinberg, 1968), their method of responding (Hornstein and Rotter, 1969), body temperature (Hoagland, 1933), and the time of the day that the test is conducted (Pfaff, 1968). Other variables that have an influence on the perception of time duration include whether the subjects are bored or busy (De Wolfe and Duncan, 1959), the modality (i.e., sound vs. vision) of the stimulus (Goldstone et al., 1959) and possibly the age of the subject (Gilliland and Humphreys, 1943). Most of these constraints were taken into account in our experimental protocol: (a) we used both a production and a reproduction method; (b) there were two attention conditions, i.e., one single-task and one dual-task; (c) we used both auditory and visual instructions; and (d) tests were performed preferably in the morning to avoid fatigue.

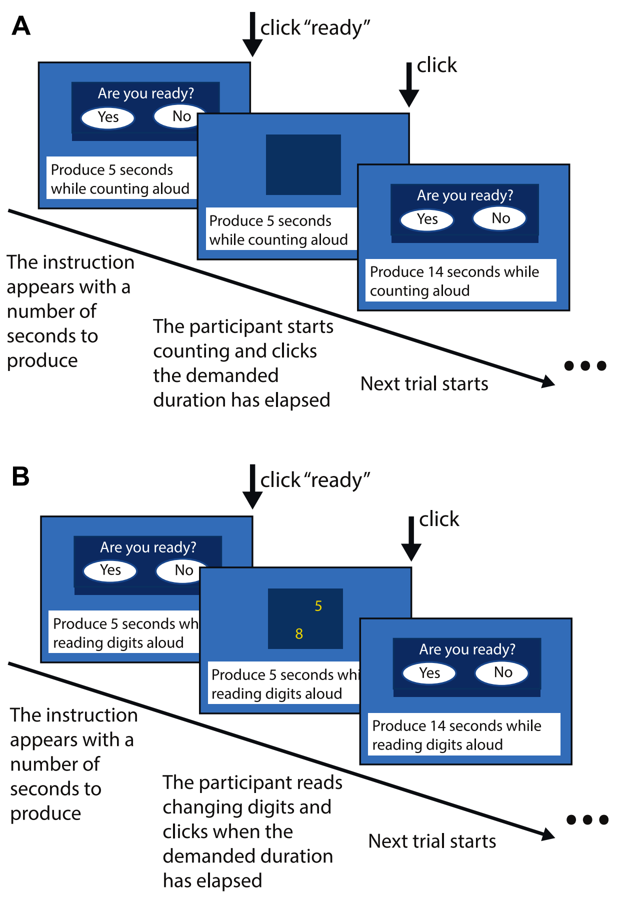

FIGURE 1
Method used for duration production in the single-task **(A)** and the dual-task **(B)** conditions.

The experimental protocol was based on the ground-based studies by Pouthas and Perbal (2004). We used two temporal tasks, i.e., reproduction and production of duration. Subjects performed these tasks in two conditions, a counting condition (single-task) and a concurrent reading condition (dual-task). Nine target durations were used: 2, 3, 5, 7, 10, 14, 20, 28, 38 s. One trial per duration was done during each testing session. The order of the duration to produce/reproduce was randomized.

During the test, subjects wore a head-mounted display (Oculus Rift, Oculus VR, Menlo Park, CA), external noise-cancelling earphones, and used a finger trackball connected to a laptop to report their responses (Navarro Morales et al., 2023). On the ground, this test was performed in the seated upright position; on the ISS, astronauts were in the free-floating conditions. During the free-floating conditions there are no proprioceptive, tactile, or static vestibular cues that participate in spatial orientation. Previous studies have demonstrated that

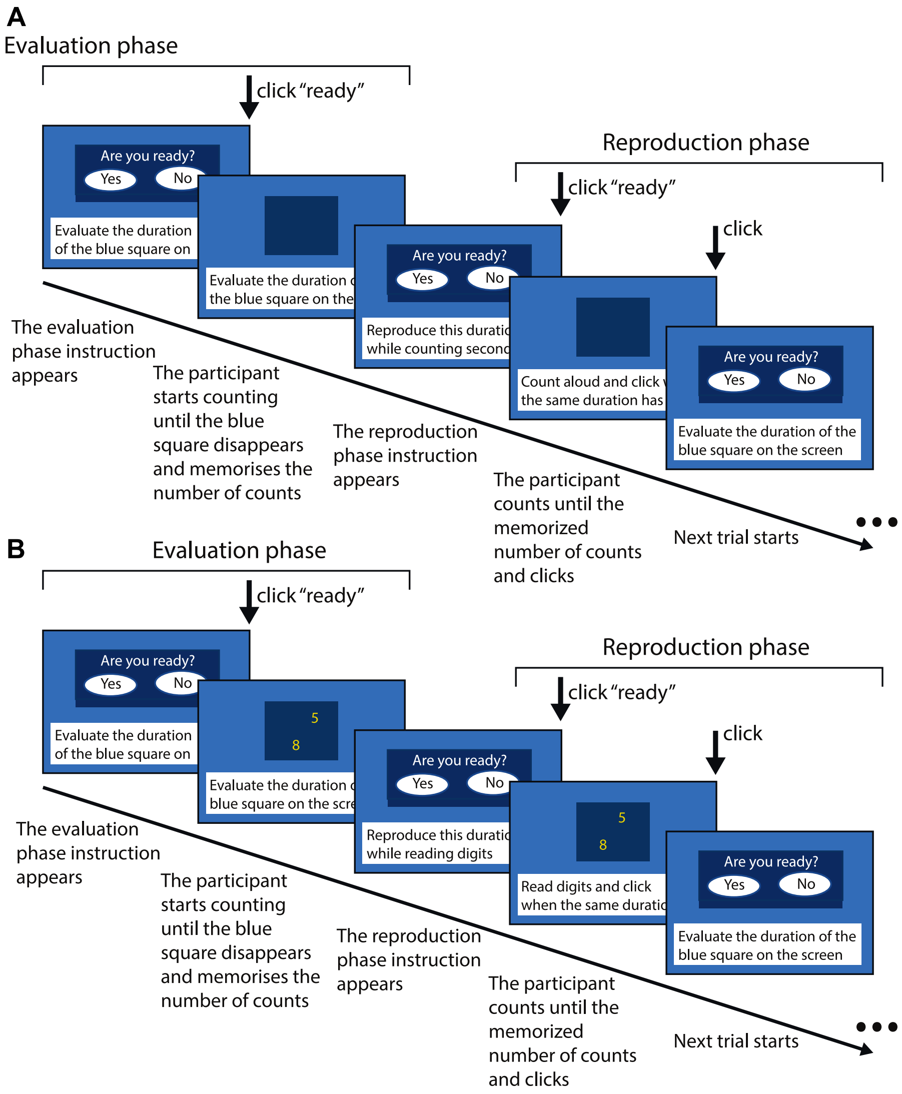

FIGURE 2
Method used for duration reproduction in the single-task **(A)** and the dual-task **(B)** conditions.

the perception of distance and the depth of objects are altered when free-floating in orbit (Clément et al., 2012; 2013). To investigate the relationship between these changes in spatial perception and changes in time perception, the time perception tests were performed in the same conditions as the previous spatial perception tests.

Reaction time

Information processing speed was assessed by a simple reaction-time task, in which participants were required to press on the keyboard with the right hand as fast as possible in response to a stimulus (a blue square) that appeared in the center of the computer screen, at a short random inter-stimulus onset interval (ranging from 1,000 to 2,000 ms) or at a long random interval (from 2,000 to 3,000 ms). Thirty trials were done during each testing session and the intervals were all different.

Duration production

Subjects were instructed to keep the stimulus (blue square) displayed in the center of the computer screen for the target duration given in seconds. At the beginning of each trial, for example the sentence "Produce 14 s" was written at the bottom of the screen and simultaneously pronounced aloud by the computer. Then, the blue square appeared and the subjects were asked to press on the response panel when they judged that the given duration has elapsed (Figure 1).

Duration reproduction

Subjects evaluated the display duration of a blue square presented in the center of a computer screen. At the beginning of each trial, the sentence "Evaluate the target duration" appeared at the bottom of the computer screen and was simultaneously pronounced aloud by a computer-generated voice. Then, the duration was presented (encoding). After the encoding phase, the sentence "Reproduce the duration just evaluated" was displayed and pronounced aloud by the computer. Then, the blue square reappeared and the subjects were asked to press the response panel to erase it when they judged that the previously displayed duration was over (reproduction phase) (Figure 2).

Single task and dual task

Both duration productions and reproductions were performed using a single and a dual-task. In the single-task conditions, the subjects were asked to count aloud for the stimulus duration as regularly as possible and at the rate they preferred throughout the encoding and the reproduction phases of the reproduction task, and during the production of the stimulus duration, given in seconds, in the production task.

In the dual-task conditions, one-digit numbers were presented in random order in the center of the blue square, with a random inter-digit interval between 350 and 950 ms. Subjects were asked to read aloud these digits.

These two conditions were used to study the effects of attention dedicated to the estimation of duration. The reproduction and production responses in the dual-task conditions require simultaneously evaluating the target duration and performing the concurrent reading task. Therefore, attention is divided between the two types of information processing, which impairs the performance during the tasks. We hypothesized that these impairments would be greater in subjects with reduced attention resources, such as when the astronauts report having difficulties with multi-tasking.

Study schedule

In the flight study, the tests were performed before, during, and after 6–8-month spaceflights ($M = 202$, SD = 28 days). The preflight test sessions occurred at launch minus (L-) 205 ± 51 days, L-149 ± 55 days, and L-116 ± 45 days. Inflight test sessions were conducted approximately every month: i.e., on flight day (FD) FD17 ± 6, FD46 ± 8, FD71 ± 6, FD99 ± 7, FD134 ± 8, and FD164 ± 7. After the astronauts returned to Earth, tests were performed at return plus (R+) 1 day, R+5 ± 1 day, and R+9 ± 1 day. The order of the tests (reaction time, single/dual duration judgement, single/dual duration production) was randomized consistent across days.

In the control study, the participants performed the same tests as the astronauts using identical hardware and software as on board the ISS. The control subjects were tested during 3 sessions, to compare with the 3 pre-flight sessions with the astronauts. The control subjects' and astronauts' pre-flight sessions were spaced by 44.1 ± 10.2 days and 45.2 ± 28.4 days respectively. The order of the tests (reaction time, single/dual duration judgement, single/dual duration production) was randomized consistent across days.

Statistical analysis

We examined repeated measures of error in duration production and reproduction (comparing the effects of a single-task and a dual-task) and reaction time before, during, and after spaceflight in 10 crewmembers participating in long-duration missions (>3 months) on board the ISS. Before the flight, crewmembers underwent repeated testing over multiple sessions to allow comparisons with healthy controls and inflight and postflight measurements. The percent errors between the duration judgments and the actual durations were calculated for each target duration, and then averaged for all target durations for obtaining the composite duration percent errors.

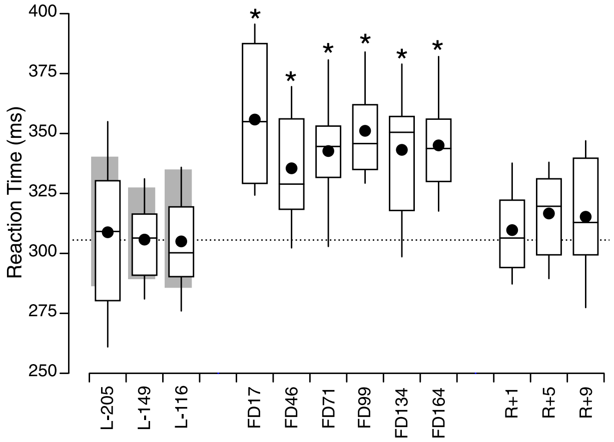

FIGURE 3
Box and whisker (dash: median, closed symbol: mean, Q1 and Q3) plots of reaction time in 10 astronauts before (L-), during (FD), and after spaceflight (R+). The grey bars show mean ± IQR of the 15 ground-control participants. The dotted line shows the mean of the 3 preflight measures in the astronauts. *$p < 0.05$ relative to the mean of the 3 preflight measures in the astronauts.

Statistical analysis of the data was conducted in R (R Core Team, 2017) using linear mixed-effects models fit by maximum likelihood from the *lme4* package (Bates et al., 2015) to take random factors into account. Analysis of variance was done on the models to assess the fixed factor effects using the Satterthwaite's method. Pairwise comparisons were made with the *multcomp* package (Hothorn et al., 2008) using the Dunnett method and FDR method *p*-value adjustment.

First, we compared the ground-based responses of the 2 subject groups to establish whether they differed, and whether the results of the 3 test sessions differed. The hypothesis was that the performance of the astronauts on Earth was not different from the control group. An analysis of variance with mixed effects design was used, with reaction time (ms) or duration judgment error (%) as the dependent variable; test sessions (L-205, L-149, L-116) and subject group (astronauts, control subjects) as fixed effects.

For the comparison between pre-, in- and postflight responses in the astronauts, an analysis of variance with mixed effects design was used, with reaction time (ms) or duration judgment error (%) as the dependent variable; test sessions (1 preflight averaged session, 6 inflight sessions, 3 postflight sessions) as fixed effects; subject and target duration as random effects. The Dunnett method was used for pairwise comparison between in- and postflight responses with the preflight responses. The hypothesis was that duration judgment would be different inflight compared to pre-flight and postflight for the time production task, but not for the time reproduction task.

TABLE 1 Post-hoc pairwise comparisons of preflight responses (mean of L-209, L-149, L-116), with inflight and postflight responses in the astronauts (Dunnett test).

Session	Estimate	SD	Z	*p*
Reaction Time				
FD17	49.295	9.619	5.125	<0.001
FD46	28.964	9.619	3.011	0.0039
FD71	36.150	9.619	3.758	<0.001
FD99	44.582	9.619	4.635	<0.001
FD134	36.641	9.619	3.809	<0.001
FD 164	38.516	9.619	4.004	<0.001
R+1	3.187	9.619	0.331	0.7403
R+5	10.108	9.619	1.051	0.3771
R+9	8.736	9.619	0.908	0.4092
Duration Production Single Task				
FD17	-6.193	1.520	-4.074	<0.001
FD46	-7.711	1.520	-5.072	<0.001
FD71	-4.119	1.520	-2.709	0.0086
FD99	-6.063	1.520	-3.988	<0.001
FD134	-7.870	1.520	-5.177	<0.001
FD164	-8.717	1.520	-5.734	<0.001
R+1	-5.165	1.520	-3.397	0.0010
R+5	-3.826	1.520	-2.517	0.0133
R+9	-2.725	1.520	-1.793	0.0730
Duration Reproduction Dual Task				
FD17	-3.940	2.726	-1.446	0.1906
FD46	-4.563	2.726	-1.674	0.1633
FD71	-8.413	2.726	-3.087	0.0087
FD99	-8.111	2.726	-2.976	0.0087
FD134	-8.648	2.726	-3.173	0.0087
FD164	-7.723	2.726	-2.833	0.0103
R+1	-4.370	2.726	-1.603	0.1633
R+5	-2.227	2.726	-0.817	0.4139
R+9	2.232	2.726	0.819	0.4139

Results

Reaction time

During the three test sessions performed on the ground before the flight, there was no significant difference in reaction time between the astronauts and the control participants [F (25, 1) = 0.242, $p = 0.626$]. There were also no significant differences between the results of the 3 ground-based tests sessions [F (50, 2) = 0.599, $p = 0.553$]. In the astronauts, reaction time was significantly different between sessions [F (90, 9) = 7.241, $p < 0.001$]. The responses during all the inflight test sessions were significantly greater than the mean of the 3 preflight sessions (Figure 3; Table 1).

Duration judgment

Preflight, there were no significant differences between astronauts and control participants in duration judgments for the duration production in a single task, [F (25, 1) = 0.013, $p = 0.910$]; the duration production in a dual task [F (24.97, 1) = 0.091, $p = 0.766$]; the duration reproduction in a single task [F (24.97, 1) = 0.001, $p = 0.976$]; or the duration reproduction in a dual task [F (24.74, 1) = 0.0954, $p = 0.760$]. There were also no significant differences between the 3 test sessions on the ground for the duration production in a single task [F (650, 2) = 0.346, $p = 0.707$]; the duration production in a dual task [F (641.82, 2) = 0.304, $p = 0.304$]; the duration reproduction in a single task [F (641.05, 2) = 1.615, $p = 0.199$]; or the duration reproduction in a dual task [F (641.84, 2) = 0.825, $p = 0.439$] (Table 1).

During the duration production preflight the subjects overestimated the target duration, and this overestimation was larger in the dual task (20.6 ± 14.3%, mean error ±SD for all target durations) than in the single task (4.7 ± 15.7%) conditions. During the duration reproduction, the subjects were quite accurate in the single-task conditions (0.7 ± 4.4%). However, they also overestimated the durations in the dual-task conditions (9.3 ± 11.7%) (Figure 4).

The duration production single task error (%) differed significantly across sessions [F (890, 9) = 6.129, $p < 0.001$]. The duration judgment errors during all inflight test sessions, as well as during the two first postflight sessions (R+1 and R+5) differed significantly (towards an underestimation) from the mean preflight errors (Table 1). No differences in errors were found between sessions for the duration production dual task [F (881.94, 9) = 1.587, $p = 0.115$] and the duration reproduction single task [F (881.77, 9) = 1.644, $p = 0.1$]. However, during the duration reproduction dual task, the error differed significantly between sessions [F (9, 881.89, 9) = 3.80, $p < 0.01$]. This was particularly the case from FD71 to FD164. The duration judgment error in the postflight sessions was not significantly different from the mean of the preflight measures (Figure 5; Table 1).

Discussion

This study evaluated reaction time and duration judgments in astronauts during space flight and on the ground, before and after flight. The reaction time increased throughout the flight compared to the preflight level and returned to baseline levels on R+1. When asked to produced durations ranging from 2 to 38 s while counting aloud (single task), the astronauts overestimated these durations before the flight. This overestimation decreased and the astronauts' judgments were essentially correct during the flight and for a few days after landing. When asked to reproduce a duration while simultaneously reading digits (dual task), the overestimation that was observed on the ground also decreased and the astronauts' judgments were essentially correct by FD71 and beyond.

Reaction time

Our results show a 39-ms increase in reaction time during spaceflight compared to pre- and postflight. In contrast, other studies in astronauts have reported no consistent changes in reaction time during a single task (Ratino et al., 1988; Benke et al., 1993; Thornton et al., 1993). This difference could be due to methodological factors in these earlier studies, such as lower number of subjects (from single case to 4) and incomplete data sets

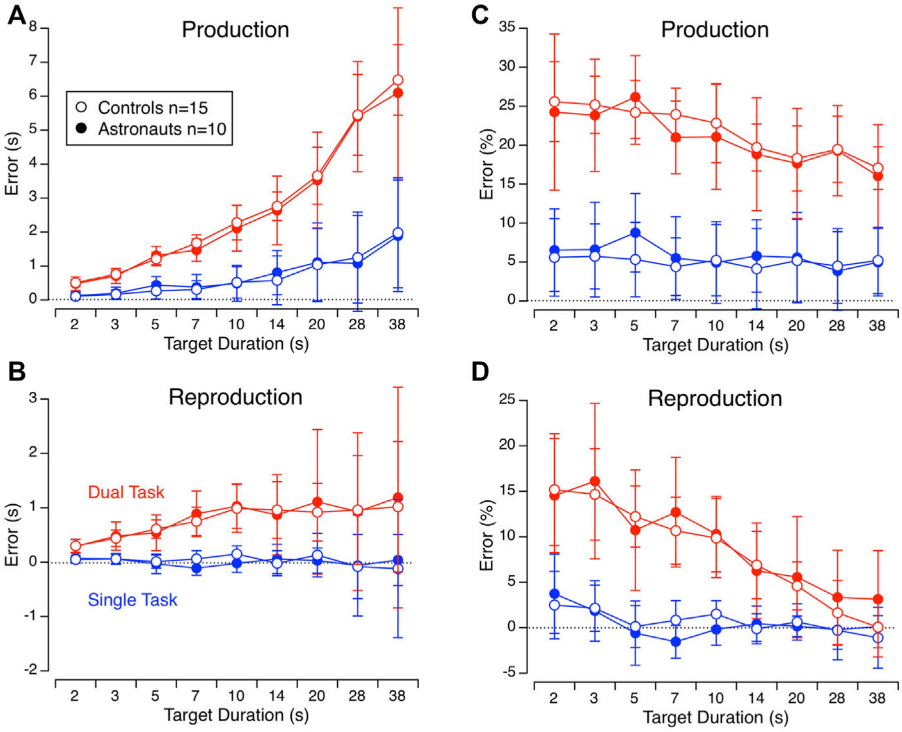

FIGURE 4
Mean ± SD of error in duration judgments (in s) for the 9 target durations in astronauts and control participants during duration production **(A)** and reproduction **(B)** in the single task (in blue) and the dual task (in red) conditions preflight. **(C,D)** Same data expressed in percent error.

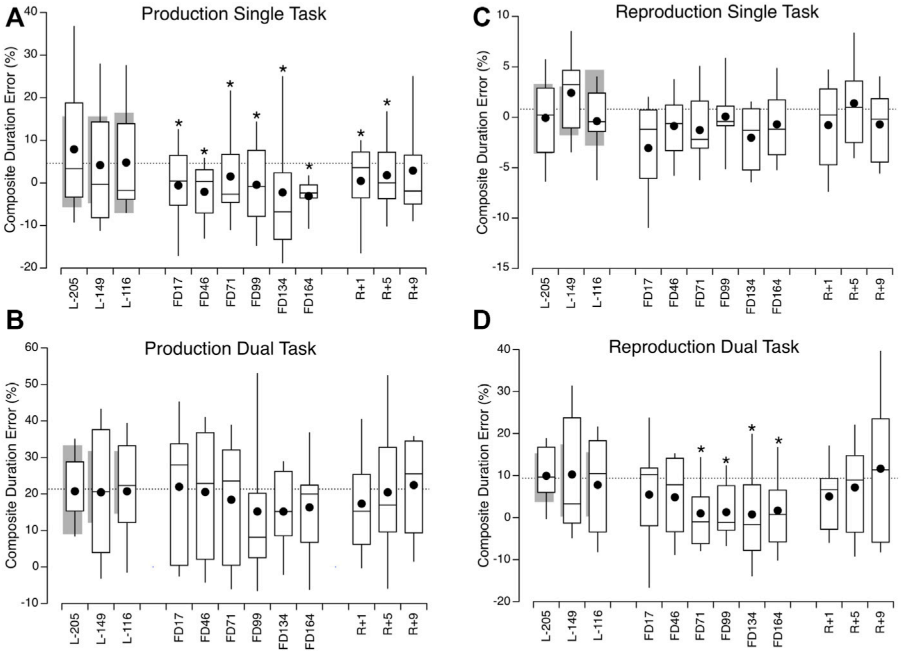

FIGURE 5
Box and whisker plots of composite duration percent error in 10 astronauts before (L-), during (FD), and after spaceflight (R+) during duration production in the single task **(A)** and dual task **(B)** conditions, and during duration reproduction in the single task **(C)** and dual task **(D)** conditions. The grey bars show mean ± IQR of the 15 ground-control participants. The dotted lines show the mean of the 3 preflight measures in the astronauts. $^*p < 0.05$ relative to the mean of 3 preflight measures in the astronauts.

(Kelly et al., 2005). Moore et al. (2019) found no change in reaction time postflight compared to preflight, which is in agreement with our results, but they did not measure reaction time during the flight. Other studies have tested astronaut's reaction time inflight using dual tasks, such as simultaneously aiming and tracking, recognizing numbers, adjusting lines, with conflicting results (Bock et al., 2010; Moore et al., 2019; Takács et al., 2021; Tays et al., 2021; Tu et al., 2022; Weber and Stelzer, 2022). Comparison with the results of these earlier studies is difficult because these tests evaluated additional cognitive resources, such as decision-making and memory, than the reaction time single task in our study. The increase in reaction time during the flight seen in our study can result from numerous factors, among which are diminished attention, or sensorimotor perturbations. "Space fog" is a complex multifactorial phenomenon that could account for the increase in reaction time observed in astronauts during this study. However, space fog seems to be particularly troublesome at the beginning of the flight, with some acute symptoms usually disappearing as the body adjusts to microgravity (Welch et al., 2009). This is differing from our results, which indicate that the increase in reaction time remains relatively consistent throughout the flight.

Single-task duration judgment

In the duration production single-task condition, the astronauts produced shorter durations inflight compared to the durations produced before the flight. In other words, their subjective time was accelerated. Similar results had previously been observed during short periods of microgravity in parabolic flight (Clément, 2018). Two main models have been proposed to describe on how our brain represents time (Maniadakis and Trahanias, 2014). The first category, also known as extrinsic or centralized models, assumes that the brain uses a time-dedicated neural circuit to encode elapsed time like a clock (Gibbon et al., 1984). In the second category, also known as intrinsic or distributed, time is encoded in the activity of general and inherent property of neurons (Wackermann and Ehm, 2006). Unfortunately, it is difficult to validate these latter models in absence of neuronal activity recordings in humans.

Therefore, we will focus this discussion on how the astronauts' results could be described using the internal clock model. This model consists of three stages: (a) the first stage includes a pulse generator (or internal pacemaker) whose activity is modulated by attention and arousal, and an accumulator which counts the number of pulses; (b) the second stage is where the pulses reach the working memory module; and (c) the third stage is where decision mechanisms compare the pulses accounted with previous lived events. An increase in the pace of the pulse generator, or an increase in the efficiency of the accumulator, will lead to the perception that external events are slow and to the production of shorter-than-demanded time intervals (Church, 1984).

Performance in the duration production task depends on the speed at which pulses are accumulated, in other words on clock speed and information processing speed. In addition, this task not only requires short-term (working) memory storage in order to maintain the temporal information (i.e., time basis pulses) throughout the trial, but also necessitates long-term memory in which the representation of several durations will be stored. Because the durations to produce are given in conventional units of time (seconds), this long-term memory can be viewed as semantic memory (Pouthas and Perbal, 2004). The underestimation in the duration production in astronauts could thus be interpreted by such an increase in the frequency of the pulse generator. The results of another space study also support a potential acceleration of the internal clock in microgravity. In the Semjen's (1998a), Semjen's (1998b) study mentioned earlier, astronauts tapped with a higher frequency when the metronome was turned off while in space compared with their pace on the ground.

Performance in the duration reproduction task not only requires short-term memory storage during the encoding of the target duration, but also necessitated retrieval from long-term storage, because of the limited capacity of short-term memory (Pouthas and Perbal, 2004). Our results did not indicate any change in the duration reproduction single task throughout the flight. This finding is also compatible with the internal clock model, which predicts that duration reproduction tasks are insensitive to the pacemaker-accumulator rhythm alterations (Church, 1984). Indeed, an increase of the rate of the internal clock pulses would lead to an overestimation of the target duration during the evaluation phase, as more pulses would accumulate, which would then be compensated by a "faster" production in the reproduction phase. In other words, what is reproduced by the subjects are not seconds or other arbitrary units, but the number of internal clock pulses, which will match in the evaluation and reproduction phases regardless of the rate of the internal clock.

Dual-task duration judgment

Assuming that the pacemaker rate was accelerated by spaceflight, then the duration production should be underestimated during spaceflight in the dual task as in the single task conditions. Such change was not observed in our study. Nevertheless, the overall errors in the dual task are much larger than the errors in the single task, and the variability across subjects is also larger in the dual task than in the single task. It is possible that other mechanisms than the acceleration of the internal clock could also affect the response. "The attentional gate model" proposes that the greater attention on time, more pulses are counted and time seems to slow down. Conversely, with distractions, fewer pulses are counted (or pulses are missed), and time seems to be accelerated (Zakay and Block, 1996). The increase in reaction time during the flight also testifies to a decrease in attention. Dual-tasking is cognitively and attentionally challenging. Attention difficulties are commonly been reported during spaceflight (Welch et al., 2009), which makes dual-tasking even more challenging. Different levels of attention in our subjects could account for greater variability in responses, which would make it more difficult to observe significant changes in our measures.

The duration reproduction dual task was the most cognitively demanding of the 4 tasks used in this study. Participant had to (a) estimate how much time had elapsed; (b) retrieve the time stored on the working memory and compare it to the time elapsed; and (c) read digits. Given that microgravity impairs attention (as indicated by the increased reaction time inflight), the cognitive demand increases even more. Nevertheless, we observed smaller errors in duration reproduction in the dual task in the astronauts from FD71 through the remaining inflight sessions compared to preflight. In fact, the duration judgments tended to be underestimated compared to preflight. Ground-based studies have shown that time intervals tended to be underestimated when the difficulty of the dual task increased (Brown, 1997; Block et al., 2010). Other ground-based studies have found that the ability to reproduce a previously experienced duration is largely affected by attention and working memory abilities (Baudouin et al., 2006; Broadway and Engle, 2011). Pouthas and Perbal (2004) have observed that amnesic patients and elderly participants under-reproduce time intervals in dual-tasks, but their time productions don't differ from control subjects. Since the duration production in a dual task does not require working memory abilities, these authors conclude that this underestimation of duration is due to an inadequate retrieval of information in the episodic memory. A strong correlation between the accuracy of the duration estimates and the responses to neuropsychological memory test in these patients reinforces this interpretation (Pouthas and Perbal, 2004).

The results of 29 studies performed on 32 crewmembers during short-duration flights indicate some cognitive performance degradation in the space environment. Choice reaction time, memory, reasoning, attention switching, pattern recognition, movement time, and dual task performance, all indicated some impairment (Casler and Cook, 1999). Astronaut's core body temperature increase during spaceflight, which could impair physical and cognitive performance (Stahn et al., 2017). Space motion sickness may have been a contributor to impairments observed in choice reaction time and memory, but other impairments were observed after space motion sickness symptoms had vanished. The deficits tend to resolve in 3 weeks. However, it is not known whether impairment persists during long-duration missions since most of the above studies were performed during flights ranging from a few days to a few weeks only. The lack of long-term studies is an issue because any effects on cognitive abilities should be more intense during longer stays (Manzey and Lorenz, 1998; Fowler et al., 2000). Tests performed with one cosmonaut during a 438-day spaceflight using a dual task with a simultaneous memory search indicated that there were significant deficits during the first month of the spaceflight. Also included in this study were measures to assess the subjective emotional balance and fatigue of the participant. An analysis showed that these measures were correlated with dual-task performance (Manzey et al., 1998).

Time and space in the brain

Brain imaging studies in returning astronauts have shown that spaceflight disrupts the connectivity in the right temporo-parietal junction (TPJ) (Van Ombergen et al., 2017). This brain area has been shown to be involved in time interval judgments and timing (Bosco et al., 2008; Davis et al., 2009). Lesion of the right TPJ or transcranial direct current stimulation of the right TPJ in healthy subjects were found to impair their spatial and temporal perception (Kaski et al., 2016; Dalong et al., 2021). Patients with right temporal resection lesions also present an acceleration in their internal clock during time production tasks (Pouthas and Perbal, 2004). It has been suggested that the disruption of the connectivity in the right TPJ in microgravity is related to changes in vestibular function (Van Ombergen et al., 2017). Indeed, the TPJ participates in the integration of multisensory modalities and in gravity estimation, and it receives constant stimulation from the vestibular receptors. In patients with unilateral vestibular hypofunction, vestibular perception may be persistently impaired in the duration domain, even when the other domains, such as position and velocity/acceleration perception, remain intact (Kwon et al., 2022). Vestibular stimulation has been found to affect the time perception in healthy subjects (Utegaliyev et al., 2022). Weightlessness unloads the graviceptive part of the vestibular system, significantly altering the sensory inflow to the brain areas treating the vestibular information, including the TPJ. Therefore, these alterations in the sensory flow might affect the function of this area, altering spatial judgments, such as the perception of distance, object size, and motion (Clément et al., 2016; Clément et al., 2015; Clément et al., 2013; Clément and Wood, 2014) as well as temporal judgments (Clément, 2018).

It has even been proposed that time perception is a way for the brain to evaluate the aspects of Newtonian dynamics and is therefore contributing to its internal models to estimate gravity (Lacquaniti et al., 2015). A recent study by Gravano et al. (2021) showed that astronauts estimated the duration of an imaginary ball motion differently inflight than before flight. The estimated duration of imaginary ball motion represents an equivalent of duration judgment but based on an internal representation of object dynamics rather than on external inputs, as is the case in the present study. However, the authors did not find a statistical difference between the perceived ball motion duration inflight and on the ground, suggesting that adaptation to spaceflight did not affect the internal representation of elapsed time, but affected the astronaut's movements.

In conclusion, this study shows an alteration of the time perception during spaceflight, which could be due to multiple mechanisms such as the acceleration of the internal clock and degradation of attention and memory. These changes might be provoked by the stress due to isolation in confined areas, heavy workload, and high-performance expectations, but also by the modifications of the vestibular inputs in weightlessness. Future studies on reaction time and duration judgement would benefit from collecting subjective reports or objectives measures of what astronauts refer as space fog to compare the results on a temporal scale.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the European Space Agency Medical Board and the NASA Johnson Space Center Institutional Review Board.

Author contributions

OK, DM, GQ, and PD contributed to data analysis and manuscript; GC contributed to study design, data collection, data analysis, and manuscript.

Funding

European Space Agency provided access to the astronauts and the International Space Station (no grant number), Centre National d'Etudes Spatiales provided the equipment and travel support for the investigators (grant # 2022/480001180), Région Normandie provided financial support for data analysis and publication (grant # 00115524-210E06581).

Acknowledgments

The authors thank François Derache and Maurice Marnat from CNES/CADMOS for their help in implementing this experiment and Tim Macaulay for editing the manuscript.

Conflict of interest

Publisher's note

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frontiers | Frontiers in Neural Circuits

TYPE Original Research
PUBLISHED 12 April 2023
DOI 10.3389/fncir.2023.1157228

OPEN ACCESS

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RECEIVED 02 February 2023
ACCEPTED 27 March 2023
PUBLISHED 12 April 2023

CITATION
Lyakhovetskii V, Chetverikov A, Zelenskaya I, Tomilovskaya E and Karpinskaia V (2023) Perception of length and orientation in dry immersion.
Front. Neural Circuits 17:1157228.
doi: 10.3389/fncir.2023.1157228

Perception of length and orientation in dry immersion

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Introduction: How does gravity (or lack thereof) affect sensory-motor processing? We analyze sensorimotor estimation dynamics for line segments with varying direction (orientation) in a 7-day dry immersion (DI), a ground-based model of gravitational unloading.

Methods: The measurements were carried out before the start of the DI, on the first, third, fifth and seventh days of the DI, and after its completion. At the memorization stage, the volunteers led the leading hand along the visible segment on a touchscreen display, and at the reproduction stage they repeated this movement on an empty screen. A control group followed the same procedure without DI.

Results: Both in the DI and control groups, when memorizing, the overall error in estimating the lengths and directions of the segments was small and did not have pronounced dynamics; when reproducing, an oblique effect (higher variability of responses to oblique orientations compared to cardinal ones) was obtained. We then separated biases (systematic error) and uncertainty (random error) in subjects' responses. At the same time, two opposite trends were more pronounced in the DI group during the DI. On the one hand the cardinal bias (a repulsion of orientation estimates away from cardinal axes) and, to a small extent, the variability of direction estimates decreased. On the other hand, the overestimation bias in length estimates increased.

Discussion: Such error pattern strongly supports the hypotheses of the vector encoding, in which the direction and length of the planned movement are encoded independently of each other when the DI disrupts primarily the movement length encoding.

KEYWORDS

visuomotor processing, motor oblique effect, hypermetria, orientation, dry immersion (DI)

1. Introduction

The problems of space travel have been in focus of scientists for several 100 years. Kepler (1634) proposed to choose men with good health and sedate them to prevent damage of start acceleration. Tsiolkovsky (1920), describing awake astronauts, predicted that they would be subject to phantasmagorical sensations due to a loss of body weight sensation. Indeed, empirical studies show that adaptation to weightlessness affects how astronauts perceive the world (Paloski et al., 2008; Arshad and Ferré, 2022). For example, Kornilova (1997) showed that such adaptation creates spatial orientational illusions that are illusions pertaining to subjects position or illusions of self- and surround-motion. Some studies show that the mental representation of the vertical dimension of objects is altered in space (Clément, 2007). However, despite a long-time interest in the topic of perceptual distortions in space, there are relatively few studies investigating how they arise.

The onset of changes varies for different visual phenomena. Clément et al. (2012) showed that the strength of inverted-T illusion (overestimation of the length of a vertical line relative to a horizontal line of the same length) measured in an adjustment task lowered significantly only on the fifth month of spaceflight, while the ratio of vertical to horizontal line during drawing a cross or square diminished earlier, after 1 month of spaceflight. That is, two similar perceptual effects related to perception of horizontal and vertical lines, but measured differently, were both affected by weightlessness but with varying onsets of changes. Such difference in dynamics of perception of vertical dimension in these two tasks may be due to more involvement of the dorsal stream in performance of the latter one (Karpinskaia et al., 2022). This highlights the importance of studying the dynamics of visual perception during adaptation to weightlessness.

In the current project, we aimed to study the dynamics of length and orientation perception in a simulated weightlessness using the dry immersion (DI). DI is one of the ground-based models of spaceflight allowing to study the effects of space flight in a well-controlled environment. During DI, the volunteer is laying on the rubber textile in the bath filled with warm water (Tomilovskaya et al., 2019). The vestibular system activity changes due to elimination of the support and minimization of proprioceptive afferentation.

Orientation and length are well-studied low-level visual features, important for downstream visual processing in the brain. However, there are only a few studies analyzing how processing of these features is affected by weightlessness (Lipshits and McIntyre, 1999; Lipshits et al., 2005; McIntyre and Lipshits, 2008). Interestingly, orientation perception is characterized by systematic anisotropies: the precision of estimates is lower for oblique orientations compared to cardinal (the oblique effect) while at the same time the responses are biased away from the cardinal orientations toward oblique ones (the cardinal bias; see Appelle, 1972; Tomassini et al., 2010; Girshick et al., 2011; Wei and Stocker, 2017). Despite the absence of a gravitational vertical, this pattern of responses persists at the end of the first month of spaceflight during performing different types of adjustment tasks (visual and haptic, McIntyre and Lipshits, 2008), that is constant and variable errors reflecting bias and SD of orientation estimation do not change.

However, previous studies used an adjustment task with a joystick even in a haptic domain, and the use of such an instrument activates to a greater extent the ventral stream (Ferrari et al., 2005) presumably less affected by gravity change (Karpinskaia et al., 2022). Considering that, firstly, DI influences the hand movements similarly to real microgravity (Kornilova et al., 2011), and, secondly, the hand movements turned out to be more sensitive to anisotropy of human perception during spaceflight than the adjustment procedure (Clément et al., 2012), we chose the motor version of oriented segments task (Smyrnis et al., 2007; Pantes et al., 2009). The use of the motor task allows also to register simultaneously the length and the orientation of a given segment. We hypothesized that DI would gradually alter the perception of segment length and/or its orientation.

2. Materials and methods

The DI group consisted of 10 male volunteers (30.9 ± 4.6 years) who were in a 7-day DI. The control group consisted of 22 volunteers (5 males and 17 females, 31.6 ± 7.6 years). In the DI group, the measurements were performed before immersion (D0), on the 1st (DI1), 3rd (DI3), 5th (DI5), and 7th (DI7) day of DI, and after its end (R + 1). The subjects were admitted to participate in the experiment by a medical expert commission and signed an Informed Consent to participate in the study in accordance with the provisions of the Helsinki Declaration of Human Rights. The research procedures were preliminary reviewed and approved by the Commission on Biomedical Ethics of the Institute of Biomedical Problems of the Russian Academy of Sciences (Protocol No. 1 of Sept. 09, 2021). To mimic the time course of measurements in DI, the control group was studied on the 1st (D0), 2nd (D1), 4th (D3), 6th (D5), and 8th (D7) days.

The black segments oriented at −22.5°, 0°, 22.5°, 45°, 67.5°, 90°, 112.5°, and 135° to the horizontal (**Figure 1A**) were presented on a white background in random order in the center of the volunteer's visual field, 4 presentations for each orientation. The set of orientations was similar to that used in Lipshits and McIntyre (1999). The centers of the segments were in the center of the volunteer's visual field. The segments started from different points of the visual field, so the volunteer didn't get used to the stable initial point of his/her movement.

In the DI group, stimuli were presented on the LCD optical multi-touch monitor (IIYAMA Prolite T2252MTS, iiyama, Tokyo, Japan) with a viewable area of 476 by 268 mm [gamma value of 2.2, color temperature (white point) of 6500K, and luminance during touch of 200 cd/m^2]. The size of the presented segment was 10 cm. A notebook (Acer Spin SP111-34N, Xizhi, Taiwan) with a touchscreen having a viewable area of 260 by 143 mm [gamma value of 2.2, color temperature (white point) of 6500K, and luminance during touch of 250 cd/m^2] was used for the longitudinal control group study. The size of the presented segment was 5.4 cm. For both groups, the screen resolution was 1920 × 1080.

The participant was in a semi-sitting position (**Figure 1C**) in a bath (during DI) or on the couch in front of the monitor, at a distance of 60−80 cm to establish the comfort hand movement over the screen surface. Their task was to reproduce the lengths and directions of the segments with the dominant (in our groups, right) hand. First, at the memorization stage, the volunteer moved the index finger of the dominant hand from left to right (from top to bottom in the case of a vertical segment) along the visible segment (**Figures 1B, C**). When the subject lifted his hand from the screen, the experimenter pressed a button on the keyboard, the segment disappeared, and the volunteer reproduced the memorized parameters of the given segment at the same location on an empty screen immediately. The experiment was performed without feedback.

The coordinates of start and end points of the hand movements were determined on the touch screen. Based on these coordinates, the estimated length of the segment was calculated as the Euclidean distance between the start and end points of the hand movement, and its direction was determined. The segment length estimation error was determined as the difference between the segment length determined by the volunteer and the known segment

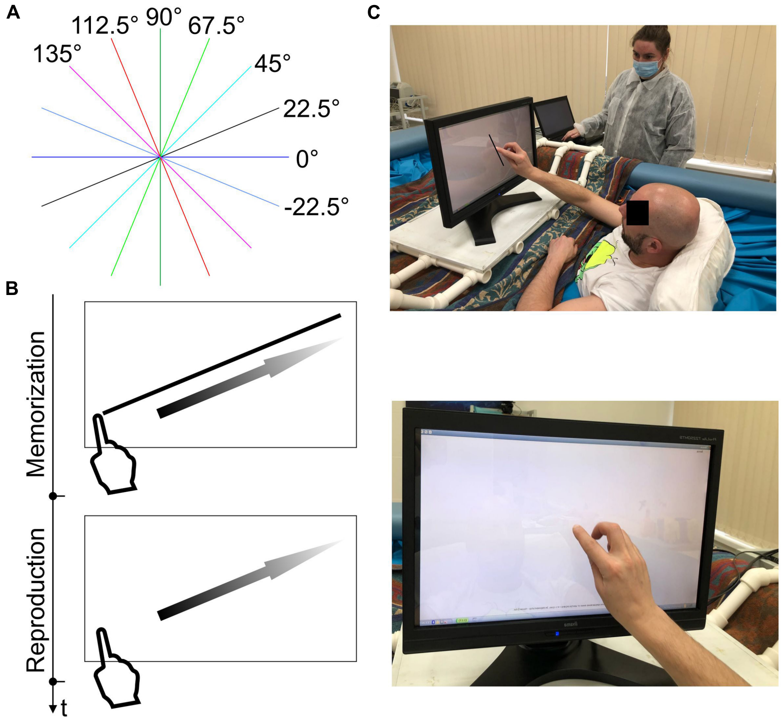
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FIGURE 1
Experimental design. **(A)** Stimuli material. One segment directed at the specified angle was presented in each probe (segments are colored for demonstration purposes). **(B)** In the memorization stage, the volunteer moved the index finger of his dominant hand over the segment. Then the experimenter pressed the button on the keyboard, the stimulus disappeared, and the volunteer reproduced the memorized parameters of the given segment at the same location on an empty screen. **(C)** Memorization and reproduction stages during dry immersion.

length, the segment direction estimation error as the difference between the segment direction determined by the volunteer and the known segment direction. To calculate the cardinal bias, we analyzed the errors for orientations between cardinal and oblique ones (−22.5°, 22.5°, 67.5°, and 112.5°) with the sign for orientations where a negative bias is expected (−22.5° and 67.5°). The bias of length estimation for segments of non-cardinal orientations was calculated as the mean non-cardinal segment length estimation error.

We analyzed separately the obtained datasets for two groups. Approximately a quarter of studied datasets were not distributed normally by D'Agostino-Pearson criterion. Thus the significance of differences between the obtained values was assessed using the paired samples Wilcoxon test with Bonferroni correction at $p < 0.05$. Data are presented as mean ± standard deviation.

3. Results

At the memorization stage, when the participant moved the hand over the visible segment, the errors of estimation of both length and orientation were considerably small (Figure 2). Both groups overestimated the length of the segment (0.32 ± 0.28 cm, $U(22) = 245$, $p < 0.001$ and 0.26 ± 0.14 cm, $U(10) = 54$, $p < 0.01$, for control and DI group, respectively), and this overestimation didn't depend on the day of measurement (with the unique exception of the increase of overestimation of the horizontal segment in DI7 relative to DI3 in the DI group, $p < 0.01$) (**Figure 2A**). The error of orientation didn't also have any pronounced dynamics. In the control group, this error diminished in D7 relative to D5 for the horizontal segment ($p < 0.001$), and increased in D7 relative to D5 for the 22.5° segment ($p < 0.01$). In the DI group, the orientation error of the −22.5° segment diminished in DI7 relative to the DI5 ($p < 0.01$) (**Figure 2B**).

At the reproduction stage when the participant moved the hand over the empty screen the length and orientation errors possessed different dynamics (**Figure 3**). Both groups overestimated the length of the segment (0.41 ± 0.39 cm, $U(22) = 234$, $p < 0.001$, and 0.98 ± 0.39 cm, $U(10) = 55$, $p < 0.01$, for control and DI group, respectively) (**Figure 3A**). In the control group, the overestimation increased in relation to D0 only for the −22.5° segment and for the 112.5° segment ($p < 0.01$). The estimated length of the horizontal segment is significantly larger than the length of the vertical segment in the D7 only ($p < 0.01$).

In the DI group, the overestimation dynamics is more pronounced. The mean linear trend of increasing overestimation was 0.10 ± 0.02 in DI group vs. 0.02 ± 0.01 in control group ($W(8) = 36$, $p < 0.01$). The overestimation increased for all orientations of the segment relative to D0 (all $ps < 0.01$). The overestimation is increased not only in comparison with D0 but for −22.5°, and 0° segments in comparison to DI1, and for the 90° segment in comparison to DI3 (all $ps < 0.01$).

In both groups, we observed the cardinal bias (Smyrnis et al., 2007) during all study (**Figure 3B**). The volunteers underestimated the orientation of −22.5°, and 67.5° segments (4.3 ± 1.4°, $U(22) = 253$, $p < 0.001$, and 2.5 ± 1.3°, $U(10) = 55$, $p < 0.01$,

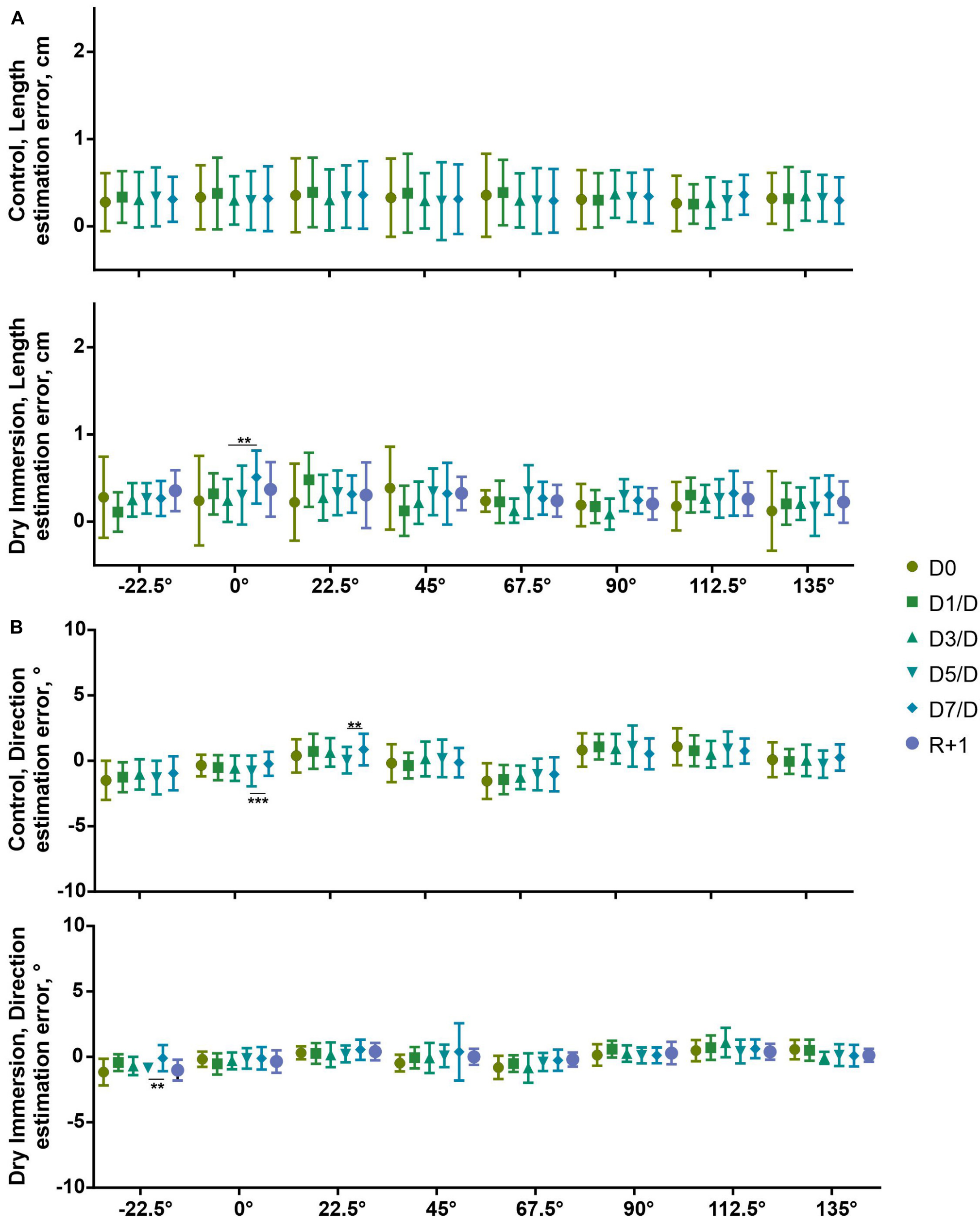

FIGURE 2
Estimation of length **(A)** and direction **(B)** of segments of different orientation at memorization stage in control (*n* = 22) and DI (*n* = 10) groups. Abscissa-orientation of given segment. D0–1st day of measurements in control and DI groups. D1, D3, D5, and D7–2nd, 4th, 6th, and 7th day of measurements in the control group, respectively. These days correspond to DI1, DI3, DI5, and DI7–1st, 3rd, 5th, and 7th day of DI. R + 1–the measurement performed 1 day after the end of the DI procedure. Mean ± SD. $^{**}p < 0.01$, $^{***}p < 0.001$.

for control and DI group, respectively). These orientations were repulsed from cardinal axes and were attracted to −45° and 45°, respectively. Similarly, the volunteers overestimated the orientation of 22.5°, and 112.5° segments (4.8 ± 2.0°, U(22) = 253, $p < 0.001$, and 3.1 ± 0.8°, U(10) = 55, $p < 0.01$, for control and DI group, respectively). These orientations were repulsed from cardinal axes and were attracted to 45° and −45°, respectively. The direction estimation errors decreased. In the control group, the direction of the 67.5° segment was estimated more accurately; in the DI group the directions of the −22.5°, 67.5°, and 22.5° segments were estimated more accurately (all *ps* < 0.01).

The bias and SD of errors for non-cardinal orientations are summarized in Figure 4. In the control group, the overestimation of segment length is increased in D1, and D5 relative to D0 (0.43 ± 0.44 cm vs. 0.26 ± 0.14 cm, W(22) = 165, $p < 0.01$, and 0.47 ± 0.44 cm vs. 0.26 ± 0.14 cm, W(22) = 163, $p < 0.01$, respectively). In the DI group the overestimation of segment length is increased to a greater extent: in DI1, DI3, DI5, DI7, and R + 1 relative to D0 (0.89 ± 0.46 cm vs. 0.54 ± 0.40 cm, W(10) = 53, $p < 0.01$, 1.04 ± 0.43 cm vs. 0.54 ± 0.40 cm, W(10) = 53, $p < 0.01$, 1.17 ± 0.50 cm vs. 0.54 ± 0.40 cm, W(10) = 53, $p < 0.01$, 1.24 ± 0.50 cm vs. 0.54 ± 0.40 cm, W(10) = 55, $p < 0.01$, and

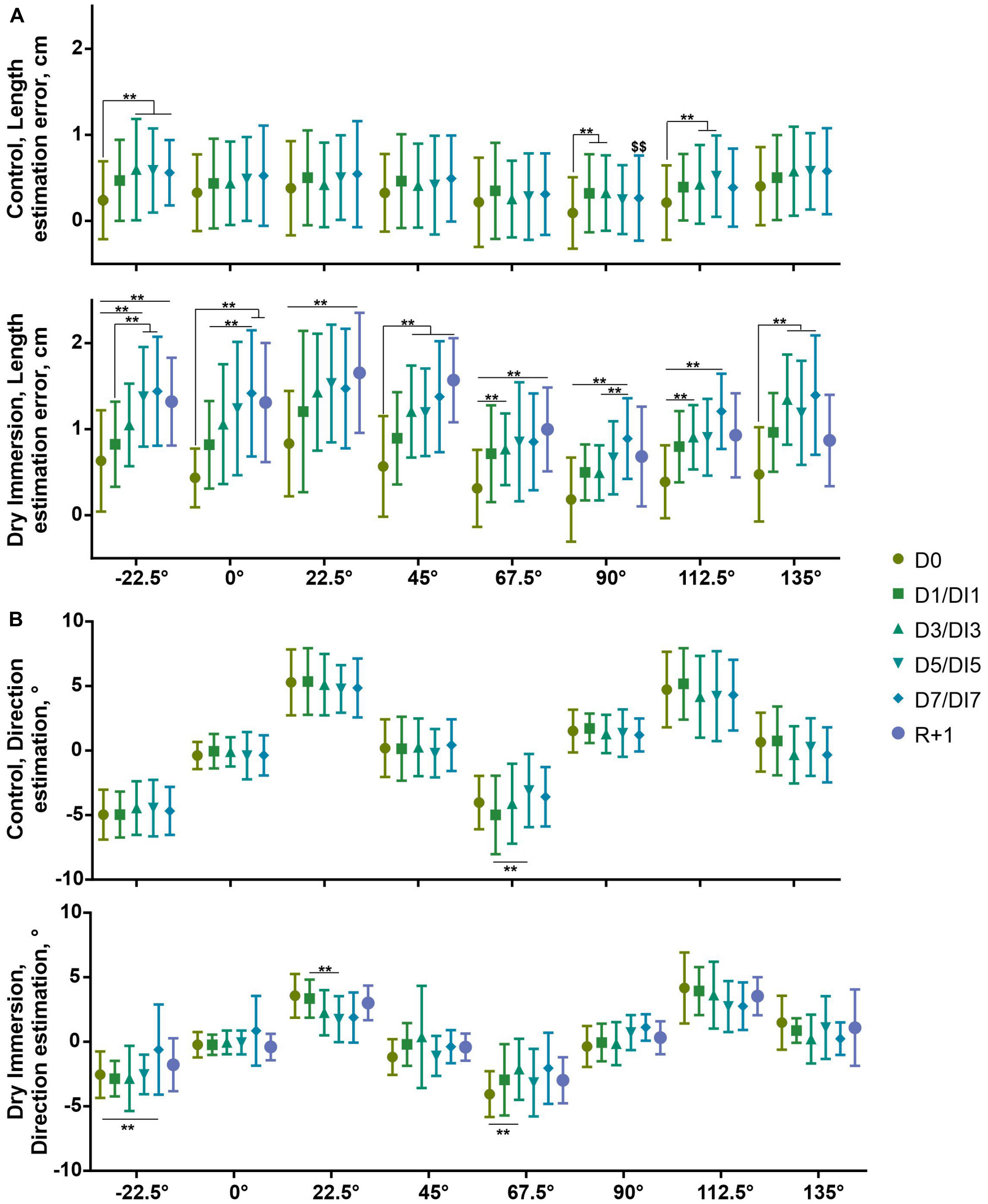

FIGURE 3
Estimation of length **(A)** and direction **(B)** of segments of different orientation at reproduction stage in control (n = 22) and DI (n = 10) groups. Abscissa–orientation of given segment. D0–1st day of measurements in control and DI groups. D1, D3, D5, and D7–2nd, 4th, 6th, and 7th day of measurements in the control group, respectively. These days correspond to DI1, DI3, DI5, and DI7–1st, 3rd, 5th, and 7th day of DI. R + 1–the measurement performed 1 day after the end of the DI procedure. Mean ± SD. \$\$$p < 0.01$ in relation to horizontal segment, **$p < 0.01$ in relation to the estimation of the segment of the same orientation on other days.

1.23 ± 0.48 cm vs. 0.54 ± 0.40 cm, W(10) = 43, $p < 0.01$, respectively); in DI7 relative to DI1 (0.89 ± 0.46 cm vs. 1.24 ± 0.50 cm, W(10) = 49, $p < 0.01$). In the control group, the direction error is decreased in D5 relative to D1 (5.1 ± 1.9° vs. 4.1 ± 1.6°, W(22) = 191, $p < 0.01$). In the DI group, again, the decrease of direction error is more pronounced (DI7 relative to D0, and DI1: 1.8 ± 1.7° vs. 3.6 ± 1.0°, W(10) = 53, $p < 0.01$, and 1.8 ± 1.7° vs. 3.3 ± 1.2°, W(10) = 55, $p < 0.01$, respectively) and accompanied by trend in decrease of its SD (DI7 relative to D0, DI1, and DI3: 2.2 ± 0.6° vs. 3.0 ± 0.7°, W(10) = 43, $p < 0.05$, 2.2 ± 0.6° vs. 2.8 ± 0.7°, W(10) = 43, $p < 0.05$, and 2.2 ± 0.6° vs. 2.7 ± 0.5°, W(10) = 47, $p < 0.05$, respectively).

4. Discussion

Here we replicated the finding of the motor oblique effect and cardinal biases (Baud-Bovy and Viviani, 2004; Smyrnis et al., 2007; Pantes et al., 2009), that is the memorized segment orientations have higher variability at oblique orientations compared to cardinal

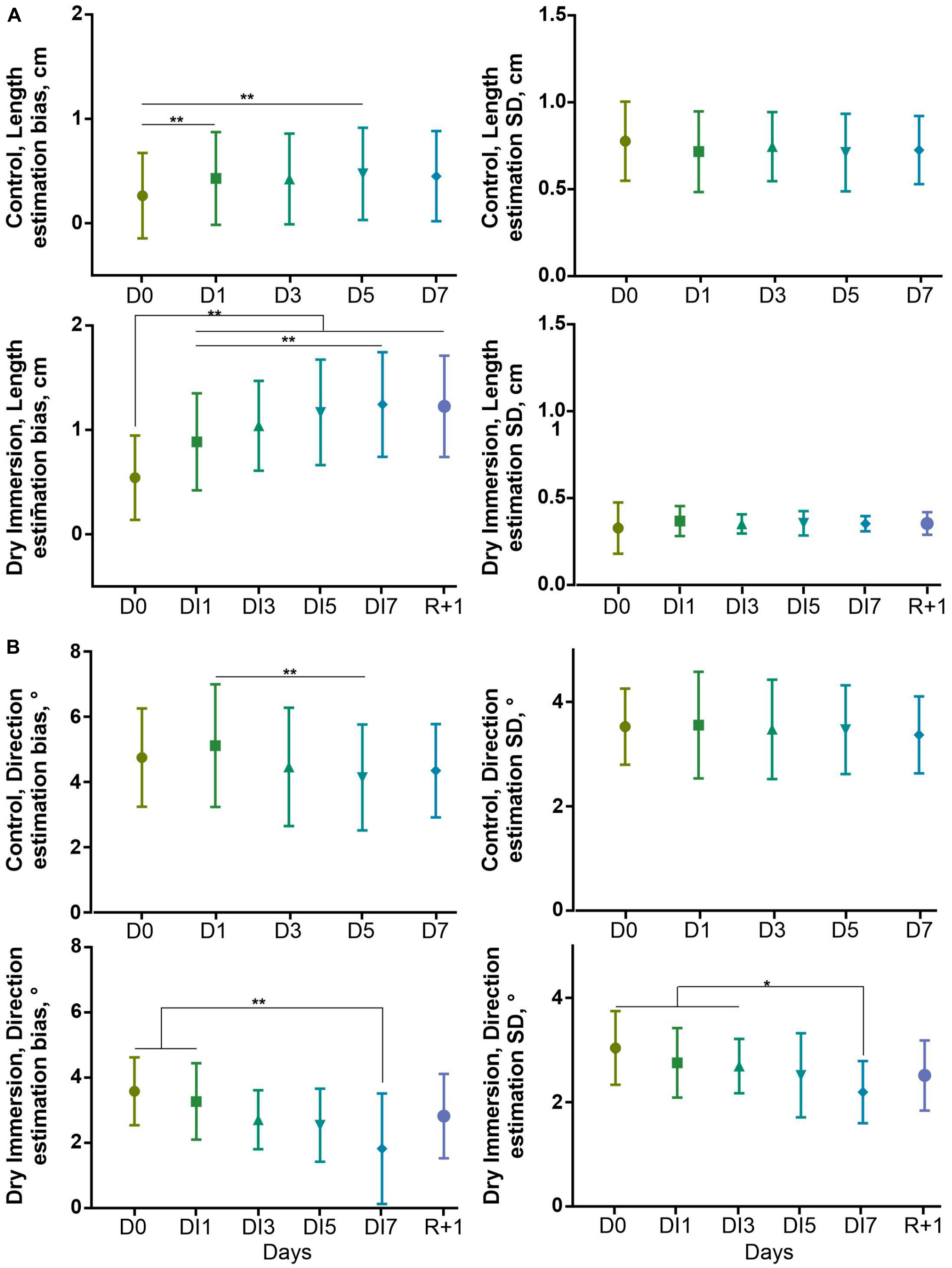

FIGURE 4

Bias and SD of estimation of length (all orientations), **(A)** and direction (non-cardinal segments), **(B)** at reproduction stage in control (*n* = 22) and DI (*n* = 10) groups. The bias of length estimation was calculated as mean non-cardinal segment length estimation error. The directional bias was calculated as $(O_{22\cdot5}+O_{112\cdot5}-O_{-22\cdot5}-O_{67\cdot5})/4$ where O is a direction error of given participants for given direction. D0–1st day of measurements in control and DI groups. D1, D3, D5, and D7–2nd, 4th, 6th, and 7th day of measurements in the control group, respectively. These days correspond to DI1, DI3, DI5, and DI7–1st, 3rd, 5th, and 7th day of DI. R + 1–the measurement performed 1 day after the end of the DI procedure. Mean ± SD. $^{**}p < 0.01$, $^{*}p < 0.05$.

and are systematically shifted away from the cardinal axes. Thus, this effect is persisted in DI as well as in space (McIntyre and Lipshits, 2008).

In our study, the segment length is overestimated in both groups, both for memorization and reproduction stages. This is in contrast to previous studies showing that elimination of visual feedback from the moving arm leads to hypometric (having smaller than required movement amplitude) pointing movements (Bock and Eckmiller, 1986) or that hiding the memorized target eliminates hypermetria (higher than required movement amplitude) induced by previous experimental manipulations (Avraham et al., 2019). It seems that the overestimation of target position or the movement length is more typical for arm movements irrespective of visual feedback (Baud-Bovy and Viviani, 2004; Pantes et al., 2009; Avraham et al., 2017, 2019). Simulated or real microgravity also leads to hypermetria. Hypermetric cyclic arm movements were observed in 6 h and 5 days DI (Lyakhovetskii et al., 2022); hypometric pointing arm movements became hypermetric during spaceflight (Tomilovskaya and Kozlovskaya, 2012).

The vertical length of hand-drawn objects [ellipses (Gurfinkel et al., 1993), letters (Clément et al., 1987), cube edges (Lathan et al., 2000)] is decreased in space. Interestingly, we saw a significant difference in reproduction of length of horizontal and vertical segments at D7 for the control group only (**Figure 3A**). Speculatively, the dynamics of change of vertical to horizontal ratio observed in space (Lathan et al., 2000; Clément et al., 2012) may be due to the effect of prolonged training and not to microgravity by itself. Thus, our study underlines the importance of use of the corresponding control group to investigate the prolonged perceptual effects.

Stimulus configuration may affect the motor responses even with visual feedback though such influence is lower compared to when the visual feedback is absent. The arrows of Muller-Lyer illusion affect the movement amplitude even when the stimulus is clearly visible (Gentilucci et al., 1996); the circles of Ebbinghaus illusion influence the movement time (van Donkelaar, 1999); the Ponzo and Muller-Lyer illusions also modulate the motor responses during the course of 5-day DI (Sosnina et al., 2019). In our case, the effects observed in the memorization phase are mainly similar to those received in the reproduction phase but they have lower magnitude.

Two broad classes of hypotheses suggest the positional (desired position is coded) or vector (direction and distance are coded) internal representations of hand movement targets (Kim et al., 2021). An analysis of errors distribution is one way to explore the internal representation used (Hudson and Landy, 2012). If the subject uses a given coding scheme during repeated trials, this encoding may become more precise during training (van der Graaff et al., 2017). Previous studies suggest that length estimation is more error-prone and more variable relative to estimation of direction, indicating vector-based encoding. Hand movements drift from hypometric to hypermetric while direction bias doesn't drift consistently during the 25 min visuomanual pointing (Vindras and Viviani, 1998). Adaptation to gain change influencing movement length (an altered relationship between distance moved on the screen and the distance moved on the tablet) is faster and more complete than adaptation to space rotation influencing direction errors (Krakauer et al., 2000). During the time course of our study in both groups the direction error of the reproduced segment is decreased while the overestimation of segment length is increased. Such a complex pattern of errors strongly supports the hypothesis on the vector encoding of movement goals, which is typical for the movements of the dominant hand, when the direction and length of the planned movement are encoded independently of each other (Gordon et al., 1994; Vindras et al., 2005). The behavioral data find support in single-cell electrophysiological recording. The neuronal discharge patterns registered in monkey primary motor and pre-motor cortex are in favor of independent amplitude and directional coding. This neuronal activity relates primarily to direction encoding; the movement amplitude is coded after the direction of movement is chosen (Riehle and Requin, 1989). Thus, the proposed experimental design may be also useful for studying the encoding scheme of hand movements.

Observed opposite changes of two types of errors are more pronounced in the DI group. It's possible that DI volunteers participating in a complex scientific experiment might be more motivated and have higher accuracy relative to the control group. This might be true for orientation errors, however, their length overestimation bias is expressed to a greater degree. One possible explanation is that according to H. Jackson dissolution theory (Meares, 1999) the properties of perception emerging late during development are the most fragile. In fact, the overestimation of distance is appeared later in development than correct estimation of orientation: overshooting of target location is absent in young children aged 6—7, observed in the adult group, and reaches maximum in the older children group aged 10—11, while the direction error is the same for different age groups (Pantes et al., 2009). The estimation of orientation is immune to Parkinson's disease: patients exhibit hypometria without any direction bias (Desmurget et al., 2003). Thus, DI influence onto the vestibular system might affect primarily the length estimation. Another possible explanation is based on the different roles of hemispheres on movement control. The left hemisphere of right-handers has a greater role in dynamic control of movement trajectory relative to the right hemisphere (Haaland et al., 2004). An exposure to DI caused a sharp decrease in the left hemisphere activity (Kirenskaya et al., 2006) that presumably may affect the movement length.

5. Conclusion

In summary, the analysis of the dynamics of the sensorimotor estimation of the lengths and directions of segments of various orientations by the leading hand in DI was carried out in comparison with the control group. We obtained here four main findings. First, the segment length is overestimated in both groups, both for memorization and reproduction stages. Second, the direction of reproduced segments of non-cardinal orientation is repulsed from cardinal axes. Third, the directional error of the reproduced segment is decreased while the overestimation of segment length is increased during study in both groups. Fourth, such opposite changes of two types of errors are more pronounced in the DI group. To conclude, even the perception of such simple objects as oriented line segments is modulated by the DI.

6. Limitations

The DI group consisted of men only while the control group consisted of men and women. The measurements in two groups were performed on the sensor monitors of different sizes. Though the rectangular frame size doesn't influence the estimation of length (Gavilán et al., 2017) and orientation (Zoccolotti et al., 1992), and sex difference in the perception of orientation (Brabyn and McGuinness, 1979) and inverted-T illusion (Brosvic et al., 2002) are absent, we limited our interest by the potential dynamics of DI influence onto the parameters studied. As it can be seen from the presented results, the observed changes occurred at the beginning of the study, in relation to the first measurements. Therefore, to simplify the recruitment of the control group, measurements in it were carried out for 8 days (and not for 9 days as in the DI group).

Data availability statement

The data from the study reported in this article is available at https://dx.doi.org/10.17605/OSF.IO/3QCJ9.

Ethics statement

The studies involving human participants were reviewed and approved by the Commission on Biomedical Ethics of the Institute of Biomedical Problems of the Russian Academy of Sciences (Protocol No. 1 of Sept. 09, 2021). The patients/participants provided their written informed consent to participate in this study.

Author contributions

AC and VL conceived the experiments and analyzed the data. VL, VK, and AC wrote the manuscript. VL, AC, VK, IZ, and ET edited the manuscript. IZ performed the research. VK and ET supervised the study. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants from the Russian Science Foundation No. 22-18-00074 (VL, IZ, and VK, experimental design, study of the control group) and No. 19-15-00435П (IZ and ET, study of the DI group). AC did not receive any funding from the Russian Science Foundation.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Neural Circuits

TYPE Original Research
PUBLISHED 17 April 2023
DOI 10.3389/fncir.2023.1135434

Sensory organization of postural control after long term space flight

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RECEIVED 31 December 2022
ACCEPTED 30 March 2023
PUBLISHED 17 April 2023

CITATION
Shishkin N, Kitov V, Sayenko D and Tomilovskaya E (2023) Sensory organization of postural control after long term space flight.
Front. Neural Circuits 17:1135434.
doi: 10.3389/fncir.2023.1135434

Background: Alterations in motor control systems is an inevitable consequence of space flights of any duration. After the flight, the crew-members have significant difficulties with maintaining upright balance and locomotion, which last several days following landing. At the same time, the specific mechanisms of these effects remain unclear.

Objectives: The aim of the study was to assess effects of long-term space flight on postural control and to define the changes of sensory organization caused by microgravity.

Methods: 33 cosmonauts of Russian Space Agency, the members of International Space Station (ISS) flights of duration between 166 and 196 days took part in this study. Computerized Dynamic Posturography (CDP) tests, which include assessment of visual, proprioceptive and vestibular function in postural stability, was performed twice before the flight and on the 3rd, 7th, and 10th days after landing. The video analysis of ankle and hip joints fluctuations was performed to investigate the basis of postural changes.

Results: Exposure to long-term space flight was followed by considerable changes of postural stability (–27% of Equilibrium Score value in the most complicated test, SOT5m). Changes in postural strategies to maintain balance were observed in the tests which provide the challenge for vestibular system. In particular, increased hip joint involvement (+100% in median value and +135% in 3rd quartile of hip angle fluctuation RMS in SOT5m) into postural control process was revealed.

Conclusion: Decrease of postural stability after long-term space flight was associated with alterations in vestibular system and biomechanically was revealed by increased hip strategy which is less accurate, but simpler in terms of the central control.

KEYWORDS

computerized dynamic posturography (CDP), joint coordination, sensory organization test, microgravity, postural balance, biomechanics, sensory reweighting, postural control strategy

1. Introduction

Postural stability deficit is an inevitable consequence of space flights (SF) of any duration (Kozlovskaya et al., 1981; Paloski et al., 1992; Black et al., 1995; Reschke et al., 1998, 2009; Wood et al., 2015). It is well known that the visual, vestibular and proprioceptive sensory systems are all critical and involved in control of the postural balance in humans (Nashner, 1971). In 1970, Nashner introduced a method termed Computerized Dynamic Posturography (CDP), which development described in Black and Paloski (1998) and proposed this approach to investigate the contributions of different sensory inputs using Sensory Organization Tests (SOT). These tests are based on creating conditions when information from either visual or proprioceptive inputs becomes unreliable or insufficient to determine the orientation of the body in relation to the gravitational vertical. The tests include tilting of the support surface and the visual environment together with the inclination of the body. It is noteworthy that, according to previous studies (Nashner, 1971) vestibular afferentation is not decisive in determining the degree of the body inclination. However, when the support surface is unstable and proprioceptive information from the lower body becomes unreliable, the contribution of vestibular afferentation for determination of the body position becomes critical. In addition, other studies in individuals with vestibular disorders have assessed the role of the vestibular apparatus in postural control (Nashner et al., 1982; Allum and Shepard, 1999). The results of those studies indicate that vestibular afferentation act as an internal reference for proprioceptive and visual inputs. Recently, an extended battery of SOT has been proposed to assess the contribution of vestibular system to postural control in astronauts (Black and Paloski, 1998; Wood et al., 2015). This method allows for the otolith input distortion using dynamic head tilts in the sagittal plane (Jain et al., 2010). It was shown that the complete recovery of postural stability in astronauts was reached within 10–15 days after long-term SF (first 25 expeditions on ISS), and the instability that persists until this time in tests with head tilts is explained by the overestimation of low-frequency otolith signals (Wood et al., 2015). Severity of disequilibrium increases and recovery is prolonged with increasing exposure time to weightlessness (Miller et al., 2018). Return of postural control to baseline occurs ∼4 days after short-duration SF and ∼12 days after long-duration SF (Clément G. R. et al., 2020). Most of investigations connect alterations in sensory-motor system with vestibular system. It is known, that the perception of the horizontal and vertical distances of a visual target changes (Clément G. et al., 2020). Weightlessness alters the input signals of the otoliths and their effect on the pattern and dynamics of changes in the vestibular function (Kornilova et al., 2017; Glukhikh et al., 2022).

Computerized dynamic posturography (CDP) reflects the body center of mass movements and does not take into account the multi-joint coordination, which is the cause of these movements. It has been shown earlier (Horak and Nashner, 1986) that there are two main types of movement strategies that can be used to return the body to equilibrium in a stance position and to keep the feet in place: the ankle strategy, when the center of pressure transition occurs mostly due to the movement around the ankle joints, and the hip strategy which involves movements around the hip joints. Biomechanical models (Alexandrov et al., 2001; Versteeg et al., 2016) have also demonstrated that of possible strategies, the ankle and hip strategies are the most efficient. The hip strategy is engaged during corrections to large postural perturbations, whereas the ankle strategy is used during corrections to minor perturbations. It is known, that hip strategy contribution increases during perturbations in elderly people (Afschrift et al., 2016). Hip strategy involvement also depends on muscle tone (Kaminishi et al., 2020, 2021). Muscle tone registered by microvibrations decreases in microgravity (Gallasch et al., 1998). We assume that this atonic state during long-term SF can lead to increase of hip strategy contribution in postural balance maintenance. Short-term SF (9–16 days) results in hip strategy contribution increase in all SOT conditions except the test with eyes closed and proprioceptive disturbance (Speers et al., 1998), these alterations are associated with changes in sensory processing for motion perception and spatial orientation. Therefore, we hypothesized that transition from the ankle to hip strategy during standing in sensory challenging environment can remain the same in the course of early recovery period (first 3 days after landing). It indicates a growing overload for the postural control to maintain balance, and such a transition could be used as an indicator of sensory deficit following spaceflights.

2. Materials and methods

The study involved 33 cosmonauts – crew members of expeditions to the International Space Station, ISS missions 16–66, with an average duration of space flights from 166 to 196 days. The group consisted of 32 men and one woman 46.6 ± 4.9 years old, weight 81.2 ± 8.5 kg, height 177.1 ± 5.3 cm. All the participants provided written informed consent to participate in the study that received ethical approval from the Physiological Section of the Biomedicine Ethics Committee at the Institute of Biomedical Problems of the Russian Academy of Sciences and Human Research Multilateral Review Board (HRMRB).

The studies were conducted twice (on average – 60 and 30 days, L-30 and L-60) before launch, as well as on the 3–4, 7–8, and 10–11 days after SF completion (R + 3, R + 7, and R + 10, respectively). All studies were conducted in the morning, physical activity was excluded before the study.

2.1. Study of stabilographic characteristics before and after long-term SF

Subjects were tested according to a modified computerized dynamic posturography (CDP) protocol with the use of EquiTest clinical system (Neurocom, USA) (**Figure 1A**).

The system consists of sway-referenced stabilometric platform, which rotation axis intersects ankle joints. The visual area is enclosed by sway-referenced visual surround. The frequency of stabilographic signal is 100 Hz. The body inclination is measured in real time by system and platform or surround rotates to make the proprioceptive or visual input unreliable (**Figures 2A, B**). Such conditions provide distortion or elimination (in the case

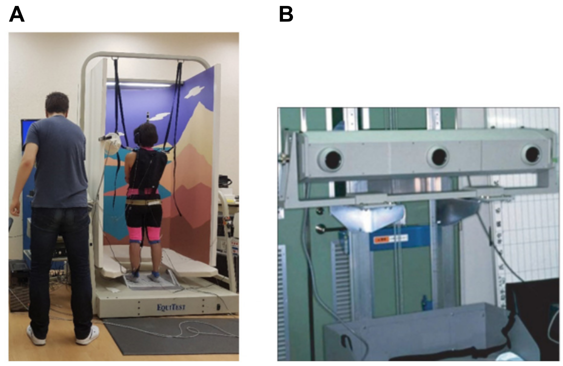

FIGURE 1
(A) Neurocom EquiTest complex. **(B)** Optotrack 3020 motion capture systems.

of vision) of different afferent inputs: proprioceptive - with a sway referenced platform, visual - with a sway referenced screen, vestibular - with head tilts. This method of testing the contributions of various sensory systems in vertical stance control was proposed by Nashner (1971), who developed the EquiTest research complex, which development described in Black and Paloski (1998). When processing the data, the complex dimensionless vertical stability indicator Equilibrium Score (EqScore) was analyzed, which was calculated by the formula:

$\mathrm{EqScore} = (1 - \alpha/12{,}5^\circ) \times 100,$

where α is the maximum angle of the center of mass fluctuation for the entire recording period (**Figure 2C**). In a normal population, this indicator is 12.5°. The displacement of the center of gravity was calculated by filtering the sagittal stabilogram with a Butterworth high-frequency filter with a cutoff frequency of 0.85 Hz (**Figure 2D**). The detailed description is in Wood et al. (2015).

During the assessment subjects wore headphones in order to block ambient noises and unwanted auditory cues as well as to play a pacing sound for the tests involving head movements. A white noise was played through the headphones to muffle ambient sounds. The pacing sound for modified tests with head tilts was represented by a continuous tone frequency modulated by a 0.33 Hz sine wave. Each experimental session consisted of seven tests with different conditions. Five tests are standard for studies using the EquiTest Neurocom complex (**Figure 3**):

- SOT1 – vertical stance with eyes open;
- SOT2 – vertical stance with eyes closed;
- SOT3 – vertical stance with eyes open and a sway referenced visual surrounding;
- SOT4 – a stand with open eyes and a sway referenced support surface;
- SOT5 – vertical stance with eyes closed and a sway referenced support surface.

The modified tests proposed by Jain et al. (2010) were also included in the program:

- SOT2m – vertical stance with eyes closed while performing dynamic head tilts in the sagittal plane with a frequency of 0.33 Hz and an amplitude of 40°;
- SOT5m – vertical stance with eyes closed, a moving platform (as in SOT5) and while performing dynamic head tilts.

When analyzing the data, two-factor analysis of variance (ANOVA) with Bonferroni correction was used for normal distribution, the graphs are presented as averages and standard deviations.

2.2. Study of kinematic characteristics

The cosmonauts were equipped with a system of infrared sensors (NDI OptoTrack, USA). Basing on the data of these sensors the body scheme was built for each subject using Rstudio software. Sensors were attached to the right heel, right popliteal cavity, right hip and headphones (to control the amplitude and frequency of head tilts). Angles in the ankle, knee and hip joints were calculated (**Figure 4**). The average velocities of the

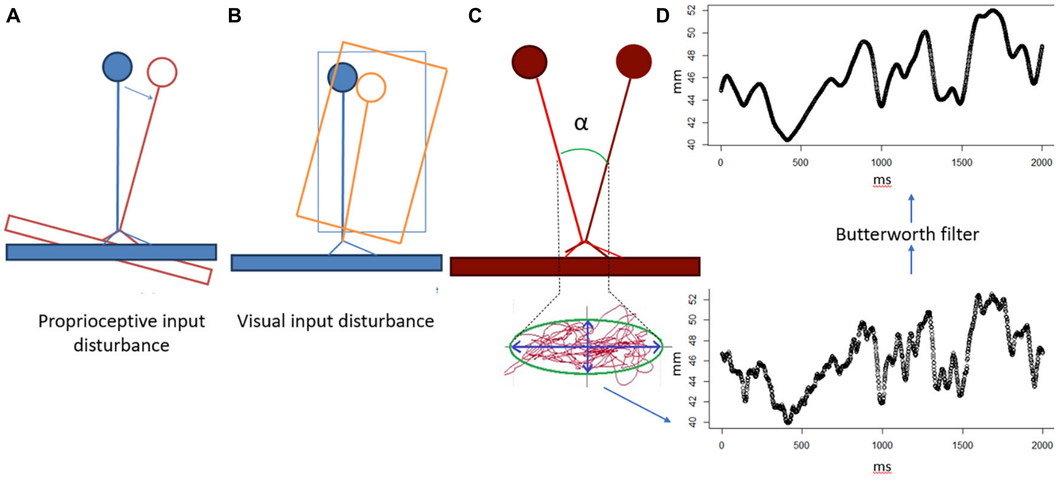

FIGURE 2
Neurocom data processing. **(A)** Sway-referenced platform for proprioceptive input disturbance. **(B)** Sway-referenced visual surround for visual input disturbance. **(B)** Center of Pressure trace and sway angle. **(D)** Stabilogram alignment with Butterworth filter.

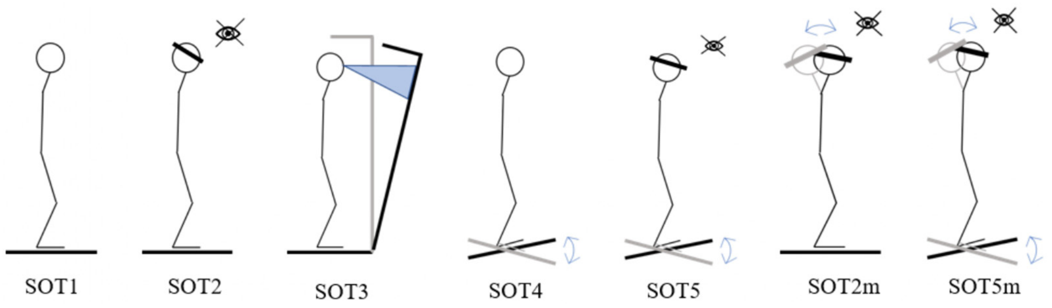

FIGURE 3
Sensory organization tests.

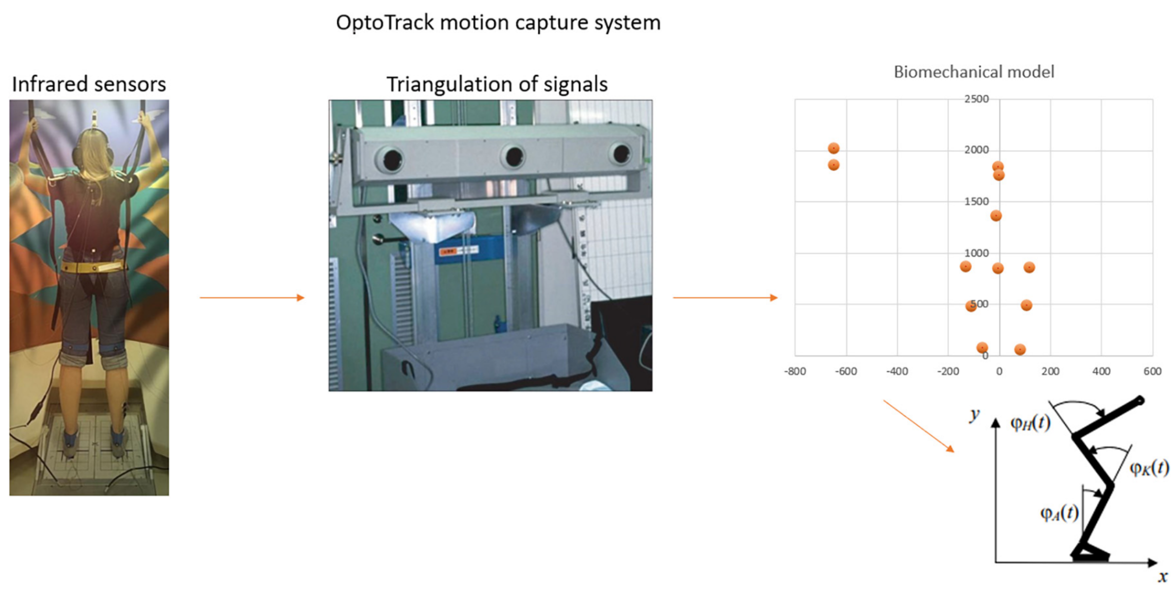

FIGURE 4
Kinematic characteristics registration and processing.

angle fluctuations and the Random Mean Square (RMS) of these fluctuations were analyzed.

Sensorimotor system applies unlimited number of ankle-hip strategy combinations (Horak and Nashner, 1986; Horak, 2006). We determined the change in the contribution of the hip/ankle strategy by calculating the ratio between the ratios of the RMS of fluctuations in the hip and ankle joints before and after the flight:

$$HASC = (HR_{R+3}/AR_{R+3})/(HR_{L-60}/AR_{L-60})$$

where HASC – hip/ankle strategy contribution changing, HR – hip angle RMS, AR – ankle angle RMS.

Due to the large variability of the data, statistical analysis was carried out using the non-parametric Wilcoxon test, which allows comparing samples with an abnormal distribution. Graphically, the data are presented as medians with an interquartile range.

We used standard level for medical investigations – $p < 0.05$. We used open source software for data science RStudio for analysis of device signals and statistical processing. We used GraphPad Prizm 8 for making figures.

3. Results

3.1. Stabilometric characteristics after long-term SF

In the simplest condition – SOT1 – on a stable platform and with eyes open – there was a significant decrease in EqScore values on the 3rd day after landing (on average from 93.5 to 90.3 points, $p = 0.017$). Significant changes were also observed in the SOT3 tests - with eyes open and a moving visual environment (from 91.6 to 87.3 points, $p = 0.0029$), in the SOT4 test - with eyes open and a sway referenced support surface (from 82.9 to 74.4 points, $p = 0.0027$), in the SOT5m test - with eyes closed, a sway referenced support surface and head tilts – from 48.2 to 35.9, $p = 0.016$ (**Figure 5**).

It was found that in one of the conditions – in the test with eyes closed, fixed support surface and head tilts (SOT2m) – no significant changes were observed on the 3rd day after landing, but they were detected on the 7th day (**Figure 6**, $p = 0.006$ for

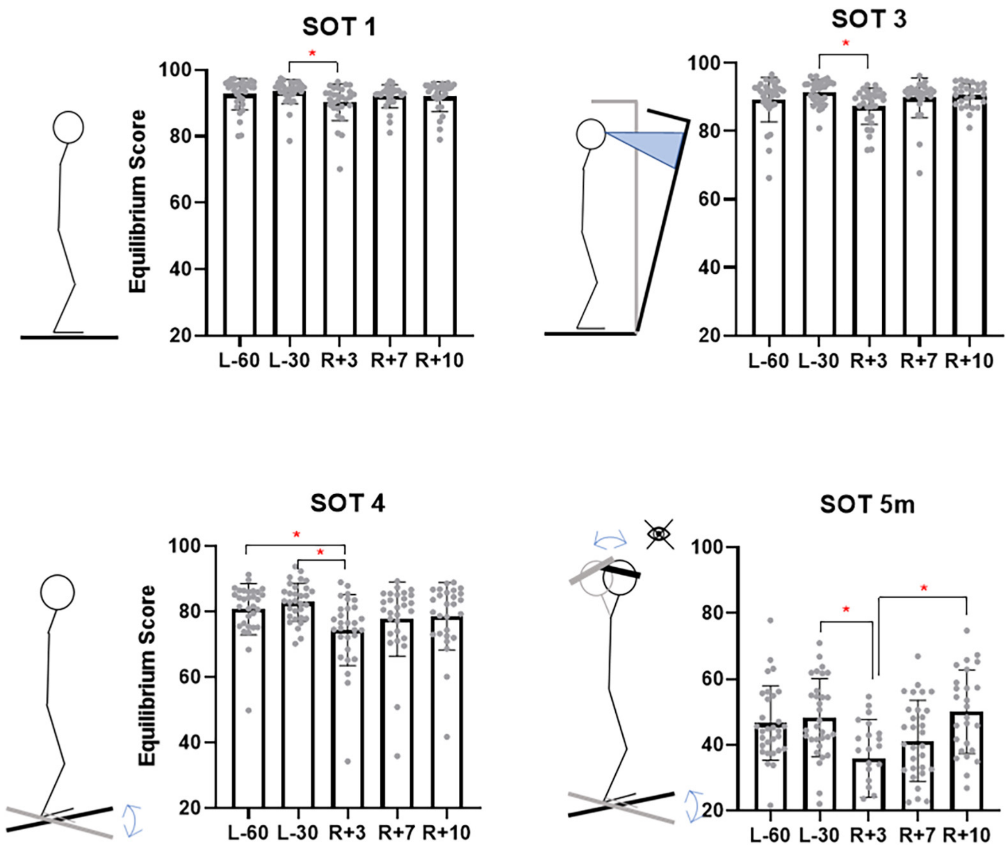

FIGURE 5
Sensory organization tests with significant changes between pre- and postflight Equilibrium Score. L-60 – 60 days before launch, L-30 – 30 days before launch, R + 3 – 3rd day of recovery period after landing, R + 7 – 7th day after landing, R + 10 – 10th day after landing.

comparison of L-60 and R + 3 and $p = 0.0019$ for comparison L-30 and R + 3).

3.2. The influence of space flight factors on the kinematic characteristics of vertical stance in cosmonauts

Under conditions of absent visual feedback, distorted proprioceptive and vestibular input (SOT5m) we saw greater root mean square of joint angles, than in other tests and on day R + 3 (0.17° in SOT1 and 0.26° in SOT5m in ankle, $p < 0.001$, 0.12° in SOT1 and 0.55° in SOT5m, $p < 0.001$) (**Figure 7**).

Vertical balance maintenance can be represented as stabilization of a three-link inverted pendulum. There are three main strategies for maintaining balance: hip, knee, and ankle ones (Alexandrov et al., 2001). These strategies are independent by central control. The ankle strategy is much more inertial than the hip one, and is used for slow movements of the center of gravity, the hip strategy – for fast movements (Horak and Nashner, 1986; Afschrift et al., 2016). The knee strategy makes a small contribution into vertical balance control (Kuo et al., 1998; Alexandrov et al., 2001), so we did not consider it. The movements of the center of gravity and, consequently, the central of pressure, are linked to the joints' angles. So, we focused our attention on the changes in those equilibrium tests in which significant changes in the stabilometric characteristics were detected.

In the SOT1 test – eyes open, fixed support surface – significant changes in the angular velocity in the ankle joint were detected (from 0.13° to 0.17° $p = 0.014$), while no changes were observed in the hip joint. Thus, the vertical balance maintenance in this case

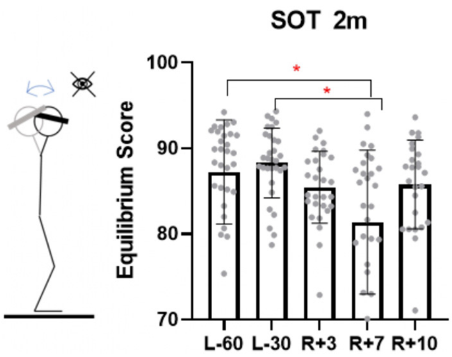

FIGURE 6
Sensory organization test with eyes closed, fixed platform and head tilting (proprioceptive testing). L-60 – 60 days before launch, L-30 – 30 days before launch, R + 3 – 3rd day of recovery period after landing, R + 7 – 7th day after landing, R + 10 – 10th day after landing.

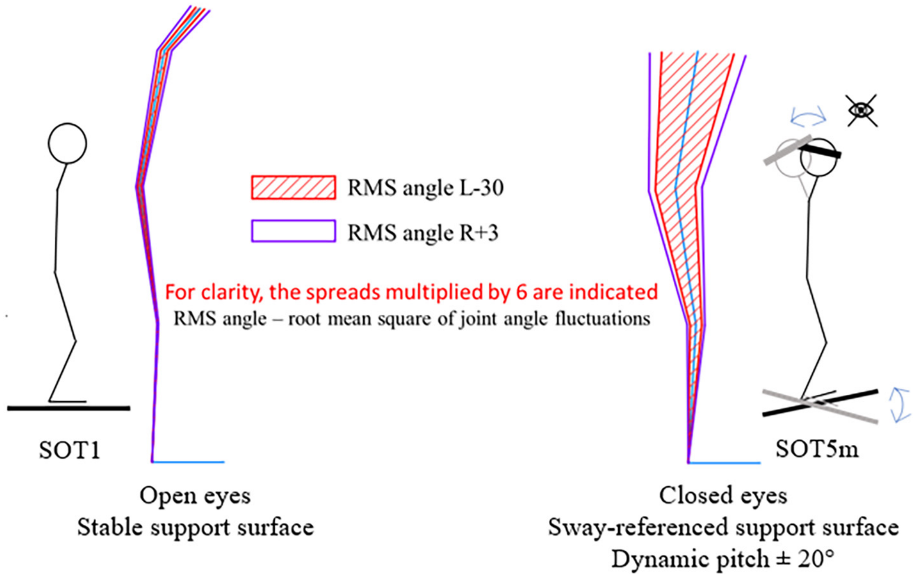

FIGURE 7
Increase of angles RMS between SOT1 and SOT5.

was provided by an ankle strategy typical for vertical stance under normal conditions (Figure 8).

In the SOT3 test – eyes open, moving visual environment– significant changes in angular velocity and RMS of the ankle joint position (from 0.11° to 0.19°, $p < 0.0001$) and a significant increase in the angular velocity in the hip joint (from 0.10° to 0.13°, $p = 0.03$) were detected, however, no significant increase in the RMS of hip joint position was registered (Figure 9). Since the increase in the angular velocity in this case is not accompanied by increase of angular RMS, we assume that these changes occur within the frame of the ankle strategy.

In the SOT4 test – eyes open, sway referenced support surface – on the 3rd day after the completion of SF, significant changes in the RMS of the hip joint position were detected (from 0.12° to 0.21°, $p = 0.03$), as well as a significant difference from SOT1 hip joint RMS, conducted in the same post-flight session ($p = 0.02$) (Figure 10). These changes suggest the recruitment of a hip strategy for maintaining vertical balance.

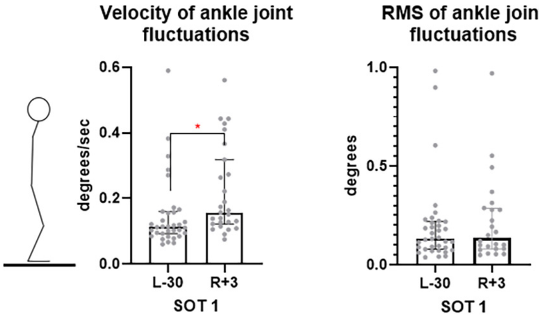

FIGURE 8
Ankle joint fluctuation velocity is SOT1 test. L-30 – 30 days before launch, R + 3 – 3rd day of recovery period after landing.

In the SOT5m test – eyes closed, sway referenced support surface and head tilts – significant changes in the angular velocity and RMS were found both in the ankle (from 0.90° to 1.26°, $p < 0.001$) and in the hip joints (from 0.27° to 0.55°, $p < 0.001$), which corresponds to 40% an increase in the median value and a 44% increase in the 3rd quartile in the ankle joint, a 100% increase in the median and a 135% increase in the 3rd quartile in the hip joint (Figure 11), which suggests an increase in the contribution of the hip strategy to maintaining balance (Kaminishi et al., 2021). This is confirmed by the hip/ankle strategy contribution changes (Figure 12), where the median value of SOT5m is the biggest one (1.4). The values less than 1 for SOT1 (0.75) and SOT3 (0.7) confirm the ankle strategy involvement to postural changes in this test.

There were falls (steps during test to avoid losing the balance) during SOT5m performance. Other tests were performed clearly. The majority of falls were in R + 3 session (33.3% from summary number of all cosmonauts attempts), but there were also falls in other experiment sessions (Figure 13). The decrease from 11.5 to 6.25% from L-60 to R + 3 could indicate the learning effect between 1st and 2nd experiment sessions and decrease from R + 3 to R + 10 – about recovery processes.

The comparison between Equilibrium Score in our study and in Wood et al. (2015) revealed that changes after SF are similar except the SOT5, 2 m, 5 m conditions. We calculated the median of these tests parameters to compare them with recovery curves in Wood et al. (2015). It was found that cosmonauts in our study have less Equilibrium score in SOT5 (65 against 75 on R + 3, Figure 14A) and greater - in SOT2m and 5 m (85 against 75 on R + 3, Figure 14B, 38 against 25 on R + 3, Figure 14C).

4. Discussion

The results allowed us to quantify changes in postural control after long-term SF. Tests that did not directly assess

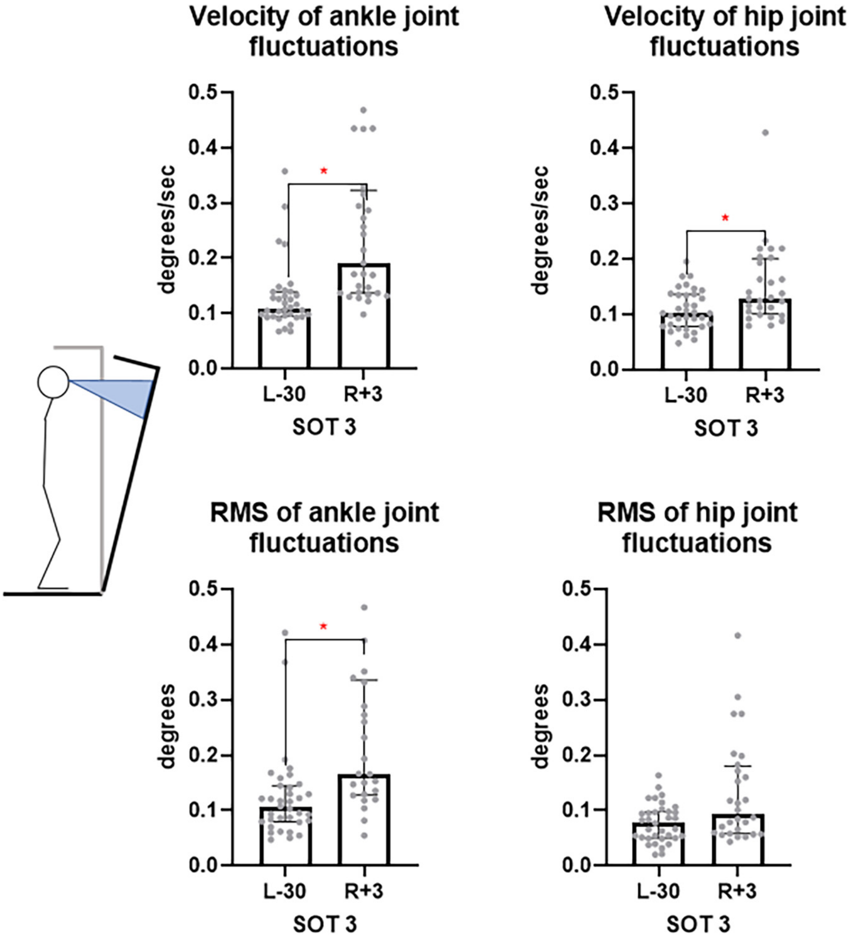

FIGURE 9
Ankle and hip joints fluctuation velocity and RMS is SOT3 test. L-30 – 30 days before launch, R + 3 – 3rd day of recovery period after landing.

the contribution of vestibular system (i.e., SOT1-SOT5), revealed recovery of postural control to the baseline values by R + 7. However, those tests that required increased engagement of vestibular system (i.e., SOT5m) indicated the recovery only on R + 10, which is in accordance to previous studies (Wood et al., 2015). Further analysis of the SOT5m test results demonstrated a progressive EqScore recovery: there was a positive dynamic of the score on R + 10 relative to R + 3 session. This observation once again confirms the significant effects of SF on the vestibular system and demonstrates that post-flight long-term recovery of balance is associated with the function of this sensory system.

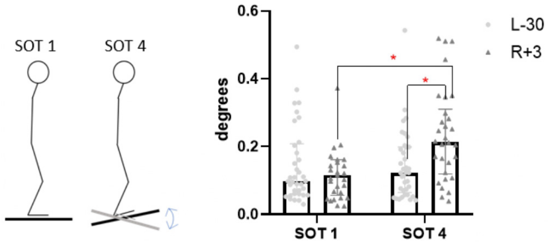

FIGURE 10
Hip joints fluctuation RMS in SOT1 and SOT4 tests. L-30 – 30 days before launch, R + 3 – 3rd day of recovery period after landing.

Comparison of our results with recovery curves in SOT5, 2 m and 5 m from Wood et al. (2015) revealed the difference between two experiments in spite of exactly the same device and experimental battery used. Five of 25 ISS expeditions used Shuttle instead of Soyuz, seven expeditions used both types of ships. It is known, that Shuttle provides significantly less g-loads during landing, so we should expect better postural stability, but this was observed only in SOT5 test.

One of the first training procedures for cosmonauts was the vestibular training (CVT, rotating chair with environment fixed to rotating axis). Previous studies of the effects of CVT (Clément et al., 2001) revealed the decrease of motion sickness severity and signs of vestibular adaptation. We can suggest that difference in EqScore values in two mentioned studies could be explained by the difference in vestibular training protocols used before SF.

The other possible cause of the difference in postural stability after landing could be the physical training protocols used by the crew members in the course of SF. Both cosmonauts and astronauts perform the program of physical training on ISS, including treadmill running, cycling and resistive training. The

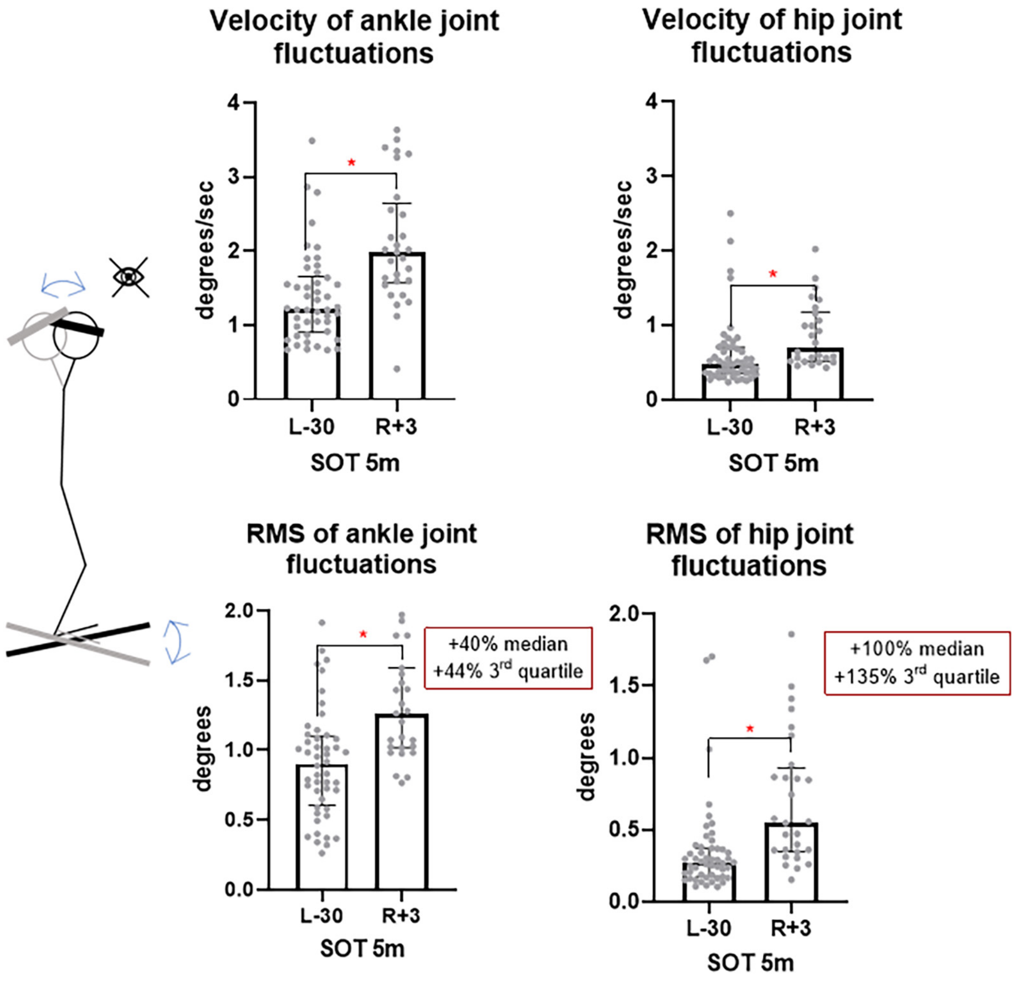

FIGURE 11
Ankle and hip joints fluctuation velocity and RMS is SOT5m test. L-30 – 30 days before launch, R + 3 – 3rd day of recovery period after landing.

benefit of physical training in microgravity is the well-known fact (Kozlovskaya et al., 2015), but we didn't find any mentions on comparative studies between RSA and NASA/ESA training programs.

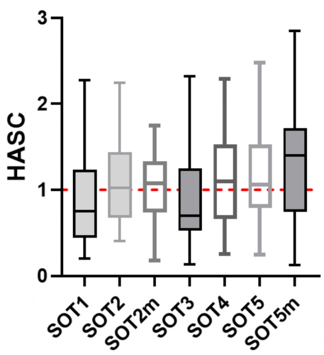

FIGURE 12
Hip/ankle strategy contribution (HASC) changes between L-30 and R + 3. In ordinate: ratio of hip/ankle strategy involvement indicator (after flight/before flight).

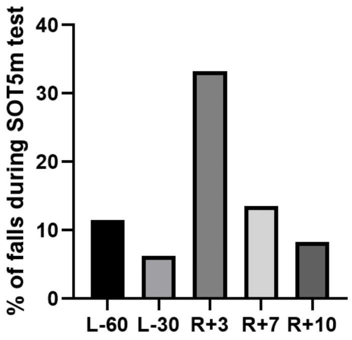

FIGURE 13
Percent of falls in SOT5m test. L-60 – 60 days before launch, L-30 – 30 days before launch, R + 3 – 3rd day of recovery period after landing, R + 7 – 7th day after landing, R + 10 – 10th day after landing.

The alterations in contribution of proprioception to postural control (SOT2m, test with eyes closed, vestibular disturbance and without proprioceptive disturbance) were not registered. Unfortunately, in our study, we had a possibility to perform the first

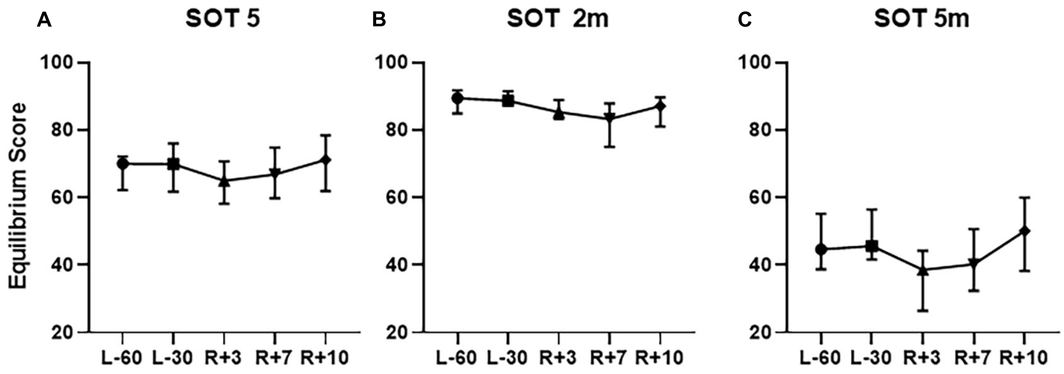

FIGURE 14
Median Equilibrium Score in **(A)** SOT5, **(B)** SOT2m, **(C)** SOT5m tests. L-60 – 60 days before launch, L-30 – 30 days before launch, R + 3 – 3rd day of recovery period after landing, R + 7 – 7th day after landing, R + 10 – 10th day after landing.

postflight tests only on the 3rd day after landing. At the same time, Wood et al. (2015) observed the 25% decrease of EqScore in this test on 1st day after landing. Perhaps these alterations could disappear by the 3rd day after landing.

It has been previously demonstrated that patients with impaired vestibular function have a reduced or even absent ability to titrate the stretch reflex response in the lower leg muscles to displacements and rotations of the supporting surface (Nashner, 1976). Other studies (Reschke et al., 2009; Miller et al., 2018) report about changes in proprioceptive input after SF and its ground-based model - head-down tilt bed rest (HDBR). However, these conclusions were made basing on the stretch reflex examination (Reschke et al., 2009) and locomotor analysis (Miller et al., 2018). The CDP was also used in these studies, but no significant changes were revealed in SOT1-5 after 42–63 days of HDBR (Reschke et al., 2009). Changes in SOT5m, revealed after 70-day HDBR (Miller et al., 2018), reflect the vestibular input changes, but not proprioceptive one. It was shown that SF is followed by the alterations of sensory processing of vestibular input, but appropriate visual and proprioceptive information could blunt the effect of this deficit. SOT5m was developed for analysis of this deficit, not for the proprioceptive system assessment (Jain et al., 2010).

Our study has also revealed changes in the postural strategies that cosmonauts used after SF under conditions when proprioceptive or vestibular inputs were distorted (i.e., SOT4, SOT5m). Other studies (Speers et al., 1998) also noted an increased contribution of the hip strategy in similar tests within a few hours after landing following short-term SF (i.e., 7 to 16 days). In our study we have information only about recovery period from 3 to 10 days after landing. The changes in postural strategies pattern are observed on R + 3, but only in tests, where vestibular input was critical. The most pronounced changes toward increase of the hip strategy contribution were revealed in the SOT5m test, when visual feedback is absent, while proprioceptive and vestibular inputs are distorted. We registered a greater usage of hip strategy in posture maintenance compared to ankle strategy usage in this test. In SOT4, the least complicated test with proprioceptive input distortion, we also observed increase of hip strategy contribution after SF. Recent studies report about the updating of a cerebellum-based internal model of the sensory consequences of gravity and about the re-weighting of extra-vestibular information (Carriot et al., 2021). Previous studies also attributed the increase of hip strategy contribution to the alterations in central processing of sensory information (Speers et al., 1998).

The greatest changes in the postural control were observed in the postflight tests introducing the greatest challenge for the vestibular system. This is not surprising given that vestibular neglect develops within the first days of SF (Kornilova et al., 2017). As it was shown in studies of the vestibular-ocular reflex after SF (Glukhikh et al., 2022) vestibular system recovery takes up to 9 days after landing, which can affect the recovery of the vestibular contribution in postural control.

5. Conclusion

1. The changes occurring in the vestibular system may play the leading role in reducing postural stability after long-term space flight.
2. The changes in postural strategy patterns remain up to 3rd day after landing, which could be the evidence of long duration alterations in central processing of spatial information.
3. Proprioceptive input processing recovers much earlier, than vestibular one.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Biomedicine Ethics Committee at the Institute of Biomedical Problems of the Russian Academy of Sciences and Human Research Multilateral Review Board (HRMRB). The patients/participants provided their written informed consent to participate in this study.

Author contributions

DS, VK, and ET designed the study. NS and VK conducted the research. NS processed the data and drafted the manuscript. VK and DS revised the manuscript. ET contributed in the global revision of the manuscript and was a supervisor of the experiment. All authors interpreted the data and have read and approved the final submitted manuscript.

Funding

This study was supported by the Russian Academy of Sciences (63.1).

Acknowledgments

The authors dedicate this manuscript to the memory of Prof. Inessa B. Kozlovskaya, the main conceptualist and leader of studies performed after spaceflights for many years. They also express their gratitude to all the cosmonauts who took part in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Frontiers in Physiology

TYPE Review
PUBLISHED 19 May 2023
DOI 10.3389/fphys.2023.1146096

OPEN ACCESS

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RECEIVED 18 January 2023
ACCEPTED 09 May 2023
PUBLISHED 19 May 2023

CITATION
Faerman A, Clark JB and Sutton JP (2023), Neuropsychological considerations for long-duration deep spaceflight.
Front. Physiol. 14:1146096.
doi: 10.3389/fphys.2023.1146096

Neuropsychological considerations for long-duration deep spaceflight

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The deep space environment far beyond low-Earth orbit (LEO) introduces multiple and simultaneous risks for the functioning and health of the central nervous system (CNS), which may impair astronauts' performance and wellbeing. As future deep space missions to Mars, moons, or asteroids will also exceed current LEO stay durations and are estimated to require up to 3 years, we review recent evidence with contemporary and historic spaceflight case studies addressing implications for long-duration missions. To highlight the need for specific further investigations, we provide neuropsychological considerations integrating cognitive and motor functions, neuroimaging, neurological biomarkers, behavior changes, and mood and affect to construct a multifactorial profile to explain performance variability, subjective experience, and potential risks. We discuss the importance of adopting a neuropsychological approach to long-duration deep spaceflight (LDDS) missions and draw specific recommendations for future research in space neuropsychology.

KEYWORDS

human spaceflight, neuropsychology, behavioral health, astronauts, human performance, cognition

Introduction

Over the past seven decades, research in space has identified multiple implications of spaceflight on physiology and performance. As governmental and commercial space industries are growing considerably and are projected to expand even more in the following decades to come (Whealan George, 2019), prospects of long-duration deep space (LDDS) missions are currently in motion. Data collected over the years have produced a detailed and nuanced understanding of the low-Earth orbit (LEO) flight environment but limited insights regarding LDDS exposure. Given that LDDS exposure holds a set of unique and distinct mission profiles and risks, the environmental, interpersonal, and psychiatric stressors diverge from LEO missions, and thus treatment needs will likely differ as well (Smith, 2022). As such, the neuropsychological risks and countermeasures needed for LDDS missions beyond LEO are not well-defined (NASA, 2022) and are often studied separately rather than integratively.

The spaceflight environment, both in LEO and deep space, is associated with several unique conditions, some able to be simulated in Earth-based settings while others are currently not. Most notably, Earth-based space-related research has utilized analog stations to simulate isolated, confined, and extreme (ICE) environments homologous to a space station, a space vessel, or an off-Earth planetary habitat. Additionally, analog missions and Earth-based training can simulate social and teamwork-related stressors, operating equipment under limited conditions, rehearsing mission protocols, delayed communication with the Ground, and other mission-specific objectives (e.g., research experiments). Such simulations are also helpful in validating findings across different environments, settings, and populations. Conversely, some space-related conditions cannot be simulated with fidelity on Earth, such as alterations in gravity, cosmic radiation, and danger in the operating environment. Among their multisystemic effects on human health, these unique space-related conditions have been documented to impact the central nervous system in a manner that requires further consideration as LDDS missions become accessible and financially attractive. Although only a paucity of scientific studies to date examined the multifaceted implications of the deep-space environment on human cognition, behavior, and mood, anecdotal evidence and mission records allow for a better understanding of potential risks.

The National Aeronautics and Space Administration (NASA) Human Research Roadmap (HRR) recognizes that the estimation of the CNS risks due to multiple and simultaneous spaceflight hazards is hindered by a lack of relevant human data (BMed-102 (NASA, 2022b)). Further, the HRR recognizes that acute spaceflight CNS risks include neuropsychological changes which may impair astronauts' performance and health (NASA, 2022b). Previous reviews provided immensely informative summaries and discussions of the impacts of the space environment on cognitive, behavioral, and neurological health (De la Torre, 2014; Strangman et al., 2014; Roy-O'Reilly et al., 2021; Smith, 2022). De La Torre (De la Torre, 2014) presented the importance and utility of neuropsychological considerations for space research (i.e., "space neuropsychology") and stated that a decade ago, there was not enough evidence in this field with regard to space health. In this review, we build on previous works and present recent evidence interwoven with a neuropsychological narrative of contemporary and historic spaceflight case studies. As future deep-space missions to Mars, moons, or asteroids will inevitably exceed International Space Station (ISS) stay durations and are estimated to require up to 3 years (NASA, 2022), we focus on considerations for long-duration spaceflight. We chose this approach to overcome the main limitations of health-related research in space; nearly all data on human physiology and psychology in space come from either LEO or analog models, mostly short-term missions (likely due to the over-representation of Space Shuttle missions for the construction of the ISS, approximately 14-days (Strangman et al., 2020)), and very small sample sizes. To highlight the need for further investigations, we provide neuropsychological considerations integrating cognitive and motor functions, neuroimaging, neurological biomarkers, behavior changes, and mood and affect to construct a multifactorial profile to explain performance variability, subjective experience, and potential risks. We then highlight the importance of these considerations for the space industry and draw specific recommendations for future research.

Structural and functional CNS alterations

Recent studies of the CNS before and after space missions indicate structural and functional alterations associated with spaceflight. Van Ombergen et al. (Van Ombergen et al., 2019) found significant increases in ventricular volume, likely due to microgravity-related reductions in cerebrospinal fluid (CSF) resorption. Consistently, prospective neuroimaging analyses by Kramer and colleagues (Kramer et al., 2020) revealed that long-duration spaceflights were associated with alterations in CSF hydrodynamics, as well as deformation of the pituitary gland. Additionally, Jillings et al. (Jillings et al., 2020) observed increases in cerebellar white matter after spaceflight. These findings also denoted a long-term (potentially permanent) structural impact as these volumetric increases remained significant even after a 7-month (Van Ombergen et al., 2019; Jillings et al., 2020) and 1-year follow-ups (Kramer et al., 2020). Most recently, Doroshin et al. (Doroshin et al., 2022) analyzed microstructural tractography changes in 12 cosmonauts after an average 6-month stay aboard the ISS and observed significant changes in multiple large white matter tracts associated with sensorimotor processes. In partial alignment with the stability of the volumetric changes observed by Jillings et al. (Jillings et al., 2020), some of the observed changes remained present at the 7-month follow-up, while others (e.g., corticostriatal tracts and corpus callosum) recovered back to baseline. Functionally, significant pre-to post-spaceflight changes in functional connectivity of visual with visuomotor and visual-frontal structures were associated with spatial working memory (Salazar et al., 2022), likely representing spaceflight-related disruptive impacts and compensatory shifts in the brain. Other studies also found decreased functional connectivity between the cerebellum and networks that play a role in vestibular, visual, motor, and sensory processing (Demertzi et al., 2016; Pechenkova et al., 2019). For a comprehensive review of brain alterations during spaceflight, see Roy-O'Reilly et al. (Roy-O'Reilly et al., 2021).

Some of the structural changes likely represent adaptive neuroplasticity in brain tissues (Jillings et al., 2020). However, spaceflight-related changes in the brain may reflect an overall risk for immediate and long-term damage, as indicated by both biomarker and performance-based evidence. Long-duration spaceflight was associated with significant increases in neurofilament light chain (NfL), a marker for axonal disintegration, and glial fibrillary acidic protein (GFAP), a marker for astrocytic activation (zu Eulenburg et al., 2021). Moreover, zu Eulenburg et al. (zu Eulenburg et al., 2021) found post-flight increases in the accumulation of amyloid-β peptides, Aβ40 and Aβ42, critical proteins in the neurodegenerative processes of Alzheimer's disease pathologies (Qiu et al., 2015). Post-flight mice models showed immunohistochemical evidence of damage to the blood-brain barrier, alterations in neurovascular and neuronal structure, reduced mitochondrial function and decreased overall brain metabolism (Mao et al., 2020). These elevated markers of brain tissue damage could represent reparatory processes due to microgravity-related intracranial hypertension (zu Eulenburg et al., 2021; Michael and Marshall-Bowman, 2015). Spaceflight-related increases in intracranial pressure (ICP) is a theoretical symptom that has largely gained acceptance as a recognized clinical phenomenon following supportive indirect evidence (e.g., increased ICP by lumbar puncture in symptomatic astronauts upon return to gravity; also, spaceflight-associated visual pathologies have a similar presentation to cases of known ICP on Earth), despite lack of direct evidence of ICP in space (Michael and Marshall-Bowman, 2015). Beyond increased risk for tissue damage, long-term intracranial hypertension is a risk factor for hemorrhage, infection, postlumbar puncture headache, and spinal cord injury (Barr, 2014; Michael and Marshall-Bowman, 2015). Although stroke poses the most immediate danger to health and performance, long-term changes in brain vasculature could augment neurocognitive deficits due to vascular reasons (e.g., "vascular dementia"), leading to clinically meaningful declines in cognitive performance, mood, and health (Bir et al., 2021).

Upward redistribution of CSF (Roy-O'Reilly et al., 2021) could interrupt systemic processes responsible for both short- and long-term cognitive health and performance. For example, impaired CSF flow might impede glymphatic system function. A recently discovered CNS waste clearance system, the glymphatic system utilizes astroglial-based perivascular "tunnels" to mobilize soluble proteins and metabolites from interstitial space to perivenous drainage pathways (Jessen et al., 2015). As such, suboptimal functioning of glymphatic clearance could progressively lead to interruption of neuronal health and the accelerated accumulation of protein waste associated with neurodegenerative diseases such as Alzheimer's (amyloid-β) and Parkinson's (α-synuclein). Post-flight elevations in GFAP and amyloid-β (zu Eulenburg et al., 2021) support this hypothesis. Indeed, a recent study by Barisano et al. (Barisano et al., 2022) analyzed volumetric alterations in perivascular spaces (PVS) of international space screws after six monoths on the ISS, and found increase in PVS volumes in the basal ganglia and white matter post-spaceflight. Such PVS changes could lead to morphplogical changes of glymphatic pathways and impair glymphatic clearance, as seen in aging (Kress et al., 2014). White matter PVS volume changes also correlated with enlargement of the lateral ventricles and shrinkage of the subarachnoid space at the vertex. Intrestingly, despite exposure to the same ISS environment for the same duration, NASA astronauts showed greater white matter PVS changes than Roscosmos cosmonauts, attributed by the authors to brain fluid redistribution due to different countermeasures and resistance exercise routines (Barisano et al., 2022). Furthremore, NASA astronauts who developed spaceflight-associated neuroocular syndrome (SANS), swelling in the back of the eye that impacts visual acuity in about 60% of astronauts (Lee et al., 2017), had greater white matter PVS volume changes (Barisano et al., 2022). A detailed summary of relevant molecular, neurochemical, and neurobiological evidence from animal models and suggestions for further rodent and primate studies can be found in a recent review by Desai et al. (Desai et al., 2022).

Radiation: the current frontier

The majority of current NASA-funded space-related CNS research is focused on the adverse effects and possible acute risks of galactic cosmic rays (GCR; highly energetic, fully ionized atomic nuclei) and solar particle events (SPE; Sun-emitted protons which are accelerated by a solar flare or coronal mass ejection) (NASA, 2022b; NASA, 2022). Ionizing radiation in the space environment may increase the risk of degeneration of bodily tissue, carcinogenesis, and acute radiation syndromes (Mi and Norman, 2020). Specific concerns were raised regarding the acute and late effects of ionizing radiation in space on the CNS, particularly in the context of LDDS missions (Mi and Norman, 2020; Pariset et al., 2021). Irradiation effects on the CNS include DNA damage, necrosis, oxidative stress, and systemic inflammation (Pariset et al., 2021). Furthermore, experimental studies in mice demonstrated that CA1 pyramidal neurons that were neutron-irradiated are less excitable (Acharya et al., 2019), consistent with previous findings showing that GCR exposure leads to reductions in neurotransmitter expression (Carr et al., 2018) and that exposed neurons in the hippocampus and perirhinal cortex undergo membrane hyperpolarization (Sokolova et al., 2015; Parihar et al., 2018) and structural alterations in dendritic spines (Carr et al., 2018). Similarly, rat models found irradiation to be associated with deficits in dopaminergic pathways, which were later correlated with attentional impairments (Cucinotta et al., 2014). Moreover, two studies suggested ionizing radiation exposure might accelerate Alzheimer's disease progression in mice (Vlkolinsky et al., 2010; Cherry et al., 2012; Cucinotta et al., 2014).

While the vast majority of relevant research has been done in rodent models, with minimal and indirect evidence in humans (George et al., 2010; Cucinotta et al., 2014; Garrett-Bakelman et al., 2019), sufficient evidence suggests that radiation dose and quality have differential detrimental effects on cognitive performance (Cacao and Cucinotta, 2019) and are linked to the emergence of distress behaviors (Acharya et al., 2019; Pariset et al., 2021). Although no direct evidence links radiation damage to cognitive sequelae in space crews (an environment with greater risk for radiation-related biological damage (Straume, 2018)), evidence from radiation therapy links neurodegenerative conditions and neurobehavioral symptoms following treatment (Crossen et al., 1994; Peper et al., 2000; Klein et al., 2002). However, the uncertainty around functional and safety threshold for exposure hinders necessary decision-making for LDDS missions such as to Mars (Straume, 2018). These led several authors and space agencies to highlight the incremental risk of LDDS radiation exposures to human cognition, astronaut acute and long-term neurological and emotional wellbeing, and mission safety.

It is important to note that evidence from radiation therapy patients is likely heavily confounded by the disease being treated. Although radiation-related effects have been studied in otherwise healthy populations, most studies mainly focused on health outcomes and not pre/post-exposure changes in performance or biomarkers. For example, recent literature suggests that long-haul high-altitude airline crew and passengers are exposed to radiation levels that likely pose a variety of health risks, specifically the risks of cancers, including brain tumors (Olumuyiwa, 2020). Similarly, analyses of cohorts exposed to the Chernobyl accident found inconsistent results but were heavily confounded by methodological pitfalls (Cucinotta et al., 2014). However, recent meta-analyses indeed found exposure to low-to-moderate doses of ionizing radiation to be associated with cardiovascular disease incidence and mortality (Lopes et al., 2022a), but not risk for developing CNS tumors (Lopes et al., 2022b). Interestingly, a linear relationship between Parkinson's disease incidence and cumulative exposure to gamma radiation was observed in employees of the Mayak Production Association, one of Russia's largest nuclear facilities (Azizova et al., 2020). This finding was later supported by the Million Person Study of American workers and veterans who were exposed to radiation from 1939, suggesting a potential dose-response relationship with Parkinson's disease incidence in at least one of the cohorts (Boice et al., 2022; Zablotska et al., 2022). Nevertheless, these data are entirely observational and likely are confounded by a variety of interindividual differences, some with potential impact on radiation effect on the CNS (Cucinotta et al., 2014).

The complex network of ionizing radiation impact on the CNS requires multifaceted preventative countermeasures and reparative treatments. In a recent review, Pariset et al. (Pariset et al., 2021) summarized various approaches currently discussed to mitigate radiation-related CNS impairments. Current approaches target one of five main mechanisms: DNA damage, inflammation, reactive oxygen species, cell survival, and tissue repair. In their analysis, Pariset et al. (Pariset et al., 2021) emphasize that, for countermeasures to be practical and efficient, they would have to be administered peripherally, with minimal need for repeated or continuous administration and little to no side effects.

Sleep and circadian health

Sleep disturbance, among the most common complaints by astronauts (Barger et al., 2014), has been robustly linked to specific deficiencies in cognitive performance on Earth (Lim and Dinges, 2010). Unsurprisingly, sleep remains impactful on cognition during spaceflight as well (Wu et al., 2018). An additional consequence of inadequate sleep (Darwent et al., 2015), excessive daytime fatigue, is a documented factor in decreased astronaut productivity and performance (Eddy et al., 1998). Although acute sleep disruption may be more impactful on basic attentional skills than on complex cognitive tasks and executive functions (Lim and Dinges, 2010; Wickens et al., 2015), prolonged disturbances in sleep are likely to impact executive functions and memory, as seen in individuals with insomnia (Fortier-Brochu et al., 2012). Indeed, several historical incidents highlight the importance of sleep and fatigue for mission safety and success. Post-incident analyses indicated critical cognitive and psychosocial factors that led to the 1997 collision of the Russian supply shuttle *Progress 234* with the *Mir* space station. The collision ruptured Mir's pressure hull, and the station was almost evacuated after developing an uncontrolled attitude drift. Cosmonaut Vasili Tsibliyev, the Progress 234 commander, reported poor sleep 2 weeks before the crash and having only 2 days of rest in the 4 months leading to the crash (Ellis, 2000). Several cognitive factors played a role in the collision, including inaccuracies in visuospatial (e.g., lack of detection of the Mir using the Toru docking monitor) and sensorimotor (e.g., in operating the attitude thrusters) performance and suboptimal decision making (e.g., the shutdown of the Kurs radar) (Ellis, 2000). Other psychosocial factors contributed, such as elevated stress (e.g., Tsibliyev failed his previous Mir docking with Progress-233 (Ellis, 2000) and was likely stressed to succeed docking with Progress-234) and the suboptimal relationship between the cosmonauts and Russian Mission Control (Oberg, 1998). Less than a month later, during a spacewalk training exercise to reconnect power cables to three solar arrays undamaged from the collision, Mir-23 Flight Engineer Aleksandr Lazutkin disconnected a wrong power cable routing power and data to the attitude control computer (NASA, 1986). As a result, the Mir lost orientation to the Sun and had a total power shutdown to the station. Furthermore, long-duration spaceflight poses greater concerns regarding the detrimental effects of inadequate sleep on performance and health. After studying astronaut Jerry Linenger's circadian markers across 112 days on the Mir, Monk et al. (Monk et al., 2001) concluded that spaceflights longer than 100 days might lead to an accumulative failure of the human endogenous circadian pacemaker to drive a 24-h circadian rhythm. Consequently, such circadian deviation can contribute to sleep problems, particularly when forcing a 24-h schedule (Monk et al., 2001; Guo et al., 2014). Anecdotally, cognitive performance in the last third of the mission was notable for increased speed (potentially due to practice effects) and reduced accuracy (Monk et al., 2001). Indeed, NASA's HRR recognized sleep as a major area of interest (Gregory, 2016); however, while operational impact and long-term health risks of sleep issues in LEO, lunar orbit, and lunar surface are largely accepted with optimization strategies, both aspects are yet to be mitigated for a LDDS Mars mission (Gregory, 2016).

Beyond direct and indirect impacts on performance, prolonged sleep and circadian deficits also pose risks to CNS health. Self-reported disrupted sleep is associated with a substantial increase in risk for Alzheimer's disease and other dementia (Benedict et al., 2020). Additionally, acute sleep deprivation leads to elevated levels of CSF of tau (Holth et al., 2019), and disrupted sleep due to sleep apnea was associated with amyloid-β. Slow-wave sleep appears to decrease with Alzheimer's disease progression, mainly tauopathy (Lucey et al., 2019), potentially reflecting a decrease in glymphatic clearance of amyloid-β and tau (Cedernaes et al., 2017). Consistently, glymphatic clearance rates in rodent models appear to be twice faster during sleep than during wake (Xie et al., 2013), highlightinh the Adequate sleep is particularly crucial with regards to glymphatic clearance (Mendelsohn and Larrick, 2013), Although dementias manifest mostly in older adults, a recent study found acute sleep loss to associate with elevated tau levels in the blood, potentially suggesting detrimental effects on brain health even in young adults (Benedict et al., 2020). Consistently, in mice, chronic short sleep is associated with reductions in CA1 pyramidal neuron quantity and volume, impaired spatial memory, and increased amyloid-β and tau (Owen et al., 2021). Aside from sleep-related risk, a growing body of evidence links circadian disruptions to a risk of developing or exacerbating neurodegenerative processes, such as accelerated temporal lobe atrophy, increased CSF biomarkers of proteinopathy, and increased risk of mild cognitive impairment in delayed activity rhythms (Cedernaes et al., 2017; Nassan and Videnovic, 2022). Furthermore, mice models of circadian disruption indicated impaired functional connectivity, greater neuronal oxidative stress, and increased permeability of the blood-brain (likely due to governing role of an endogenous circadian rhythm on the barrier transporter functions) (Cedernaes et al., 2017; Cuddapah et al., 2019). Additionally, disruptions to sleep-related clearance of perivascular waste can interfere with the movement of molecules across and along the blood-brain barrier leading to increased permeability and barrier breakdown (Cedernaes et al., 2017; Cuddapah et al., 2019). In LDDS the risks of sleep and circadian disruptions are not isolated from radiation and gravity effects. As such, the potential accumulation of stress on the CNS is particularly salient for LDDS missions, and the need to formalize risks and develop effective countermeasures for prolonged disturbed or inadequate sleep is high.

Clinical and performance implications

Cognitive performance in space

Although no evidence to date indicates an increased prevalence of neurodegenerative disease in humans who were exposed to spaceflight environments, current literature suggests that longer spaceflights pose considerable neurocognitive risks. Failures of attention or task planning can and have put the lives of astronauts and cosmonauts at risk. For example, during the 96-days-long Salyut 6 EO-1 mission in 1977, mission commander Yuri Romanenko forgot to attach his safety cord while preparing for a spacewalk. He was pushed outside, and flight engineer Gregory Grechko managed to grab Romanenko's safety cord with one hand and pull him back into the airlock (JSTOR, 1978; Harland, 2007).

Tracking the independent impact of long-duration spaceflight-related brain alterations on cognition is a difficult task, particularly when cognitive functioning is commonly confounded by sleep, fatigue, and other contextual factors. For example, before the implementation of modern computerized batteries, neuropsychological testing during spaceflight was considerably limited (Strangman et al., 2020). Older measures were conceptualized through a brain injury paradigm and lacked sensitivity in normal brain functioning and above-average populations such as astronauts (Strangman et al., 2020). Furthermore, most tests were not designed for recurring administration, and practice effects were notable across many studies (Strangman et al., 2014). As such, rather than highlighting consistent cognitive domains sensitive to the spaceflight environment, data suggests intraindividual alterations in cognitive performance (Strangman et al., 2014). For example, the NASA Twin Study (Garrett-Bakelman et al., 2019) compared cognitive performance, using the Cognition (Basner et al., 2015) computerized test battery, over 1 year between inflight and Earth-based identical twin astronauts. Cognition was developed for astronauts and was recently found to have good acceptability in astronaut and astronaut-surrogate cohorts across various mission settings and durations (Casario et al., 2022). From early to late flight, the inflight astronaut had significant reductions in visuospatial distinction (Abstract Matching), visuomotor speed (Digit Symbol Substitution Task), and in the Emotion Recognition Task (Garrett-Bakelman et al., 2019). Interestingly, compared to the Earth-based control astronaut, the inflight astronaut demonstrated decreases in visual learning and matching and greater risk-taking (Balloon Analog Risk Test) (Garrett-Bakelman et al., 2019).

A multitude of factors can impact cognitive performance during spaceflight, including living in an ICE environment (Connaboy et al., 2020) or unexpected events such as dehydration (Wittbrodt and Millard-Stafford, 2018), carbon dioxide (CO2) spikes (Scully et al., 2019), exposure to toxic gases and substances (Strangman et al., 2020), and noise (Szalma and Hancock, 2011). In their review of cognitive performance in spaceflight, Strangman et al. (Strangman et al., 2014) reported modest evidence in spaceflights >90 days (31 subjects across seven studies) for impairments in attention, speed of visuomotor tasks, and time perception (underestimation), while performance on mental rotation of visual objects was intact or had minimal improvement. Interestingly, they also found spaceflight to be associated with increases in the variability of cognitive performance (Strangman et al., 2014). It is important to note that although these findings are classified for "very long-duration" spaceflights, future missions planned for years might involve risks that are not well-captured in shorter durations. In a more recent study, Roberts et al. (Roberts et al., 2019) demonstrated that spaceflight-related brain changes are associated with alterations in cognitive and motor performance and progress based on mission duration. The authors tested relationships between structural brain changes and neuropsychological performance in 12 long-duration astronauts on the ISS using the Spaceflight Cognitive Assessment Tool for Windows (WinSCAT) and with motor performance in eight astronauts using the Functional Task Test. Spaceflight-related changes in cognitive performance were significant for reduced accuracy on a processing-speed and learning task (Code Substitution; CDS), but faster reaction times on both the CDS and a measure of sustained attention (Continuous Performance Test; CPT), interpreted by the authors as a likely consequence of practice effects (Roberts et al., 2019). Structural post-flight changes in the bilateral optic radiations (right more than left) and splenium (the posterior end of the corpus callosum) were negatively associated with a change in CPT reaction time. Additionally, post-flight ventricular enlargement had a strong negative association with CPT reaction time. These volumetric changes were interpreted as a compensatory process that allowed the preservation of intact performance (Roberts et al., 2019). Interestingly, post-flight ventricular enlargement was also negatively correlated with CDS accuracy, but not after correcting multiple comparisons. Lastly, changes in the right lower extremity primary motor area (or midcingulate) were significantly associated with the completion time of the Seated Egress and Walk Test, a complex motor task involving an obstacle course. Importantly, the extent of ventricular changes was negatively correlated with age, indicating that younger astronauts may experience greater CNS alteration (Roberts et al., 2019). The findings by Roberts et al. (Roberts et al., 2019) might also indicate differences between the space environment and Earth-based ICE environment, as a recent study in ICE environment analogs (Connaboy et al., 2020) found that almost all WinSCAT measures improve over 5-month missions.

Accumulating evidence robustly links microgravity with sensorimotor and visuospatial alterations. Conceptual frameworks have suggested that when vestibular inputs are disrupted, the CNS rapidly adapts by updating internal prediction models of sensory implication on motion and proprioception and up-weighting non-vestibular information that appears more reliable (Clément and Ngo-Anh, 2013; Carriot et al., 2015). For example, gravity alterations interfere with visual perception stability (Clément and Demel, 2012), and both short (e.g., 2 weeks) and prolonged (e.g., 6 months) exposure to microgravity appears to disrupt vestibular inputs and processing, leading to declines in postural control, balance, and mobility (Wood et al., 2015; Ozdemir et al., 2018; Tays et al., 2021). However, these effects appear to recover back to baseline within two to 4 weeks (Wood et al., 2015; Ozdemir et al., 2018; Tays et al., 2021). Beyond the impacts on sensorimotor performance, gravity-related alterations of vestibular signals can impact spatial cognitive functions such as mental imagery, visuospatial reasoning, and number processing (Mast et al., 2014). When such vestibular disruptions are present, other multisensory stimuli can aid in representational stability. For example, Tays et al. (Tays et al., 2021) showed a trend toward better in-flight performance on the cube rotation task when crewmembers were able to anchor themselves to the floor using foot loops. Using a parabolic flight paradigm, Salatino et al. (Salatino et al., 2021) found that zero gravity enhances bottom-up visuospatial attention while weakening voluntary sustained attention. These findings emphasize the possibility that bottom-up processes drive some of the cognitive alterations observed in space crews (e.g., faster reaction times). Furthermore, the vestibular system is responsible for several multisensory components of body representation and, as such, plays a role in neuropsychological processes such as psychomotor performance, pain, and orientation and can influence mood and behavioral health (Mast et al., 2014), potentially portraying vestibular dysfunctions as a risk factor for psychiatric symptomatology.

Interestingly, in a bidirectional manner, top-down processes (e.g., mental imagery) can modulate the perception of and response to vestibular stimuli. Consistently, maladaptive top-down processing may negatively impact vestibular functioning, as there appears to be high comorbidity of psychiatric symptoms and vestibular dysfunctions (Mast et al., 2014). In studies funded by the Italian Space Agency, individuals with a stronger trait-like ability to facilitate experiential changes in response to verbal suggestions (i.e., hypnotizability) showed lesser dependence on sensory inputs, better locomotion accuracy, and greater performance benefits from practice (Menzocchi et al., 2009; Menzocchi et al., 2010), suggesting that psychological traits may moderate the effects of vestibular disruptions on performance and other related systems. Overall, vestibular alterations in space may be intrinsically related to cognitive and behavioral health, and addressing developing relevant countermeasures for LDDS missions is needed not only for the in-flight duration but also for the adaptation periods when gravity is reintroduced (e.g., planetary mission) (Clément and Ngo-Anh, 2013).

Space adaptation syndrome (SAS; also called space motion sickness (Strangman et al., 2020)) and complaints about a subjective deterioration of attention and the ability to think clearly (i.e., "mental viscosity," "space fog," or "space stupids" (White et al., 2016)) might represent the subjective manifestation of neurocognitive and vestibular adjustments to the space environment (De la Torre, 2014). It is estimated that approximately 70% of space travelers experience SAS (De la Torre, 2014), but these are mostly transient phenomena that resolve after a few days in the case of space fog (Welch et al., 2009) and days to weeks for SAS (Strangman et al., 2020), thereby aligning with the arguments for a neurocognitive adaptation period to spaceflight (Roberts et al., 2019; Roy-O'Reilly et al., 2021). Russian psychologists and flight surgeons identified a long-duration spaceflight syndrome characterized as a "nervous or mental weakness," and its symptoms include physical or emotional tiredness and fatigue, loss of strength and hypoactivity, attention and memory deficits, sleep disturbance, irritability, volatile mood, poor appetite, and low sensation threshold (Petrovsky and Yaroshevsky, 1987; Kanas and Manzey, 2008). The syndrome was termed "asthenia" (a milder form of neurasthenia (Kanas and Manzey, 2008), F48.8 in ICD-10) and was argued to be somatic in nature and to develop following "excessive mental or physical strain, prolonged negative emotional experiences, or conflict." (Petrovsky and Yaroshevsky, 1987) There is a paucity of evidence regarding asthenia in space, and findings largely fail to consistently support it (Kanas and Manzey, 2008).

Mood and behavior

Alongside potential alterations in basic and high-order cognitive processes, the individual and compounded effects of the demanding ICE environment, sleep disturbances, structural and functional brain changes, and radiation exposure inevitably impact mood and behavior. Indeed, concerns about psychological problems in LDDS exploration were raised in the early phases of the space race by both NASA (e.g., Werner von Braun in 1954) and ROSCOSMOS (e.g., by cosmonaut Valery Ryumin in 1980) (Stuster et al., 2020).

Besides the fact that space missions are long-awaited by the crew, which could increase mission-related stress and the strive for mission success, the space-related CNS-compromising factors reviewed above may have implications on space crews' mood and behavior. Specifically, alterations in emotion regulation can have direct implications on astronauts' wellbeing, performance, and mission safety and success. The superior temporal gyrus and the supplementary motor area, brain regions that have been found in meta-analytic evidence to be involved in emotion regulation (Kohn et al., 2014; Morawetz et al., 2017), undergo significant morphological changes during spaceflight (Koppelmans et al., 2016; Van Ombergen et al., 2019; Hupfeld et al., 2020). Attentional abilities, which may be impaired in long-duration missions, play a central role in emotion regulation, particularly in changing the focus of attention to and from emotionally salient stimuli (i.e., attentional deployment) (Turnbull and Salas, 2021). Following a 169-day-long mission, a cosmonaut experienced decreased intrinsic functional connectivity in the right insula (Demertzi et al., 2016), a region that is involved in emotion regulation independent from strategy, with greater involvement in attention-related emotion regulation (Morawetz et al., 2017). Sleep is also a key factor in emotion regulation. Inadequate sleep is linked to increased negative and reduced positive emotions and can directly and indirectly (e.g., via motivation and goal-reward evaluation) interfere with cognitive regulatory processes of emotion (Palmer and Alfano, 2017).

There have been several cases of disproportional emotional responses and consequent behaviors in long-duration LEO space missions. For example, STS-51B payload specialist Taylor Wang had an experiment delayed due to a faulty instrument, but NASA denied him the opportunity to repair it. In recounting his experience, he described that, out of desperation, he said that if he is not given a chance to repair his instrument and repeat his experiment, he is "not coming back" (Reichhardt, 2002). This statement reportedly led NASA to assign a psychologist to interview the STS-51B crew members about Wang's mental wellbeing. Mission commander, astronaut Bob Overmyer, indicated that Wang was depressed over the failure of his experiment (Reichhardt, 2002). Similarly, after receiving the news of his mother's passing, Mir 18 Commander Vladimir Dezhurov separated from the crew and secluded himself in a module for days (Dudley-Rowley, 2006). Despite the emotional toll of losing a parent, extreme response to grief may be influenced by compromised emotion regulation processes. Cosmonaut Valery

Ryumin contemplated that "all one needs to effect a murder is to lock two men in a cabin eighteen feet by twenty feet and keep them there for 2 months." (Oberg, 1981) And, indeed, during his 211-day-long mission on the Salyut 7, cosmonaut Valentine Lebedev estimated that 30% of time-in-mission was spent in interpersonal conflict (Palinkas, 2001) and that physical and verbal mannerisms became sources of interpersonal tension between him and his crewmember, cosmonaut Anatoly Brezevoy (Kanas et al., 2020). Consistently, in a 520-day-long analog mission, as part of the MARS 500 study, two crewmembers with the highest stress and exhaustion levels accounted for 85% of the conflicts (Basner et al., 2014). Notably, one of these individuals developed insomnia symptoms with chronic partial sleep deprivation, daytime tiredness, and frequent impairments to alertness (Basner et al., 2014). However, crew-mission control conflicts were five times more prevalent than within-crew interpersonal conflicts (Basner et al., 2014).

Potentially necessary for in-flight maintenance during LDDS missions, spacewalk itself can bring a wide spectrum of emotional experiences. For example, after having been ordered to climb back into the capsule at the completion of the first American spacewalk, Gemini 3 Astronaut Ed White stated it was "the saddest moment of my life." (MSFC, 2009) On the other hand of the spectrum, during his 132-days-long mission between STS-81 and STS-84, Linenger described the feeling of spacewalking as "difficult to discount the sensation that you are moving away, alone, detached . . . You are hanging to the thinnest limb of the tallest tree in the wind. The tree is falling" (NASA, 1997).

Compounding on the space-related compromise to emotion regulation abilities, LDDS missions are going to introduce considerable differences from lunar or LEO missions (e.g., ISS) due to the length of travel. While LEO missions often include a busy schedule to maximize research and task output in a given timeframe, LDDS missions are likely to become increasingly autonomous (NASA, 2022b). As such, LDDS inevitably requires a different model of psychological wellbeing, addressing the lack of live ground support. Given the different nature of LDDS missions from ongoing space missions, this new psychological model will lean mostly on findings from Earth-based analog missions, as well as insights from homologous environments. Remote polar and space missions have identified time effects on psychological functioning. Specifically, subjective reports indicate an increase in emotional difficulties and interpersonal problems after the halfway point of the mission (aptly termed the "third-quarter phenomenon") (Kanas et al., 2020; Stuster et al., 2020). Although it is possible that an emotional letdown follows the realization of the need to spend an equivalent amount of time before the return home (Kanas et al., 2020), it is also possible that space-related brain changes accumulate over time and show greater effects on mood and behavior after a substantial amount of time has passed. However, this phenomenon did not appear to have a statistically significant effect on mood or interpersonal cohesion in either the Mir or ISS, possibly due to psychosocial support from crewmembers who had increased or no change in emotional status after the halfpoint (Kanas et al., 2020).

Another potential for emotional compromise in LDDS missions stems from the distance from Earth. Across studies done in both the ISS and remote duty stations, conflicts with ground control proved a major contributor to space crews' stress (Stuster et al., 2020). This issue could prove substantially more challenging as communications delays between the crew and Earth-based control increase with distance from Earth (Kanas et al., 2020), as confirmed by the MARS 500 analog missions (although the impact was mainly due to the presence of delays rather than their length) (Ushakov et al., 2014). In a survey about the emotional reaction to being in space, all 39 astronauts and cosmonauts endorsed at least some level of positive change (Ihle et al., 2006). A content analysis revealed one significant factor in producing such a change: perceptions of Earth. Of the different items under this factor, the highest impact came from an increasing appreciation of the Earth's beauty. This item, together with two other items about realizing how much one cares for the Earth and appreciates its fragility, were significantly related to endorsing increases in environmental involvement after returning to Earth. This psychological phenomenon was previously termed The Overview Effect by philosopher Frank White (White, 1998). Viewing the Earth appears to be emotionally salient to astronauts. Within the first 3 years of the ISS, almost 200,000 photos of Earth were taken, with almost 85% being crew-initiated (Yaden et al., 2016). Consistently, anecdotal evidence suggests that denying crew the opportunity to view the Earth may exacerbate conflicts (e.g., Skylab IV) (Yaden et al., 2016). In LDDS missions, however, crewmembers will likely lose direct visual contact with the Earth. This may have implications for crewmembers' sense of safety (a reminder of the distance from help in case of emergency), belonging, motivation, and wellbeing. For further reading about behavioral health risks and supportive measures in LDDS missions, see a scoping review by Smith (Smith, 2022).

Future research and clinical directions

Given the multicomponent complexity of the effects of deep-space environments on the CNS, an integrated approach to identifying optimal measures, interventions, and countermeasures is warranted. Here, we apply a neuropsychological approach, taking together evidence from neuroimaging, cognitive performance, and behavioral functioning based on recently published evidence and historical accounts. This approach is consistent with NASA's HRR design, identifying a need for practical tools for monitoring and measuring changes in cognitive and behavioral health and performance (NASA, 2022b). Most importantly, the interactions and combined effects of prolonged exposures to gravity alterations, radiation, and sleep and circadian disruptions during LDDS missions, and the interrelatedness between cognitive and behavioral health highlight a clear need for assessment tools that can account for these combined effects, rather than evaluating them separately. Such tools should be developed for flight surgeons and operational psychologists to use in-mission and utilize both objective assessments and crewmembers' subjective reports. Furthermore, developing such integrated methods could aid in optimal astronaut selection and training and personalize communication, expectation, and interventions (NASA, 2022b; Smith, 2022). First and foremost, there is a crucial uncertainty about whether gravity alterations, radiation exposure, and potential sleep and circadian disruptions in LDDS missions pose a risk for acute neurological damage such as stroke or tissue atrophy due to the possibility of intracranial hypertension. This is a priority, as identifying the severity of such risk would advise the implementation of preventative strategies to reduce it. Moreover, evidence suggests that prolonged exposure to radiation (particularly in high doses as expected in LDDS missions) and sleep loss could accelerate neurodegenerative processes. At this point, not only is there insufficient data to evaluate the likelihood of this risk in humans but no estimate of the speed of neurodegenerative progression and whether it is reversible or permanent (particularly in light of transient and reversible structural changes observed in 6-month missions in LEO). Furthermore, it is yet unclear whether these changes underlie the observed alterations in cognitive performance in space, although current data suggests only a moderate impact in LEO missions.

Historically, psychological screening has proved insightful in several anecdotal cases. For example, both American and Russian psychologists expressed concerns regarding astronaut John Blaha's readiness for a long-duration mission on the Mir. And indeed, Blaha was later reported to experience depression and anger bursts during the mission (Dudley-Rowley, 2006). Given advancements in measures and greater access to more comprehensive sets of behavioral, cognitive, and neural data, psychological screening should adopt a neuropsychological approach and integrate the multitude of information sources to draw more informed conclusions and make more accurate predictions about astronauts' strengths, weaknesses, and potential risks. This is ever more relevant for LDDS missions due to the increased CNS risk involved. While such approaches currently exist in clinical contexts, further development of a neuropsychological process for astronauts and other high-performing individuals is needed. Such development should expand available normative data, design optimal assessment protocols, delineate a mechanism to integrate all available data points, and provide a detailed personalized output for agencies to work from.

Alongside behavioral and neurocognitive evaluations, sleep assessments before, during, and after missions are essential. Apart from sleep duration, a central outcome variable for sleep health, monitoring the subjective quality of sleep may be crucial for detecting sleep-related deficits to emotion regulation (Palmer and Alfano, 2017). Additionally, people vary substantially, in a trait-like manner, in the extent to which their cognitive and behavioral performance is impacted by inadequate sleep. Similar trait-like factors could also be identified for susceptibility to acute or late cognitive and behavioral detriments, as well as a propensity for CNS damage in the space environment (e.g., synaptic dysfunction, impaired neurogenesis, neurodegeneration, proteinopathies, neuroinflammation) (NASA, 2022b). At this point, no such metrics exist for LDDS missions, nor do validated norms for many of the currently measurable variables (NASA, 2022b). Identifying correlates of this and other trait-like factors could reduce the burden and urgency of managing acute risks while ensuring crewmembers' health and wellbeing. Furthermore, although circadian-based interventions, such as light therapy, scheduled physical activity, and melatonin supplementation, have been tested in LEO missions, the development and validation of new treatments for LDDS could help maintain circadian homeostasis and possibly combat the risk for accelerated neurodegenerative processes (Nassan and Videnovic, 2022).

However, even after accounting for individual abilities to perform under stress and duress, space agencies seek validated performance outcome limits (POLs) and Permissible Exposure Limits (PELs) (NASA, 2022b). POLs and PELs are intertwined, as PELs should be determined based on POLs and health measures, while PELs should be taken in the context of environmental factors. For example, alongside research into the biological impacts of radiation exposure, further research is needed into the cognitive and behavioral implications in humans (NASA, 2022). Although sufficient evidence has been accumulated to safely assume that GCR and SPE negatively impact the CNS, identifying their effect on human performance (POL) will help set exposure boundaries (PEL). Similarly, a better understanding of the implications of space-related CNS structural and functional changes on human performance, health, and wellbeing is acutely needed. Further research is needed into the optimal operational definition and classification of POLs and PELs, given the available and constantly growing data pools. From an integrative standpoint, there is an operational need for the development of PELs of inadequate sleep before sleep-related cognitive and behavioral impairment appears, as well as PELs of negative moods before a negative impact on sleep and cognitive performance is observed.

Lastly, adopting and promoting a neuropsychological approach to LDDS missions (i.e., "space neuropsychology" (De la Torre, 2014)) could accelerate Earth-based brain health research and development. For example, the design and development of direct and embedded tools to evaluate real-time cognitive performance could be used for or adapted to clinical evaluations or operational applications such as military, humanitarian, or emergency service organizations. For example, the Cognition test battery (Basner et al., 2015), which was developed for astronauts, has been utilized for several Earth-based investigations (Beckner et al., 2021; Abeln et al., 2022; Makowski et al., 2022; Tait et al., 2022). Moreover, space-oriented investigations are in progress to test whether introducing artificial gravity during long bouts of simulated microgravity (bed rest) can counteract the development of neurocognitive declines (NASA, 2023aa) or structural and functional alterations in the human brain (NASA, 2023ab). Furthermore, repurposing drugs currently used for CNS disorders may prove useful for preventing and, in some cases, repairing CNS damage in space. In turn, this could increase resources allocated to advancing drug development and off-label clinical research. Similarly, as radiation-related CNS damage is understood as a form of neurological damage or accelerated aging (Pariset et al., 2021), the development of radiation countermeasures may prove beneficial for aging and neurological disorders on Earth.

Conclusion

In this review, we utilize a neuropsychological approach to integrating clinical, performance, neuroimaging, and biomarker evidence from spaceflight studies to better characterize the potential risks of LDDS missions. Although the current literature draws heavily on LEO and relatively short-duration missions, we highlight potential risks for long-term exposure to the space, and particularly deep space, environment. We argue for a need for specific Earth- and space-based investigations and call for more research to adopt a neuropsychological approach to LDDS missions.

Author contributions

AF: conceptualization, literature curation, writing; JC: conceptualization, literature curation, writing; JS: conceptualization, literature curation, writing. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

Acknowledgments

Support from the Translational Research Institute for Space Health through NASA Cooperative Agreement NNX16AO69A is gratefully acknowledged. JS is supported by the Friedkin Chair for Research in Sensory System Integration and Space Medicine at Baylor College of Medicine.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 08 June 2023
DOI 10.3389/fphys.2023.1141015

OPEN ACCESS

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RECEIVED 09 January 2023
ACCEPTED 26 May 2023
PUBLISHED 08 June 2023

CITATION
Malaya CA, Parikh PJ, Smith DL, Riaz A, Chandrasekaran S and Layne CS (2023), Effects of simulated hypo-gravity on lower limb kinematic and electromyographic variables during anti-gravitational treadmill walking.
Front. Physiol. 14:1141015.
doi: 10.3389/fphys.2023.1141015

Effects of simulated hypo-gravity on lower limb kinematic and electromyographic variables during anti-gravitational treadmill walking

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Introduction: This study investigated kinematic and EMG changes in gait across simulated gravitational unloading levels between 100% and 20% of normal body weight. This study sought to identify if each level of unloading elicited consistent changes—particular to that percentage of normal body weight—or if the changes seen with unloading could be influenced by the previous level(s) of unloading.

Methods: 15 healthy adult participants (26.3 ± 2.5 years; 53% female) walked in an Alter-G anti-gravity treadmill unloading system (mean speed: 1.49 ± 0.37 mph) for 1 min each at 100%, 80%, 60%, 40% and 20% of normal body weight, before loading back to 100% in reverse order. Lower-body kinematic data were captured by inertial measurement units, and EMG data were collected from the rectus femoris, biceps femoris, medial gastrocnemius, and anterior tibialis. Data were compared across like levels of load using repeated measures ANOVA and statistical parametric mapping. Difference waveforms for adjacent levels were created to examine the rate of change between different unloading levels.

Results: This study found hip, knee, and ankle kinematics as well as activity in the rectus femoris, and medial gastrocnemius were significantly different at the same level of unloading, having arrived from a higher, or lower level of unloading. There were no significant changes in the kinematic difference waveforms, however the waveform representing the change in EMG between 100% and 80% load was significantly different from all other levels.

Discussion: This study found that body weight unloading from 100% to 20% elicited distinct responses in the medial gastrocnemius, as well as partly in the rectus femoris. Hip, knee, and ankle kinematics were also affected differentially by loading and unloading, especially at 40% of normal body weight. These findings suggest the previous level of gravitational load is an important factor to consider in determining kinematic and EMG responses to the current level during loading and unloading below standard g. Similarly, the rate of change in kinematics from 100% to 20% appears to be linear, while the rate of change in EMG was non-linear. This is of particular interest, as it suggests that kinematic and EMG measures decouple with unloading and may react to unloading uniquely.

KEYWORDS

gait, hypogravity, unloading, hysteresis, kinematics, EMG, anti-gravity treadmill

Introduction

Previous work has demonstrated that human proprioception diminishes in hypogravity; limb matching tasks are less effectively completed (Lackner and DiZio, 1992) as well as approximations of limb position (Bringoux et al., 2012; Young et al., 1993). Mouchnino et al. (1996) found that anticipatory postural adjustments were notably absent below standard Earth gravity. Other studies have also found decreases in illusory kinesthetic responses to vibration (Lackner and DiZio, 1992; Roll et al., 1998) as well as significant differences in cortical waveforms and transmission in hypogravity (Mouchnino et al., 2017; Saradjian et al., 2013). These findings suggest pervasive alterations (both central and peripheral) to proprioception in response to hypogravity.

Hysteresis is the dependency of a system on its previous states, or history. In humans, hysteretic influences have been found not only at a cellular—receptor-based—level (Villalba-Gabea and Chiem, 2020; Villalba-Gabea, 2016; Xiao et al., 2010; Wei et al., 1986a; Wei et al., 1986b), but also in brain networks during transitions between consciousness and unconsciousness (Kim et al., 2018), as well as in the human visual and somatosensory cortices (Sayal et al., 2020; Prud'homme & Kalaska, 1994).

Wei et al. (1986a), Wei et al. (1986b) provided early evidence of hysteresis in muscle spindle receptors. In a series of studies examining the spindle outputs of the ankle musculature in anesthetized cats across a variety of joint angles, neural outputs were strongly influenced by whether stimulation had been increasing or decreasing, even at similar angles. These effects, however, extend beyond the scale of individual receptors. Prud'homme & Kalaska (1994) demonstrated the influence of hysteresis in primate proprioception—even further localizing these changes to the primary somatosensory cortex—during reaching tasks. Subsequent studies have extended these findings to include human joint position sense (Artz et al., 2015; Weiler and Awiszos, 2000).

In insects, the selection of gait type is sensitive to different locomotion speeds, and dependent on the direction of change (Fujiki et al., 2013). Despite the wide variety of morphologies, similar effects have also been examined in ostriches, dogs, horses and, notably, humans (Thortensson & Roberthson, 1987; Mohler et al., 2007; Aoi et al., 2011; Aoi et al., 2013; Abdolvahab & Carello, 2015; Daley et al., 2016). This dependency on previous states, then, appears to be a ubiquitous factor in locomotion under standard Earth-like conditions in both quadrupeds and bipeds.

However, the exact mechanisms behind these changes are not yet well understood. In particular, it is unclear what exact factors drive these changes and if these changes are borne primarily of internal responses, external stimuli, or—more likely—some combination of both. To examine this, previous investigations have focused on manipulating the gait characteristics of an individual within an Earth-like environment. Few studies have sought to examine hysteresis in human gait through manipulation of the environment itself (Bringoux et al., 2012; Ivanenko et al., 2002; Young et al., 1993). Yet even a brief consideration of the ontology of gait reveals the absolute importance of environmental conditions to human locomotion.

In this study, we sought to manipulate the environment surrounding human gait; specifically, we simulated reducing gravitational conditions for healthy adults in order to investigate the effects of gravity as a driving force for hysteretic changes during treadmill walking with loading and unloading. This study has important ramifications in the rehabilitation of lower extremity injuries, where loading and unloading are common parameters of therapy (Ülger et al., 2018; Łyp et al., 2016; Tanaka et al., 2013).

These questions were addressed through the use of zero-dimensional (traditional kinematic and electromyographic measures) and one-dimensional (utilizing statistical parametric mapping) analyses. Previous use of these methods has been found to provide complementary information that was not otherwise apparent given use of only one or the other (Layne et al., 2022a; Layne et al., 2022b).

Materials and methods

Participants

The participants in this study were 15 healthy adults (26.3 ± 2.5 years; 65.5 ± 4.7 inches; 151.7 ± 36.8 lbs; 53% female). Participants also did not have a history of, or any current systemic, degenerative or neuromusculoskeletal injuries or disease that could affect their ability to walk with differential loading for 15 min.

Experimental protocol

Kinematic sensors

Participants were fitted with seven XSens (XSens Technologies) inertial measurement units (IMUs) arranged in a lower-body configuration. These sensors were placed bilaterally over the insteps of the feet, as well as anteriorly over the tibia at mid-shank and laterally over the mid-thigh. The final sensor was placed over the sacrum, centered at the S2 tubercle. All XSens sensors were secured by proprietary neoprene straps with non-slip, rubber backings.

Electromyographic sensors

Four dry surface electromyographic sensors (Biometrics Ltd.—model SX230) were adhered—using hypo-allergenic, double-sided tape—over the rectus femoris, biceps femoris, medial gastrocnemius and tibialis anterior of the right lower limb. These sensors were placed over the belly of each respective muscle—conduction surfaces in line with the muscle fibers—after the skin was shaved and scrubbed with an alcohol wipe. The electromyography control unit was held against the lower back of each participant by an elastic, Velcro-secured neoprene waistband.

Unloading system and walking protocol

Participants were asked to wear a pair of AlterG (AlterG Inc.) compatible neoprene shorts over their clothing. These shorts are designed to allow the participant to be secured into an AlterG Unloading Treadmill System, and a shell surrounding the treadmill system to inflate, thereby creating a positive pressure environment. This positive pressure environment can be used to reduce participants' effective weight.

After being fitted into the system, participants were asked to walk at 100% normal loading for 5 min at a self-selected, comfortable speed that they could easily maintain for at least 15 min (mean speed: 1.49 ± 0.37 mph). This allowed participants to become familiar with the system and allowed time for their gait to stabilize. Participants were also instructed not to hold onto the stability bars of the Alter-G system, but to allow their arms to swing normally. After the five-minute acclimation period, participants were unloaded to 20% of their body weight, in 20% increments, spending one full minute at each level during the descent. After completing one minute of walking at 20%, the protocol was reversed; participants walked for one minute at 40%, 60%, 80% and 100% of their body weight, respectively and in that order. For all levels of unloading and loading, the treadmill speed remained at the participants previously self-selected speed. Participants underwent this pyramidal design of unloading and loading with immediate movement to the next level in the protocol (i.e., no rest or quiet stance in between levels). Kinematics and electromyography data were recorded for the final minute of the acclimatization period, as well as the full minute of walking at all levels of unloading and loading. The reduction in load required approximately 10 s during which time data was not collected.

Data processing

Kinematic data were streamed wirelessly from the XSens IMUs to a computer running a data collection software suite (MVN Awinda). This software collected and internally calculated joint angles for the hip, knee, and ankle, bilaterally. Joint angle waveforms were separated into strides and normalized to 100 points using the peak knee as a reference. Mean, maximum and minimum angles were extracted for all joints. Data were exported, organized, and statistically analyzed in MATLAB using custom scripting.

Electromyographic (EMG) data were collected by a surface EMG system (Biometrics Ltd.). Four channels of data were simultaneously recorded by a waist-mounted control unit, as well as streamed to a computer running a data collection software suite (DataLOG). Data collected were exported into MATLAB for processing. Each channel was individually bandpass filtered (20–450 Hz) using a 2nd order Butterworth filter. Waveforms were then full wave rectified and enveloped using a low pass filter with an additional 2nd order Butterworth filter utilizing a cutoff frequency of 40 Hz (Winter et al., 1980). EMG data were separated into strides and normalized to 100 points using the kinematic peak knee timestamps as a reference. After processing, peak amplitude values, root-mean-square (RMS) and integrated areas were calculated for all muscles. RMS was calculated as the square root of the mean of all values squared over the entire time interval at each level of loading, as a measure of the amplitude of the EMG signal (Cifrek et al., 2009). Integrated areas were also collected over full time intervals and represent the total electrical signal or drive from the central nervous system to the motorneuron (Carpentier et al., 2001; Barton and Hayes, 1996; van der Hoeven et al., 1993; Linssen et al., 1993; Enoka, 1988).

TABLE 1 All comparisons in which $p < 0.05$ are presented. * denotes significance after correction for multiple comparisons. U denotes decreasing load (i.e., 40% load down from 60%); L denotes increasing load (i.e., 60% load up from 40%). Zero-dimensional kinematic pairwise testing.

	Measure	Level of unload	$\mu^\circ \pm std$	p-value
Hip	*ROM*	80U	19.9 ± 6.2	$p < 0.0000$*
		80L	24.9 ± 5.4	
		40U	25.0 ± 4.8	$p = 0.0001$*
		40L	17.1 ± 5.1	
	Min	40U	−2.8 ± 9.9	$p = 0.0009$*
		40L	4.3 ± 8.4	
Knee	*ROM*	80U	56.1 ± 6.5	$p < 0.0000$*
		80L	59.8 ± 6.5	
		60U	60.5 ± 7.1	$p < 0.0000$*
		60L	56.7 ± 6.3	
		40U	63.4 ± 7.7	$p < 0.0000$*
		40L	52.4 ± 7.0	
	Mean	40U	15.7 ± 5.2	$p = 0.0295$
		40L	18.6 ± 6.4	
	Max	80U	54.6 ± 8.2	$p < 0.0000$*
		80L	59.2 ± 6.9	
		60U	58.5 ± 9.1	$p = 0.0008$*
		60L	55.4 ± 7.9	
		40U	60.9 ± 8.8	$p < 0.0000$*
		40L	52.5 ± 9.7	
	Min	40U	−2.4 ± 5.7	$p = 0.0314$
		40L	0.1 ± 6.5	
Ankle	*Max*	100U	14.8 ± 7.5	$p = 0.0020$*
		100L	9.5 ± 3.8	
		60U	11.4 ± 7.4	$p = 0.0332$
		60L	8.6 ± 4.3	
	Min	100U	−14.0 ± 9.0	$p = 0.0004$*
		100L	−19.4 ± 8.5	
		60U	−16.9 ± 10.3	$p = 0.0379$
		60L	−19.8 ± 11.8	

Difference waveforms were also created for both kinematic and electromyographic waveforms. Adjacent kinematic and electromyographic waveforms for the hip, knee and ankle were subtracted from their nearest neighbor (e.g., 100% load—80% load; 80%–60% load, etc.) creating four total waveforms per joint and muscle. These resulting waveforms represent the distance between

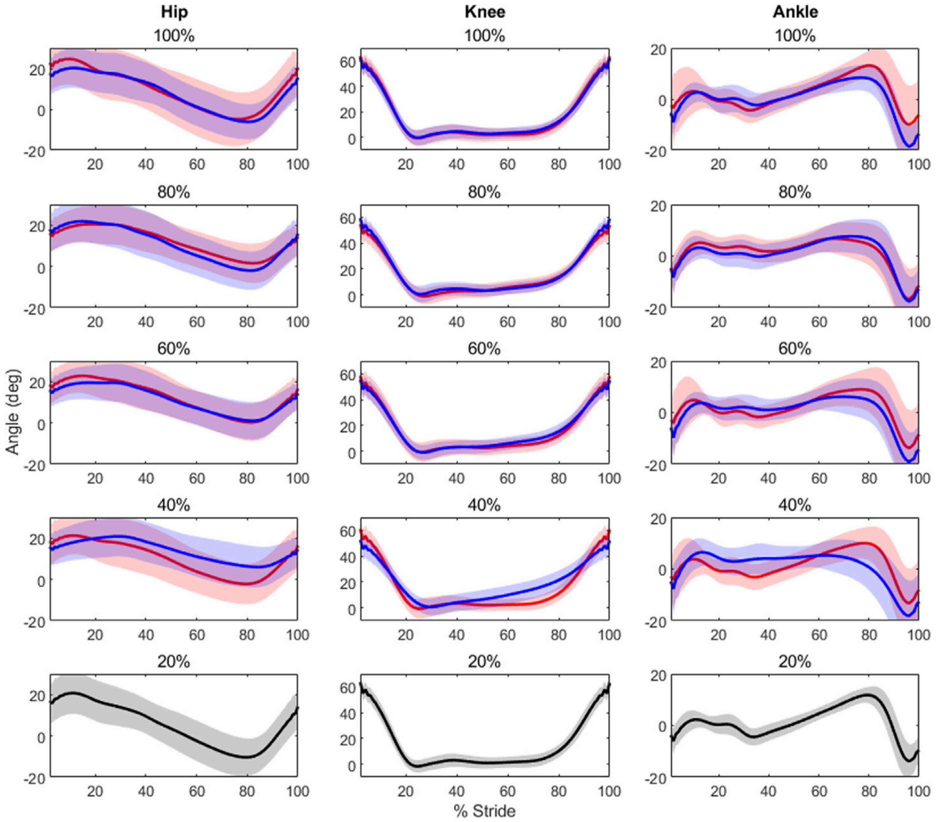


FIGURE 1
Each plot contains the average kinematic waveforms for its respective unloading (in red) and loading (in blue) condition, along with a 2-standard deviation shaded area around each waveform. All 20% load conditions are in black to avoid any confusion, as only a single waveform is present. Note the low variability of the knee waveforms across loading levels, and irrespective of absolute level of load. Conversely, the ankle shows higher variability between like levels, though it remains similar across absolute levels of load.

two adjacent waveforms (e.g., 100% load, and 80% load) and thus, when compared, offer insight into the linearity of change between levels of load.

Phase diagram and angle-angle diagrams were also created for the hip, knee, and ankle joints in order to compare both the coordination and movement strategies employed at 100% and 20% loading.

Statistical analysis

Kolmogorov-Smirnov and Shapiro-Wilk tests revealed all data were normally distributed and Mauchly's test showed sphericity was preserved.

Zero-dimensional analysis

Kinematic and EMG variables were tested for normality and sphericity using the Kolmogorov-Smirnov and Shapiro-Wilk tests, as well as Mauchly's test, respectively. Mean, maximum and minimum angles and range of motion (ROM), for each joint, as well as peak value, RMS and integrated areas were compared across all levels of loading using repeated measure ANOVAs. Post hoc testing was performed with corrected, paired t-tests, as appropriate.

One-dimensional analysis

Differences waveforms for kinematic and EMG data were compared across all levels of loading utilizing SPM f-tests. Post hoc testing was performed with individual SPM paired t-tests, as appropriate.

Results

Kinematics

Results showed that level of unloading had a statistically significantly effect on hip mean [F(8,112) = 2.354, p = 0.0223], minimum [F(8,112) = 7.960, $p <$ 0.0000] and ROM [F(8,112) = 12.2, $p <$ 0.0000] values; knee mean [F(8,112) = 2.159, p = 0.0359], maximum [F(8,112) = 30.711, $p <$ 0.0000] and ROM [F(8,112) = 8.34, $p <$ 0.0000] values; as well as ankle maximum [F(8,112) = 6.649, $p <$ 0.0000] and minimum values [F(8,112) = 3.692, p = 0.0007]. Post-hoc testing results are displayed in Table 1, and average kinematic waveforms by level of load are displayed in Figure 1.

Electromyography

Results showed level of unloading had a statistically significant effect on peak muscle activity in the rectus femoris [F(8,126) = 3.1, p = 0.0032] and medial gastrocnemius [F(8,126) = 4.72, $p <$ 0.0000]. Root-mean-

TABLE 2 All comparisons in which $p < 0.05$ are presented. * denotes significance after correction for multiple comparisons. U denotes decreasing load (i.e., 40% load down from 60%); L denotes increasing load (i.e., 60% load up from 40%). Zero-dimensional EMG pairwise testing.

	Measure	Level of unload	$\mu\ (mV) \pm std$	p-value
Rectus Femoris	*Peak*	100U	4.4646 ± 2.7421	$p = 0.0306$
		100L	3.9922 ± 2.6994	
		60U	3.2659 ± 1.2942	$p = 0.0148$
		60L	2.5617 ± 0.7725	
		40U	3.7457 ± 1.5659	$p = 0.0012$*
		40L	2.0757 ± 0.5369	
Medial Gastrocnemius	*Peak*	60U	21.2675 ± 7.6419	$p < 0.0000$*
		60L	14.7524 ± 8.5479	
		40U	26.6887 ± 11.8060	$p = 0.0006$*
		40L	15.7406 ± 9.4869	
	RMS	60U	7.7948 ± 3.4918	$p = 0.0002$*
		60L	5.2989 ± 3.2454	
		40U	9.9422 ± 3.9645	$p < 0.0000$*
		40L	5.2791 ± 2.9565	
	Integrated Area	100U	779.2357 ± 325.6160	$p = 0.0433$
		100L	677.7923 ± 308.9550	
		80U	392.8107 ± 179.3109	$p = 0.0006$*
		80L	581.6962 ± 230.9010	
		60U	527.7233 ± 224.8672	$p = 0.0003$*
		60L	374.6759 ± 209.7692	
		40U	642.2513 ± 217.69.67	$p < 0.0000$*
		40L	358.9621 ± 160.8824	

square and integrated area values were also statistically significant in the medial gastrocnemius [F(8,126) = 5.87, $p < 0.0000$; F(8,126) = 6.21, p< 0.0000, respectively]. There were also significant differences in the rectus femoris [F(3,42) = 5.3959, $p = 0.0031$] and medial gastrocnemius muscle waveforms across levels of load [F(3,42) = 21.3502, $p < 0.0000$]. Post-hoc testing results are displayed in Tables 2, 3 and average EMG waveforms by level of load are displayed in Figure 2.

Post-hoc testing by percentage of body weight

The following percentage changes are calculated with the unloading condition as reference.

100% body weight

Average ankle joint angle maximum values decreased by 35.8% (14.8 ° to 9.5 °; $p = 0.0020$). Average angle joint angle minimum values decreased by 39.3% (−14.0 ° to −19.4 °; $p = 0.0004$).

TABLE 3 * denotes significance after correction for multiple comparisons. U denotes decreasing load (i.e., 40% load down from 60%); L denotes increasing load (i.e., 60% load up from 40%). One-dimensional EMG pairwise testing.

	Level of unload	Comparators	p-value
Rectus Femoris	100/80	80/60	$p = 0.0011$*
		60/40	$p = 0.0001$*
		40/20	$p = 0.0011$*
Medial Gastrocnemius	100/80	80/60	$p = 0.0050$*
		60/40	$p = 0.0002$*
		40/20	$p = 0.0000$*

80% body weight

Average knee maximum joint angles increased by 8.42% (54.6 ° to 59.2 °; $p < 0.0000$). Average hip ROM increased by 25% (19.9 ° to 24.9 °; $p < 0.0000$). Average knee ROM increased by 6.6% (56.1 ° to 59.8 °; $p < 0.0000$).

Average integrated area of the medial gastrocnemius increased by 48.1% (392.8107–581.6962 mV; $p = 0.0006$).

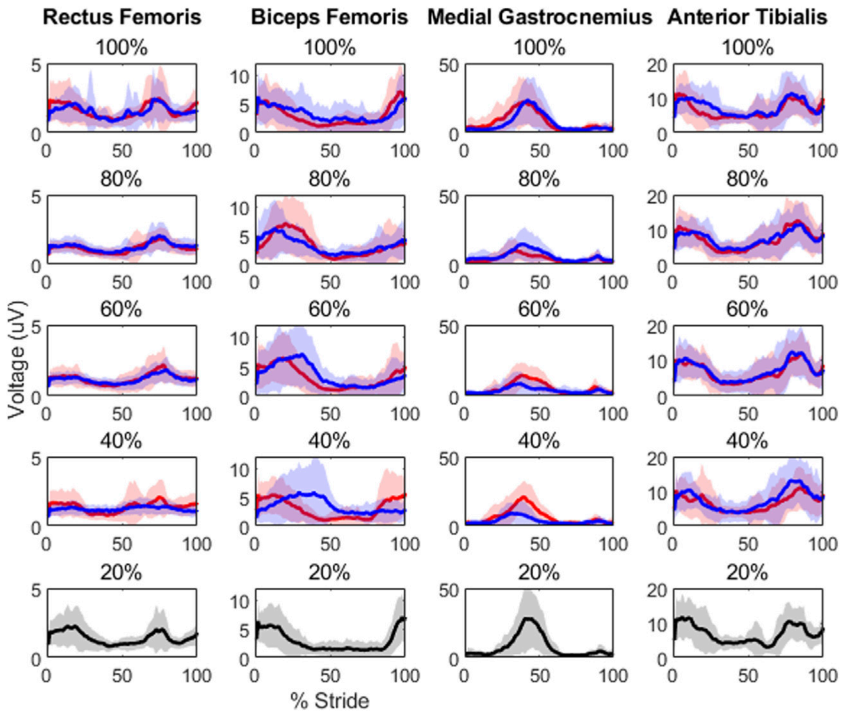


FIGURE 2
Each plot contains the average EMG waveforms for its respective unloading (in red) and loading (in blue) condition, along with a 2-standard deviation shaded area around each waveform. All 20% load conditions are in black to avoid any confusion, as only a single waveform is present. Though the phasic properties of these muscles appear to be robust with unloading, note the clear peak differences in the medial gastrocnemius as well as in the rectus femoris at 40% load depending on whether participants were loaded or unloaded previously.

60% body weight

Average knee maximum joint angles decreased by 5.2% (58.5 ° to 55.4 °; $p = 0.0008$). Average knee ROM decreased by 6.2% (60.5 ° to 56.7 °; $p < 0.0000$).

Average peak muscle activity in the medial gastrocnemius decreased by 30.6% (21.2675–14.7524 mV; p< 0.0000). Medial gastrocnemius RMS decreased by 32% (7.7948–5.2989 mV; $p = 0.0002$). Average integrated area of the medial gastrocnemius decreased by 28.8% (527.7233–374.6759 mV; $p = 0.0003$).

40% body weight

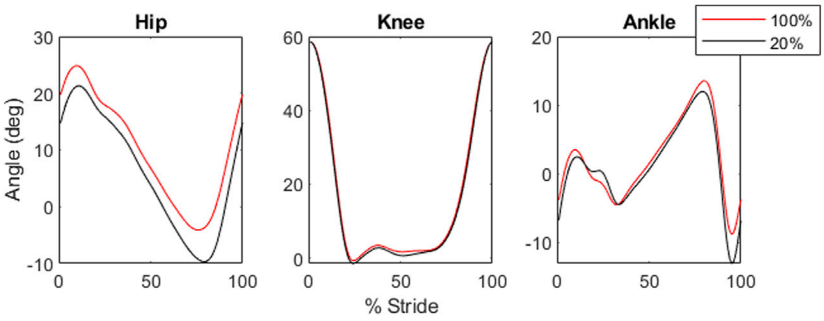
Average hip minimum joint angles increased by 253% (−2.8 ° to 4.3 °; $p = 0.0009$). Average hip ROM decreased by 31.6% (25 ° to 17.1 °) from unloading to loading ($p = 0.0001$). Average knee maximum joint angles increased 13.8% (60.9 ° to 52.5 °; p< 0.0000). Average knee ROM decreased by 17.3% (63.4 ° to 52.4 °; p< 0.0000).

Average peak muscle activity in the rectus femoris decreased by 44.5% (3.7457–2.0757 mV; $p = 0.0012$). Average peak muscle activity in the medial gastrocnemius decreased by 41% (26.6887–15.7406 mV; p< 0.0006). Medial gastrocnemius RMS also decreased, dropping 47% (9.9422–5.2791 mV; $p < 0.0000$). Average integrated area of the medial gastrocnemius decreased by 44.1% (642.2513–358.9621 mV; $p < 0.0000$).

Discussion

This study investigated the kinematic and EMG changes in human gait across different levels of simulated gravitational unloading between 100% and 20% of normal body weight. It specifically sought to identify if each level of unloading elicited robust, consistent changes—particular to that percentage of normal body weight—or if the changes seen with unloading could be influenced by the previous level(s) of unloading. We found that hip, knee, and ankle kinematics as well as electromyographic (EMG) activity in the rectus femoris, and medial gastrocnemius were significantly different at the same level of unloading, having arrived from a higher, or lower level of unloading, respectively. Similarly, the rate of change in kinematics from 100% of normal body weight, down to 20% appears to be linear, as evidenced by the lack of significance in difference waveforms between these levels; however, significant disparities in rectus femoris and medial gastrocnemius electromyographic difference waveforms suggest that the differences seen in EMG data between 100% and 80% load are not the same as those found between 80% and 60%, 60% and 40%, and 40% and 20%. This is of particular interest, as it suggests that kinematic and EMG measures decouple with unloading and may react to unloading uniquely.

The results of this study provide additional evidence that kinematic and electromyographic features do not scale across load levels proportionally with each other (Cappellini et al., 2006; Ivanenko et al., 2002). While it possible to accurately predict muscle activity from kinematics alone (Manzano and Serrancoli, 2021),



	Mean	Max	Min
Hip 100%	9.4	25.3	-5.7
Hip 20%	5.4	20.9	-10.8
Knee 100%	15.3	63.7	-2.4
Knee 20%	15.4	63.5	-3.3
Ankle 100%	2.0	14.8	-14.0
Ankle 20%	1.1	12.5	-14.3

FIGURE 3
The graphs in this figure depict both the average 100% (baseline, red) and 20% (black) unloading conditions for the hip, knee, and ankle. In the hip, smaller joint angle values correspond with increased extension, while higher joint angle values correspond with increased flexion. In the knee, higher values are flexion, and lower are extension. In the ankle, higher values indicate plantar flexion, while lower values indicate dorsiflexion. The table below shows the mean, maximum, and minimum joint angle values (in degrees) for these conditions.

work by Mauntel et al. (2017) did find kinematic-EMG decoupling depending on the type of movement being performed. In that way, the findings of this study—that kinematics scale linearly down to 20% of body weight, while muscle activity displays non-linear scaling as weight is decreased similarly—are not particularly surprising. Indeed, this suggests that muscle activity may be a more sensitive responder to load, whereas joint angles and coordination may be more robust to changes in levels of loading. This is supported by the phase diagrams comparing 100%–20% load (see Figure 5). Similarly, the overall reductions in hip, knee, and ankle ROM as well as general reductions in muscle activity of the medial gastrocnemius are consistent with previous work examining unloaded gait (Apte et al., 2018; Awai et al., 2017). However, at 80% load, this study found that the maximum angles of the knee as well as ROM of both the hip and knee increased, alongside overall muscle activity of the medial gastrocnemius. These findings contrast with established literature, but potentially provide insight into participant responses to this unloading paradigm. All of the participants in this experiment were unloading-naïve, having never walked or run in an unloading system nor experienced unloading in any other scenario. As such, two possible explanations for the increase in medial gastrocnemius activity and ROM are due to the novelty of the unloading treadmill and/or the unloading environment. However, as participants were given an acclimation period, it is unlikely that the novelty of treadmill system itself was the driving effector behind these alterations. Rather, it is possible these changes were exploratory strategies in response to the new unloading environment. This is also supported by our findings utilizing statistical parametric mapping (see Table 3), which found that the change in EMG waveforms for the rectus femoris and medial gastrocnemius between 100% load and 80% were significantly different from all other changes between levels. This suggests that the initial experience of unloading can drive gait alterations independently of the level of unload. Future work in this area should consider acclimation not only to the medium of locomotion (e.g., treadmill, overground) but to the experimental paradigm as well (i.e., unloading, re-loading).

Phase diagrams (also known as phase portraits) are a graphical representation of a dynamic system in state space (Stergiou, 2003); more specifically, a phase portrait represents all of the possible behaviors of a system over a given time course. In this study, our phase portraits show the possible positions (the joint angle) and velocity (its rate of change) that a joint could inhabit over the course of single stride. An examination of the phase portraits between 100% and 20% load reveal a number of interesting details. The knee is arguably the most striking, revealing an almost perfect overlap between the two conditions (see Figure 5)—this is further supported by the clear lack of differences between the knee mean, maximum and minimum at these respective levels (see Figure 3). By contrast, the hip and ankle appear to translate at 20% of load, occupying similarly shaped phase spaces but in altered locations. That is, these similarly shaped phase spaces occur at different percentages of two waveforms. Considering the coordination between joints (as seen in Figure 4), it becomes apparent that the changes seen with unloading to 20% are driven primarily by coordinative changes in the hip and ankle, and, more specifically, the relationship between the two joints (Figure 4, middle panel). It is worth noting however, the robustness with which gait appears to scale; indeed, the coordinative relationships between

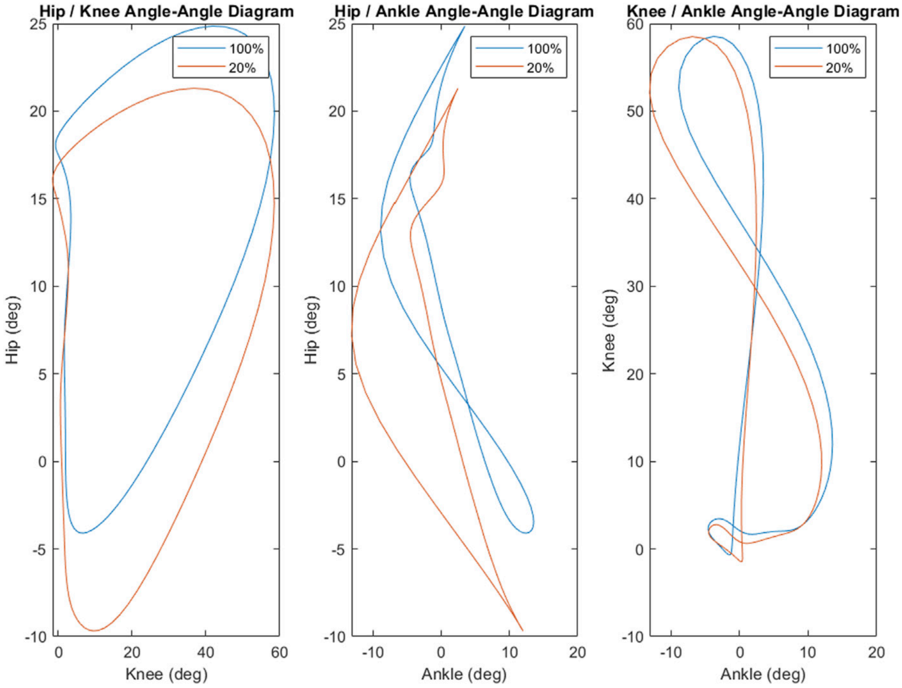


FIGURE 4
The coordination strategy between the joints of the lower extremities appears to be generally robust as load was decreased. However, there is clear stretching and translating in the coordinative strategies between the hip and knee as well as the hip and ankle. The hip and ankle, in particular, demonstrates a marked shift in coordinative strategy as the hip enters hyperextension. Coordination between the knee and ankle appears to be mostly preserved between 100% and 20% loads, though there is some stretching and shifting as load is decreased.

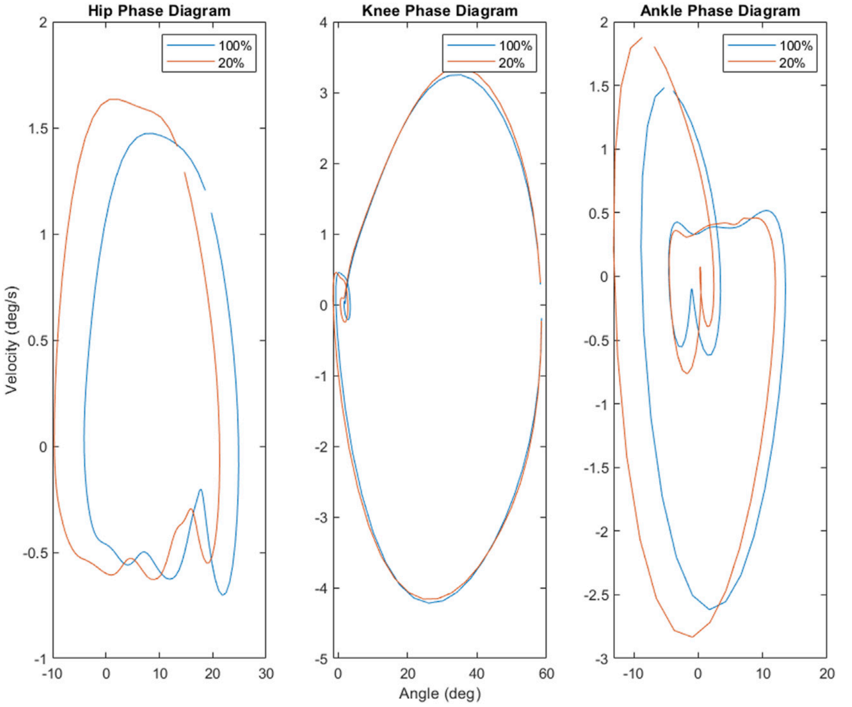


FIGURE 5
Phase portraits for the hip, knee and ankle suggest that the hip and ankle are most sensitive to shifts in load. Both the hip and ankle demonstrate notable expansion of the phase space (and thus possible states), while the available states of the knee are almost entirely unaffected by the decrease in load.

joints of the lower extremities are mostly preserved, despite the relative change in joint angles.

While this study did not specifically quantify proprioception, the reduction in proprioceptive information at hypogravity is a likely effectual factor at work as our participants were unloaded. Interestingly, this study found that several equal levels of unloading were significantly different depending on whether the participants were being loaded (increasing weight) or unloaded (decreasing weight) to a given level. Work by Thiel et al. (2014) found that the strongest effects of hysteresis were found when sensory information was the weakest. Indeed, it is clear that perceptual judgements can be affected by the availability—or paucity—of information about an impending action (Abdolvahab & Carello, 2015).

As unloading decreases the amount of proprioceptive information, a possible explanation for the differences in equal loading levels is that they are not—in this case—environmentally different, but that the movement from less sensory information to more (loading), or more sensory information to less (unloading) invokes hysteretic changes. Put simply, as participants' load increases, the relative utilization of environmental sensory information will drive their behavior more strongly than the previous level of load; inversely, as participants' load decreases, the reduction of sensory information will facilitate the use of information from the previous level of loading. This is supported physiologically by work by Kostyukov & Cherkassky (1997) which found that discharge rates in spindles were always higher after stimulation rate increases, and, in fact, lower after decreases. Further, it appears that some of these effects are modulated through plantar pressure stimulation. Previous investigations of unloading have found that the removal of plantar support triggers reflexive decreases in slow-twitch muscle unit activity (Kozlovskaya et al., 2007). This in turn leads to rapid atony of extensor muscles with a potentially linked reductions in proprioceptor activity (Shenkman and Kozlovskaya 2018; Shenkman et al., 2017). Over longer periods of unloading than this study examined, this can lead to decreases in strength-speed properties, as well as changes in motor control (Saveko et al., 2022; Shpakov et al., 2008). Though interestingly, some of these alterations from unloading can be mitigated with plantar pressure stimulation (Litvinova et al., 2004).

Given this sensitivity of spindle receptors to changes in stimulation, gravitational changes—or more applicably here on Earth, weight—are likely a strong driving force behind the hysteretic changes seen in this study and others. This has far-reaching implications for a number of fields. In rehabilitation, loading and unloading cannot be considered equivalent activities, even if they are achieving the same loading conditions. In that way, increasing patient load could foster a greater reliance on the sensory information pertaining to the actual environment, whereas decreasing patient load would drive hysteretic changes in which the patient bases their response more fully on the previous level of load. This potentially allows for more targeted therapeutic interventions towards proprioceptive systems versus musculoskeletal effectors. Also, as there are marked kinematic and electromyographic changes at particular levels of load, providers should be cautious to ensure that patients are responding to the desired level of load, and not a previous one. Considering the hysteric changes seen in this study, moving from a level of lower loading to the (higher) desired level of load should ensure that patients are responding to the desired level—due to the relative abundance of sensory information - and not basing their gait on previous models and estimations.

It is important to note that the average comfortable speed selected by our participants ($1.49\,mph$; $\approx 0.67\,\frac{m}{s}$) can approach walk-to-run and run-to-walk transitions as unloading increases. A study by Ackermann and van den Bogert (2012) found that at walking speeds of $1.1\ \frac{m}{s}$, individuals sub-volitionally shifted to a bounding/skipping-type gait when unloaded to equivalent Moon gravity ($1.63\ \frac{m}{s^2}$, or about 16.6% of Earth gravitational acceleration), though participants did maintain a walking-style gait at Mars-level gravity ($3.72\ \frac{m}{s^2}$, $\approx$ 38% of Earth gravity). Given such, there appears to be a transition point in gait-type between these two levels, which contains our lowest unloading condition of 20% body weight. This could influence some of the hysteretic effects observed in this study at transitions to-and-from 20% of body weight. It is useful in this instance, however, to consider this issue in light of the dynamic similarity hypothesis (Alexander, 1976) and specifically, the Froude number. The Froude number (Fr) is a dimensionless parameter relating potential and kinetic energy given by the equation $Fr = \frac{v^2}{gh}$, where v is the participants walking speed, g is the acceleration due to gravity and h is the height of the center of mass, approximated by leg length. Using our participant's average selected walking speed ($0.67\ \frac{m}{s}$), lowest gravitational acceleration of $1.962\ \frac{m}{s^2}$ (20% Earth gravity) and the expected Froude number associated with gait transitions of 0.5 (Alexander, 1989; Kram et al., 1997), we are left with $Fr = 0.5 = \frac{(0.67)^2}{(1.962)h}$, which, solving for h equals 2.18 m. Clearly, the average participant in our study could not morphologically have a center of mass or equivalent leg length of 2.18 m. However, our fastest walking participant did achieve a comfortable speed of $0.89\ \frac{m}{s}$, though they had a leg length of 90cm, which resulted in a Fr 0.44, and still below 0.5 at 20% load. Further, Figures 4, 5 present the average coordination waveform and phase diagrams utilized by participants for locomotion at 100% load and 20% load, and though there is definite shifting and stretching of these waveforms, they appear to maintain a robust walking-style shape, despite the unloading. With the above in mind, we feel comfortable that the effects of unloading and loading seen in this study are primarily due to hysteretic effects, rather than a gait shift. That being said, gait transitions could be important potential factors in hysteretic changes under reduced loads, and future work should consider addressing this.

Although admittedly speculative, given the changes in coordination and kinematics with unloading observed in this study, there are potential implications for the development of spacesuits. In previous, unpublished work, we found the switch to bounding gait did not occur until very close to 20% of load. With notably different gravitational conditions found on the Earth, its Moon as well as Mars, a single spacesuit designed with any of the single environments in mind may not be able to accommodate the others efficiently and could lead to stress and injury if applied in the wrong environment. Further, designers should be considerate of the previous level of gravitation that users have experienced, as this can influence even responses in the current one. In that way, it may be more effective to design spacesuits with a variable ability to support astronaut's body weight. This would allow users to be unloaded below the target level of gravitation, before being loaded up to the target. This would help ensure the user was biomechanically responding to the actual environment, and not a previous one.

This study requires replication and acknowledges its limitations. The design of the unloading system used in this study may provide some support or restrict movement about the hips in a way that could influence gait. This could have affected participant's movement strategies in this study. Indeed, two participants actually increased the peak activity of their medial gastrocnemius muscles at the lowest level of load compared to all other levels, contrary to previous works. Likely this has to do with inter-individual differences, but also potentially with the apparatus being used to test these individuals. Future studies should consider examining this phenomenon in more detail. That being said, while this should be kept in mind when interpreting the above results, it is also important to note that all experimental unloading systems have shortcomings such as unloading only the trunk (suspension systems), offering excess inertial resistance (submersion) or enforcing short epochs of study (parabolic flight). In light of this, the AlterG system successfully allows for unloading paradigms to be studied, albeit with its own potential limitations.

This study was a novel use of both zero-dimensional and one-dimensional kinematic and electromyographic analysis. It found that unloading from 100% of normal body weight to 20% elicited distinct electromyographic responses in the medial gastrocnemius, as well as partly in the rectus femoris. Hip, knee, and ankle kinematics were also affected differentially by loading and unloading, especially at 40% of normal body weight. These findings suggest the previous level of gravitational load is an important factor to consider in determining kinematic and electromyographic responses to the current level during loading and unloading below standard g.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Houston Institutional Review Board. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors contributed to the conception and design of the study. CM wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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TYPE Systematic Review
PUBLISHED 16 June 2023
DOI 10.3389/fncir.2023.1150233

Pharmacological and non-pharmacological countermeasures to Space Motion Sickness: a systematic review

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Introduction: Space Motion Sickness (SMS) is a syndrome that affects around 70% of astronauts and includes symptoms of nausea, dizziness, fatigue, vertigo, headaches, vomiting, and cold sweating. Consequences range from discomfort to severe sensorimotor and cognitive incapacitation, which might cause potential problems for mission-critical tasks and astronauts and cosmonauts' well-being. Both pharmacological and non-pharmacological countermeasures have been proposed to mitigate SMS. However, their effectiveness has not been systematically evaluated. Here we present the first systematic review of published peer-reviewed research on the effectiveness of pharmacological and non-pharmacological countermeasures to SMS.

Methods: We performed a double-blind title and abstract screening using the online Rayyan collaboration tool for systematic reviews, followed by a full-text screening. Eventually, only 23 peer-reviewed studies underwent data extraction.

Results: Both pharmacological and non-pharmacological countermeasures can help mitigate SMS symptoms.

Discussion: No definitive recommendation can be given regarding the superiority of any particular countermeasure approach. Importantly, there is considerable heterogeneity in the published research methods, lack of a standardized assessment approach, and small sample sizes. To allow for consistent comparisons between SMS countermeasures in the future, standardized testing protocols for spaceflight and ground-based analogs are needed. We believe that the data should be made openly available, given the uniqueness of the environment in which it is collected.

Systematic review registration: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021244131.

KEYWORDS

Space Motion Sickness (SMS), pharmacological countermeasures, non-pharmacological countermeasures, human space flight, aerospace medicine

OPEN ACCESS

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RECEIVED 23 January 2023
ACCEPTED 19 May 2023
PUBLISHED 16 June 2023

CITATION
Khalid A, Prusty PP, Arshad I, Gustafson HE, Jalaly I, Nockels K, Bentley BL, Goel R and Ferrè ER (2023) Pharmacological and non-pharmacological countermeasures to Space Motion Sickness: a systematic review. *Front. Neural Circuits* 17:1150233. doi: 10.3389/fncir.2023.1150233

1. Introduction

Deep space exploration to the Moon and Mars are no longer in the distant future. Since the first space missions, however, it has been clear that exposure to weightlessness (i.e., microgravity) leads to dramatic functional and structural changes in human physiology, including alterations in the musculoskeletal, cardiovascular, and neural systems (Buckey, 2006). *Space Motion Sickness* (SMS) is a clinical syndrome that affects around 70% of astronauts within the first 72 h of traveling to and returning from microgravity (Heer and Paloski, 2006). SMS symptoms include dizziness, vertigo, headaches, cold sweating, fatigue, nausea, and vomiting. Consequences range from discomfort to severe sensorimotor and cognitive incapacitation. SMS can therefore cause problems during re-entry and emergency exits from a spacecraft; for this reason, no extra-vehicular activities or spacewalks are allowed during the first few days of space missions (Souvestre and Landrock, 2005). Both pharmacological and non-pharmacological countermeasures have been proposed to mitigate SMS symptoms. However, the effectiveness of these countermeasures is still largely debated. The National Aeronautics and Space Administration's (NASA) Human Research Program has recently identified countermeasures against SMS as a critical unaddressed "knowledge gap" (NASA Human Resources Roadmap, 2022). Here we aim to bridge this gap in the knowledge by performing the first systematic review on the effectiveness of pharmacological and non-pharmacological SMS countermeasures. We have collated evidence from published peer-reviewed studies, critically evaluated the current findings, and highlighted potential further research.

Space is a hostile environment: microgravity, extreme temperatures, ionizing radiation and changes in ambient pressure are just some of the stressors space travelers encounter. That is, spaceflight exposes astronauts and cosmonauts to a number of environmental factors that are likely to cause short and long term consequences on human health. For example, exposure to cosmic radiation has dramatic effects on physiological processes (Gundel et al., 1997), and it is associated with a higher risk of cancer and cardiovascular diseases (Townsend, 2005). The lack of atmospheric pressure and solar light severely impacts the neurophysiology processes involved with circadian cycles (Gundel et al., 1997). Microgravity alters different aspects of bodily physiology, including changes in the central nervous system (CNS). Often, these changes occur during and post-flight in the form of neurovestibular problems (Van Ombergen et al., 2017). On Earth, sophisticated organs in the inner ear—the vestibular otoliths—detect gravitational acceleration. When the head moves with respect to terrestrial gravity, the vestibular otoliths shift with the direction of gravitational acceleration, moving the hair cell receptors and signaling to the brain where the head is with respect to the direction of gravity. Vestibular signals are integrated with sensory inputs from vision, and proprioception, to form an *internal model* of terrestrial gravity (Zago and Lacquaniti, 2005; Jörges and López-Moliner, 2017; Lacquaniti et al., 2017). Critically, the internal model created from integrating multiple sensory sources allows a subject to shape their behavior to adapt successfully to the terrestrial gravity environment.

Neurovestibular changes during spaceflight might account for the onset of SMS symptoms. Egorov and Samarin (1970) have considered the asymmetry in the vestibular otoliths as a potential explanation for SMS. In microgravity the vestibular cues for head tilt become irrelevant and lead to a reinterpretation of physical tilt into a translation sensation by the brain (Russomano et al., 2019). This distortion in vestibular signaling is due to asymmetries between the vestibular utricle and saccule on both sides of the head. Critically, the described physiological asymmetries might be aggravated in microgravity conditions leading the central nervous system to misinterpret the signal transmitted by the otolith organs and potentially lose the usual compensatory dynamics for these asymmetries. This might then induce SMS symptoms.

The fluid shifts induced by microgravity may also contribute to SMS (Parker et al., 1983). In space, bodily fluids (i.e., blood and lymph) are dramatically redistributed to the upper parts of the human body due to the absence of hydrostatic pressure. This fluid shift may affect the balance between endolymphatic and perilymphatic pressures in the vestibular labyrinth, causing SMS symptoms (Parker et al., 1983). According to this model, SMS symptoms such as nausea and vomiting might be triggered by unusual patterns of vestibular activity. Importantly, similar symptoms have been described in patients experiencing changes in vestibular structures, such as labyrinthine hydrops or rising intracranial pressure (Noskov and Grigoriev, 1994). However, an account for SMS solely based on fluids shift does not fully explain the symptoms reported by astronauts and cosmonauts. The most destabilizing effects of SMS last from the first to the fifth day of weightlessness and reoccur within the first 10 days after returning to Earth (Oman et al., 1986). In contrast, the shift in fluids develops immediately after entering into orbit and persists until the end of a mission, suggesting alternative etiologies for SMS (Oman et al., 1986).

So far, the most promising approach explaining SMS focuses on sensory conflict (Kohl, 1983). Similarly to terrestrial motion sickness, vestibular and visual cues for spatial orientation might conflict due to the lack of a gravitational reference. In microgravity, signals from the vestibular system no longer provide direct information about gravitational acceleration, which might affect the processing in the brain areas where sensory integration for orientation takes place between vision, proprioception, and vestibular information (e.g., the thalamus, insular cortex, temporoparietal junction, and somatosensory cortices). Accordingly, exposure to this sensory conflict results in SMS symptoms, vestibular illusions, and spatial disorientation (Weerts et al., 2015).

Individual factors such as age, sex, prior flight experience, and individual susceptibility have been suggested to impact the occurrence and severity of SMS. Few studies have explored these factors in SMS directly. Susceptibility to SMS has been shown to decline with flight experience (Golding et al., 2017). Studies have found that, age negatively correlates with motion sickness susceptibility, and females have a higher susceptibility to motion sickness than males (Dobie et al., 2001; Flanagan et al., 2005; Paillard et al., 2013). Differences in hormonal systems and stress expression may explain individual factors in susceptibility (Kohl, 1983), and hereditary susceptibility (Golding et al., 2005) to motion sickness.

Given its impact on space travelers' health, SMS has received much attention in the past years. While SMS is typically experienced in microgravity environments, ground-based research methods have been used to identify its characteristics and investigate potential countermeasures. These methods include centrifugation, parabolic flights, and rotating environments. Centrifugation creates altered gravities through centrifugal force by circular rotations. Parabolic flights elicit short periods of hypergravity (1.8 g), hypogravity (0.38 g, 0.16 g) and microgravity (0 g) through a series of accelerations and free-fall phases. Rotating environments, such as rotating rooms and chairs, disrupt the visual and vestibular information interpreted by the body and brain. Although these ground simulations cannot perfectly mimic spaceflight conditions, they are effective tools to explore SMS.

Is it possible to overcome SMS? Pharmacological methods of reducing SMS have been proposed and widely investigated. Several drugs from different pharmacological classes and with varying doses have been explored, including promethazine, scopolamine, dimenhydrinate, prochlorperazine, meclizine, metoclopramide, phenytoin, and lorazepam, among others. A reduction in SMS has been observed after consumption of promethazine or scopolamine during spaceflight (Graybiel, 1976, 1981; Oman et al., 1986; Davis et al., 1993a,b). Similar effects have been reported in parabolic flights (Norfleet et al., 1992; Golding et al., 2017), rotating environments (Graybiel, 1979; Hordinsky et al., 1982; Kohl et al., 1993; Lackner and Graybiel, 1994; Cowings et al., 2000; Dornhoffer et al., 2004; Weerts et al., 2012) and centrifugation (Weerts et al., 2015). However, side effects triggered by promethazine and scopolamine have also been reported, including fatigue, drowsiness, dry mouth, and problems with sensorimotor coordination. Clearly, these side effects are particularly detrimental in high-pressure environments where attention and coordination are critical for performance and survival. Some progress has been made to counteract the adverse side effects of SMS drugs, mainly drowsiness, with the addition of stimulants such as amphetamine (Graybiel, 1981; Hordinsky et al., 1982; Davis et al., 1993a; Kohl et al., 1993). However, more research is needed to understand the underlying mechanisms and effectiveness of using this combined pharmacological approach for the symptomatic treatment of SMS.

Alongside pharmacological approaches, non-pharmacological methods have been explored to mitigate SMS symptoms. These include the use of tilt-transition devices (Harm and Parker, 1994), autogenetic feedback training exercises (Cowings and Toscano, 2000), Virtual Reality training (Stroud et al., 2005), head or body rotation exercises (Reschke et al., 2006; Cloutier and Watt, 2007) and Galvanic Vestibular Stimulation (Dilda et al., 2014). These studies have predominantly focused on building tolerance against SMS. These and reported a reduction in SMS or motion sickness-associated symptoms (Cowings and Toscano, 2000). Thus, non-pharmacological countermeasures might be effective as a pre-flight training countermeasure, particularly in building resilience against SMS. However, the number of studies exploring non-pharmacological countermeasures is severely limited.

Here we performed a systematic review of the published peer-reviewed research on the effectiveness of pharmacological and non-pharmacological countermeasures of SMS. The non-pharmacological countermeasures considered in our systematic review included devices that exposed participants to the stimulus challenges of microgravity, biofeedback training, stroboscopic vision, torso rotation and Galvanic Vestibular Stimulation (Harm and Parker, 1994; Cowings and Toscano, 2000; Stroud et al., 2005; Reschke et al., 2006; Cloutier and Watt, 2007; Dilda et al., 2014). We initially identified 3,207 potential peer-reviewed studies containing SMS keywords, which was reduced to 23 peer-reviewed studies for inclusion following systematic screening (17 on pharmacological countermeasures, five on non-pharmacological countermeasures, and one study that compared both approaches). Results indicate that both pharmacological and non-pharmacological countermeasures have had some success in mitigating SMS symptoms. However, no definitive recommendation can be given about whether one type of countermeasure is more effective given the vast heterogeneity of research methods, the lack of a standardized research approach in evaluating outcomes, and the small sample size overall. Nonetheless, this review provides the first systematic summary of all of the peer-reviewed studies on SMS countermeasures. This can help clarify the state-of-the-art and inform future research on this critical unaddressed knowledge gap.

2. Methods

This systematic review was performed under the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). The Librarian (KN), in collaboration with other team members, devised search keywords. Literature searches using Cinahl (via Ebsco), the Cochrane Library, Medline (via Ovid), Scopus, and Web of Science Core Collection databases were performed for relevant articles on 9th April 2021. A follow up search of PubSpace was conducted via PubMed Central on 17th May 2021. Full search strategies are reported in Supplementary material. References from the searches were exported to the Zotero reference management application Zotero (RRID:SCR_013784) to organize references and identify duplicate records, and then exported to Rayyan (Rayyan QCRI (RRID:SCR_017584), a software designed for the screening part of a systematic review through its features to label and sort papers by inclusion or exclusion criterion. Rayyan was therefore used for double-blind screening. A large number of references (3207) were screened for inclusion. Search restrictions were set for peer-reviewed literature, human studies, and the English language. Each article was evaluated for inclusion by four authors (AK, PPP, HEG, and IJ) independently, and all disagreements were resolved by consensus. Out of 3,207 abstracts, 41 full-length articles were screened out, and 23 articles were included as per the inclusion and exclusion criteria stated below. The PRISMA diagram outlining this process is presented in the Supplementary Figure 1.

The inclusion criteria were determined a priori and included specific search terms to ensure all peer-reviewed studies exploring pharmacological and non-pharmacological countermeasures for SMS were captured. Studies outside of our inclusion criteria were rejected, while studies that met the criteria underwent

TABLE 1 Summary of study characteristics for pharmacological countermeasures in chronological order.

Study	Sample size	M:F ratio	Spaceflight/analog	Type of study	Specific countermeasure	Main findings
Graybiel (1976)	31	N/A	Spaceflight Slow rotation room Parabolic flight	Descriptive	Promethazine 25 mg/ephedrine 25 mg Promethazine 25 mg/ephedrine 50 mg Scopolamine 0.3 mg/ephedrine 25 mg Scopolamine 0.3 mg/d-amphetamine sulfate 5 mg Scopolamine 0.3 mg Scopolamine 0.6 mg Dimenhydrinate 50 mg (Route of administration for all is N/A)	Promethazine 25 mg/ephedrine 25 mg were both beneficial in alleviating SMS symptoms.
Graybiel (1979)	40	N/A	Slow rotation room	Descriptive	Transdermal scopolamine (Dose N/A) Oral scopolamine 0.3 mg Oral promethazine 25 mg/ephedrine 25 mg Oral promethazine 25 mg/ephedrine 12.5 mg Oral prochlorperazine 10 mg/isopropamide 5 mg Oral meclizine 25 mg/ephedrine 25 mg Oral dimenhydrinate 25 mg/ephedrine 25 mg	Oral promethazine 25 mg/ephedrine 25 mg showed the best response.
Graybiel (1981)	6	6:0	Spaceflight	Descriptive	Scopolamine 0.35 mg/dexedrine 50 mg Promethazine 25 mg/ephedrine 50 mg (Route of administration for all is N/A)	Scopolamine had confirmed efficacy when given pre-flight.
Hordinsky et al. (1982)	9	9:0	Rotary chair	Repeated measures Double blind Placebo	Transdermal scopolamine 1.5 mg Oral scopolamine/dextroamphetamine combination 0.4 mg/5 mg Oral promethazine and ephedrine 25 mg/25 mg Intramuscular promethazine, 25 mg	While oral promethazine/ephedrine was the most effective at alleviating SMS, transdermal scopolamine was recommended as it is effective with fewer side effects.
Oman et al. (1986)	4	N/A	Spaceflight	Descriptive Repeated measures	Oral scopolamine 0.4 mg/dexedrine 2.5 mg Promethazine 25 mg/ephedrine 25 mg (Route of administration is N/A) Metoclopramide 10 mg (Route of administration for all is N/A)	Scopolamine and promethazine were effective.
Norfleet et al. (1992)	21	21:0	Parabolic flight	Repeated measures Crossover design Placebo Single blind	Buccal scopolamine 1 mg	Buccal scopolamine significantly lowered scores for nausea and vomiting compared to a placebo.
Kohl et al. (1993)	53	53:0	Rotary chair	Repeated measures Crossover design Double blind Placebo	Oral doxepin 70 mg Oral scopolamine 0.4 mg/amphetamine 5 mg	Both medications showed a significant difference in adaptation to stressful Coriolis stimuli compared to placebo.
Davis et al. (1993a)	96	N/A	Spaceflight	Repeated measures	Intramuscular promethazine 50 mg	Intramuscular promethazine after symptom development was significantly effective in immediate symptom relief.
Davis et al. (1993b)	34	N/A	Spaceflight	Repeated measures Quasi-experimental groups	Scopolamine 0.4 mg/dextroamphetamine 2.5–5.0 mg Promethazine 25–50 mg	Promethazine was most effective.

(Continued)

TABLE 1 (Continued)

Study	Sample size	M:F ratio	Spaceflight/analog	Type of study	Specific countermeasure	Main findings
Lackner and Graybiel (1994)	18	18:0	Rotary room	Experimental groups Repeated measures Placebo	Oral promethazine 50 mg	Oral promethazine delayed the onset of nausea compared to a placebo group.
Knox et al. (1994)	6-13	N/A	Parabolic flight	Repeated measures Double blind Placebo Crossover design	Oral phenytoin 500–1,200 mg pre-flight Oral phenytoin 100–200 mg as needed	Oral phenytoin was effective as only 7.7% of participants had level 3 or greater nausea (i.e., severe, performance of tasks affected or vomiting).
Cowings et al. (2000)	12	12:0	Rotary chair	Repeated measures Double blind Placebo	Intramuscular promethazine 25 mg Intramuscular promethazine 50 mg	Both doses significantly increased motion sickness tolerance compared to the placebo. The incidence of performance-impaired subjects almost doubled with 50 mg dose compared to 25 mg dose.
Dornhoffer et al. (2004)	75	45:27	Rotary chair	Repeated measures Prospective study Double blind	Oral lorazepam 1 mg Oral meclizine 25 mg Oral promethazine 25 mg Oral scopolamine 0.4 mg	Oral scopolamine was significantly more effective.
Weerts et al. (2012)	16	7:9	Rotary chair	Repeated measures Single blind Placebo	Oral lorazepam 1 mg Oral meclizine 25 mg Oral promethazine 25 mg Oral scopolamine 0.4 mg	Oral meclizine, oral scopolamine, and oral lorazepam were recommended for future studies.
Weerts et al. (2014)	20	20:0	Rotary chair	Repeated measures Double blind Placebo	Oral meclizine 25 mg Oral promethazine 25 mg/d-amphetamine 10 mg Oral dimenhydrinate 40 mg/cinnarizine 25 mg	Oral meclizine and oral dimenhydrinate/cinnarizine were recommended for future studies.
Weerts et al. (2015)	19	19:0	Unilateral centrifugation	Repeated measures Double blind Placebo	Intranasal scopolamine 0.4 mg	Intranasal scopolamine significantly reduced vestibular ocular reflex gain and total calorific response during electronystagmographic recording.
Golding et al. (2017)	246	192: 54	Parabolic flight	Experimental groups	Subcutaneous scopolamine 0.175 mg or less	Subcutaneous scopolamine reduced vomiting compared to flyers who did not take medication.

TABLE 2 Summary of study characteristics for non-pharmacological countermeasures in chronological order.

Study	Sample size	M:F ratio	Spaceflight/analog	Type of study	Specific countermeasure	Main finding
Harm and Parker (1994)	27	N/A	Tilt-transition device	Repeated measures	Pre-flight adaptation training	Tolerance time increased as motion sickness symptoms decreased over time.
Cowings and Toscano (2000)	33	33:0	Rotary chair	Repeated measures Double blind Placebo	Autogenic-feedback training exercise (AFTE) Intramuscular promethazine 25 mg Intramuscular promethazine 50 mg	AFTE was significantly more effective than either dose of intramuscular promethazine.
Stroud et al. (2005)	30	17:13	Virtual reality DOME system (Device for orientation and motion environment)	Experimental groups Repeated measures	Variable training Non-variable training	Variable training resulted in fewer nausea symptoms.
Reschke et al. (2006)	32	19:13	Head movements	Repeated measures Crossover design Control	Stroboscopic vision and shutter glasses	While flashing, the strobe-illuminated environment and the shutter glasses significantly lowered motion sickness.
Cloutier and Watt (2007)	25	5:20	Head nodding	Repeated measures	Torso rotation	Torso rotation significantly decreased motion sickness.
Dilda et al. (2014)	10	7:3	Galvanic vestibular stimulation	Repeated measures	Galvanic vestibular stimulation	During 12 weekly GVS exposures, body sway and postural dynamics were comparable to pre-GVS baseline at 7–8 weeks into the 12-week programme. The effect was still maintained 6 months post-GVS exposure.

double-blind evaluation. This process ensured that the paper selection was unbiased and systematic. The inclusion criteria for the studies were stated in the form of the Population, Countermeasure, Comparison, Outcomes (PICO) format. They were as follows: (1) P: Adult humans (18 years of age and over) experiencing SMS in altered gravity (spaceflight and ground-based analogs) (2) I: Pharmacological/non-pharmacological (3) C: None (4) O: Miller and Graybiel scale (1968) and subjective self-ratings, or reduced severity/absence of SMS if the countermeasure was done prophylactically (5) Others: Quantitative/Qualitative countermeasure study. The exclusion criteria included: (1) P: People that have had/currently have a stroke, cerebrovascular accidents (CVAs), and peripheral vestibular disorders such as Benign Paroxysmal Positional Vertigo (BPPV), Vestibular Neuritis, Meniere's Disease, Mal de debarquement syndrome); Animal studies, (2) I: None, (3) C: None, (4) O: Terrestrial motion sickness, (5) Others: Non-English Language papers.

The following information was extracted: Title of Paper; Name of the journal; Author (Surname); Year; Funding source (e.g., NASA/European Space Agency [ESA], etc.); Publication Type (Journal article, conference, abstract); Method (Quantitative, Qualitative, Mixed Methods, Other); Altered Gravity Method (Space/Space Analog/Isolation, Confined and Extreme environments [ICE]/Centrifuge/Other); Number of total participants; Number of participants in the control group; Types of participants (Astronauts, cosmonaut, healthy adults, etc.); Participants (Male: Female ratio if available); Participant's age (mean age, standard deviation/range of age); Number of trained participants/naïve; Was any inclusion/exclusion criteria applied to participants? (Yes/No/Maybe); Group allocation; How were participants divided into groups (if applicable); Was there a control group (Yes/No/Not Sure); Duration of exposure in microgravity/altered gravity environment (making sure time is standardized, i.e., all in hours/days/weeks); Measurement timeline (e.g., pre-flight/in-flight/post-flight); How was SMS measured (self-report, biomarkers etc.); Note on any data exclusion and why; Type of countermeasure used for SMS (pharmacological or non-pharmacological); Name of countermeasure used for SMS (if pharmacological, include mode of administration and dose); Duration of countermeasure used for SMS; How was SMS affected (+ meaning reduced, – meaning increased, or = meaning negligible), Double signs with space between them if statistically significant; If effective, specify which symptoms were improved; Any side effects of countermeasure; Any secondary outcomes and if so, main result(s) of this; Advantages of countermeasure; Any limitations of the countermeasure itself. The type of study was also identified.

3. Results

Our systematic review focused on the effectiveness of pharmacological and non-pharmacological countermeasures to counteract SMS. Notably, only one study (Cowings and Toscano, 2000) directly compared both types of countermeasures. Overall, considerable heterogeneity emerged in the characteristics and methodologies of the studies (e.g., sample size, type, and duration of the altered gravity methods and how the effect of SMS was measured). Of the 23 studies, 17 looked at pharmacological countermeasures (Table 1). There were 15 different drugs or drug combinations used, which varied in dosage, timing, and mode of administration. The most studied drugs and their doses were 0.4 mg of oral scopolamine and 25 mg or 50 mg of oral or intramuscular promethazine. Every study reported a beneficial effect on SMS, defined mainly as a reduction in SMS symptoms experienced by participants. In 10 of the 17 studies, this result was reported as statistically significant. Golding et al. (2017) are notable for their study characteristics of a relatively large sample size of 246, including female participants, and choice of parabolic flight over a space analog (Golding et al., 2017). The most common side effect was drowsiness reported with promethazine consumption.

Of the 23 studies, six looked at non-pharmacological countermeasures (Table 2). The specific types were devices that exposed participants to the stimulus challenges of microgravity, biofeedback training, stroboscopic vision, torso rotation and Galvanic Vestibular Stimulation (Harm and Parker, 1994; Cowings and Toscano, 2000; Stroud et al., 2005; Reschke et al., 2006; Cloutier and Watt, 2007; Dilda et al., 2014). Unlike the pharmacological studies, all but the stroboscopic vision study carried out their countermeasure prophylactically rather than therapeutically (Harm and Parker, 1994; Cowings and Toscano, 2000; Stroud et al., 2005; Cloutier and Watt, 2007; Dilda et al., 2014). Like the pharmacological studies, each of the six non-pharmacological studies also reported a beneficial effect of SMS by reducing symptoms. In four of them, this result was reported as statistically significant.

4. Discussion

Here we have systematically reviewed the available literature to explore the effectiveness of both pharmacological and non-pharmacological countermeasures against SMS. Despite the potential consequences of SMS on crewmember well-being and space mission success, findings remain inconsistent and contradictory in places. While positive results were found in both types of countermeasures, no clear and reliable evidence emerged about which countermeasure is most effective for addressing SMS symptoms. Evidently, across the pharmacological and non-pharmacological studies, a lack of a standardized protocol makes comparisons within and between the approaches almost impossible.

The pharmacology literature dramatically shows the lack of consistency and standardized approaches. Some studies have administered drugs such as scopolamine through transdermal means (Graybiel, 1979; Hordinsky et al., 1982) and others via oral intake (Oman et al., 1986; Davis et al., 1993a; Dornhoffer et al., 2004). Differences in administration may affect uptake and how quickly the drug impacts SMS symptoms. In addition, varying doses were reported in the literature with ambiguity around the time of administration, the number of doses, and how soon after SMS symptoms were measured. Little effort has been made to discriminate when the administration of drugs is most effective in relation to flight times, e.g., pre-, during, or post-flight. Research has also heavily focused on scopolamine and promethazine with little exploration of alternatives, given their side effects. It is, therefore, difficult to conclude which pharmaceutical drug is most effective in reducing SMS and when.

Similarly, drawing concrete conclusions or comparing non-pharmacological countermeasures is also tricky. A noticeable lack of replication or evaluation puts into question the reliability of these countermeasures in reducing SMS. More research and replication are needed, even using ground-based analogs that are more widely and relatively cheaply accessible, to explore the effectiveness of non-pharmacological countermeasures, to assess whether the resistance against SMS is genuinely achieved and whether a consistent reduction of symptoms is experienced.

SMS can be debilitating, and more efforts are needed to address symptoms. More consideration should be given to adopting a combined approach, not only of pharmaceuticals but also of pharmacological and non-pharmacological countermeasures. For instance, non-pharmacological countermeasures could increase tolerance to SMS during pre-flight training, while pharmacological countermeasures could be applied in-flight and post-flight to ease symptoms directly. Previous research has also primarily focused on addressing nausea-related symptoms of SMS. While this is crucial, SMS encompasses a range of symptoms that can affect the operational effectiveness of astronauts, including increased body warmth, sweating, loss of appetite, fatigue, and anorexia (Heer and Paloski, 2006). More efforts should be made to address other SMS symptoms as well.

Comparisons within each countermeasure domain are also complicated since some studies have explored SMS in actual spaceflight conditions, whereas others have used ground-based analogs. For example, comparing symptoms of SMS during an International Space Station (ISS) mission with a terrestrial rotary chair may not be a valid comparison given the stark differences in physiological, musculoskeletal, neurobiological factors and potentially different causative elements for SMS in both cases. Despite gravity always being present, ground-based analogs and simulations have been widely adopted across space research and could help develop effective countermeasures against SMS. However, standardization is required if fair comparisons are to be made.

Importantly, most of the current literature relies heavily on self-reported measures to capture the prevalence and severity of SMS symptoms (Hordinsky et al., 1982; Davis et al., 1993a; Kohl et al., 1993; Knox et al., 1994; Cowings and Toscano, 2000; Dornhoffer et al., 2004; Stroud et al., 2005; Reschke et al., 2006; Cloutier and Watt, 2007). Although widely used, this qualitative approach may be susceptible to bias impacting the accuracy and validity of the findings. More objective and quantitative methods of measuring SMS symptoms should be considered, such as physiological measures (e.g., heart rate, respiration, or skin conductance). These may act as precursors to actual SMS and could help develop targeted countermeasures while providing a more holistic and representative understanding of the onset and prevalence of SMS. If adequately validated, deviations in physiological measures can also be integrated into some early warning systems.

Our systematic review reveals that the current research suffers from severely restricted and biased samples. Participant samples are male-dominant and consist primarily of highly trained personnel, often recruited multiple times across different studies. As shown in Table 1, several studies consisted of all male participants.

Addressing the lack of gender balance is critical since there are key hormonal and physiological differences between males and females that may impact the onset and severity of SMS symptoms (Reschke et al., 2014). With more efforts by space agencies and commercial companies to recruit females for crewed missions (Guzman, 2019), it is crucial to understand how SMS impacts both genders.

The reviewed literature provides a promising indication that both pharmacological and non-pharmacological approaches can be used to address SMS; however, given some of the challenges of doing space research mentioned above, our review paints an incomplete and inconsistent picture of the effectiveness of current countermeasures. Despite our systematic approach, no single countermeasure appears superior in addressing SMS. Importantly, there is an apparent lack of research into non-pharmacological studies, which might undermine its potential. Some consideration should also be given to combining the strengths of pharmacological and non-pharmacological approaches to reduce SMS symptoms maximally. Critically, the findings presented here are a snapshot of the current SMS literature. The vast majority of data generated by leading space agencies may not be published due to clinical confidentiality, time limitations, or non-significant results. To better understand SMS, researchers need to move toward an open science and transparent approach whereby data and peer-reviewed papers are made widely available sooner than later.

SMS's high prevalence and potentially lethal consequences reinforce the need to quickly find effective countermeasures to alleviate symptoms and ensure the success of human space missions. There is no doubt that long duration spaceflight and exposure to microgravity will increase the risk of developing SMS and, therefore symptoms that might very likely impact the physical and cognitive functioning of space travelers. Understanding the mechanisms of SMS and developing countermeasures is imperative for safety, health, and productivity of space crewmembers during future missions to the Moon, Mars, and beyond.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AK, PPP, IA, and IJ identified the keywords for scoping searches. KN carried out database searches using a search strategy. AK, PPP, IJ, and HG screened papers. AK, PPP, IA, HG, IJ, and BB completed data extraction on included papers and contributed to manuscript writing. EF and RG provided guidance throughout the systematic review and helped with manuscript editing. All authors read and approved the final manuscript.

Acknowledgments

We would like to acknowledge the Space Generation Advisory Council and UK Space Life and Biomedical Association. In particular, Dr. Rochelle Velho, Dr. Anthony Yuen, Zainab Mavani, Emma Barratt, Dr. Sergio Covarrubias-Castillo, Dr. Karan Ghatora, Ahmed Baraka, Bethany Evans, and Dr. Justin Koh.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fncir.2023.1150233/full#supplementary-material

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frontiers | Frontiers in Neuroscience

TYPE Original Research
PUBLISHED 23 June 2023
DOI 10.3389/fnins.2023.1180314

OPEN ACCESS

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RECEIVED 07 March 2023
ACCEPTED 31 May 2023
PUBLISHED 23 June 2023

CITATION
Sherman SO, Jonsen A, Lewis Q, Schlittenhart M, Szafir D, Clark TK and Anderson AP (2023) Training augmentation using additive sensory noise in a lunar rover navigation task.
Front. Neurosci. 17:1180314.
doi: 10.3389/fnins.2023.1180314

Training augmentation using additive sensory noise in a lunar rover navigation task

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Background: The uncertain environments of future space missions means that astronauts will need to acquire new skills rapidly; thus, a non-invasive method to enhance learning of complex tasks is desirable. Stochastic resonance (SR) is a phenomenon where adding noise improves the throughput of a weak signal. SR has been shown to improve perception and cognitive performance in certain individuals. However, the learning of operational tasks and behavioral health effects of repeated noise exposure aimed to elicit SR are unknown.

Objective: We evaluated the long-term impacts and acceptability of repeated auditory white noise (AWN) and/or noisy galvanic vestibular stimulation (nGVS) on operational learning and behavioral health.

Methods: Subjects (n=24) participated in a time longitudinal experiment to access learning and behavioral health. Subjects were assigned to one of our four treatments: sham, AWN (55 dB SPL), nGVS (0.5mA), and their combination to create a multi-modal SR (MMSR) condition. To assess the effects of additive noise on learning, these treatments were administered continuously during a lunar rover simulation in virtual reality. To assess behavioral health, subjects completed daily, subjective questionnaires related to their mood, sleep, stress, and their perceived acceptance of noise stimulation.

Results: We found that subjects learned the lunar rover task over time, as shown by significantly lower power required for the rover to complete traverses (p<0.005) and increased object identification accuracy in the environment (p=0.05), but this was not influenced by additive SR noise (p=0.58). We found no influence of noise on mood or stress following stimulation (p>0.09). We found marginally significant longitudinal effects of noise on behavioral health (p=0.06) as measured by strain and sleep. We found slight differences in stimulation acceptability between treatment groups, and notably nGVS was found to be more distracting than sham (p=0.006).

Conclusion: Our results suggest that repeatedly administering sensory noise does not improve long-term operational learning performance or affect behavioral health. We also find that repetitive noise administration is acceptable in this context. While additive noise does not improve performance in this paradigm, if it were used for other contexts, it appears acceptable without negative longitudinal effects.

KEYWORDS

stochastic resonance, auditory white noise, noisy galvanic vestibular stimulation, macrocognition, long duration exploration mission, longitudinal effects

Highlights

- Applying vestibular and/or auditory white noise during repeated learning sessions does not affect operational task performance.
- Repetitive noise administration does not affect immediate or longitudinal behavioral health.
- Repetitive noise administration is perceived to be acceptable by users.

Introduction

Astronauts must complete a large variety of complex, operational tasks in quick succession to accomplish mission goals; thus, they have to start training for these tasks upon being selected up until their mission. However, this training can be time consuming and many simulated environments fail to replicate the space environment accurately, as future space missions will impose unknowns that could necessitate learning new skills that were not included in mission design (Anglin et al., 2017). Skill decay is a concern for long-duration space missions as well (Pieters and Zaal, 2019). This creates the need for enhanced training techniques for on-ground and in-flight environments enabling quick skill acquisition. Additionally, the spaceflight environment creates physiological and psychological stressors that may impact cognitive and behavioral health, as well as the operator's ability to learn (Morphew, 2020; Roy-O'Reilly et al., 2021). A technique or countermeasure aimed at enhancing training should be robust to these stressors and not further burden the crew. It is theorized that improved performance in cognitive tasks can impact learning ability (Ackerman et al., 1995; Shi and Qu, 2022). A potential training technique focused on enhancing cognitive functioning is computerized cognitive training (CCT), where subjects exercise specific cognitive concepts through computerized games in hopes of training mental ability (Jaeggi et al., 2011). However, the generalizability and transfer of construct training is often invalid for separate constructs or more complex tasks (Noack et al., 2014). Thus, it would be advantageous to develop alternative technologies that enhance cognitive functioning and learning while being appropriate for the spaceflight environment.

One such technological field being explored is neuromodulation, which refers to using a stimulus to alter nerve activity (Horn and Fox, 2020), and in some cases has been shown to enhance learning. For example, transcranial direct current stimulation (tDCS) has been shown to contribute to motor learning and motor memory formation in healthy humans (Reis et al., 2008), and improve learning in tasks involving concealed object learning (Clark et al., 2012) and recognition (Manuel and Schnider, 2016). tDCS has also been shown to improve learning for operationally relevant tasks, such as complex flight simulations (Choe et al., 2016). However, there is evidence that tDCS can leave long-lasting effects on cortical excitability after stimulation has occurred (Medeiros et al., 2012). Additionally, some neuromodulation methods may have unintentional secondary effects on other mental states, such as behavioral health. Transcranial magnetic stimulation (TMS) has been shown to reduce depression states in clinical trials (Mantovani et al., 2012). While this is a beneficial behavioral health effect, it demonstrates that there are additional side effects to these neuromodulation techniques which require further exploration. Additionally, these techniques are difficult to self-administer and can require the user to be stationary during stimulation. These limitations could make these methods inappropriate for the spaceflight environment. Considering these effects and mission constraints, it is worth exploring neuromodulation alternatives that are more applicable to the dynamic spaceflight environment. One such alternative may be stochastic resonance, which is a method of neuromodulation that is induced through noisy sensory stimulation. While there are many open questions involved in applying this technique, it could be useful for spaceflight because appropriate sensory stimulation is safe, easy to administer, requires a low design budget, and can be used in dynamic situations.

Stochastic Resonance (SR) is the phenomenon where noise improves the throughput of a non-linear signal (Moss et al., 2004). It has been postulated that this phenomenon can be utilized as a neuromodulation technique for human information processing through the use of external sensory noise. Human experimentation has shown that SR is exhibited within and across sensory channels, where perceptual thresholds (the lowest intensity stimuli a person can reliably recognize) are reduced (Zeng et al., 2000; Lugo et al., 2008; Galvan-Garza, 2018; Voros et al., 2021). Additional models in human experiments have shown that noise-enhanced sensory information could be utilized by the whole central nervous system (Hidaka et al., 2000), suggesting that SR could affect higher order neuronal processing. Along this notion, sensory noise has been shown to improve elements of cognition, such as working memory (Wilkinson et al., 2008; Söderlund et al., 2010). Further, previous research conducted in our lab showed that certain individuals may show comprehensive cognitive improvement (Sherman et al., 2023a). This evidence implies that SR could be useful for improving information processing. It is postulated that being able to efficiently encode new information can help us repair or restructure our current knowledge (Chi, 2009). So, if SR can improve mental ability it might be able to improve learning ability as active cognitive processes may improve constructive and interactive processes. When it comes to learning as a result of noise, the literature suggests that noisy galvanic vestibular stimulation (nGVS) can enhance learning of challenging locomotor tasks (Putman et al., 2021) and that auditory white noise (AWN) can improve new-word learning in adults (Angwin et al., 2017). It is unclear whether learning in these two paradigms would extend to complex operational skill acquisition through procedural memory formation. This gap in the literature warrants further investigation to understand whether sensory noise can improve learning in complex tasks.

Further, no studies were identified which investigate lasting effects of sensory noise on behavioral health (e.g., mood, stress, sleep, etc.). Considering the behavioral effects that other neuromodulation techniques have on neuronal excitability and behavioral health outcomes, it would be beneficial to know whether sensory noise induces effects that are not beneficial for spaceflight operators. Thus, this work investigates the effects that repetitive administration of sensory noise has on operational learning and behavioral health. We hypothesized that compared to a sham group (i.e., wearing hardware, but presented no noise), the groups where we applied a stimulation treatment during operations would have improved learning in our operational task (i.e., lunar rover simulation). Further, we explored the hypothesis that sensory noise would impact measures of operator behavioral health, either as a benefit or a detriment.

Noise from any sensory modality may improve signal detection and improve cognitive abilities. However, it is prudent to consider sensory modality options that integrate well with, or possibly target other complications resulting from, living in a spaceflight environment. Living in microgravity imposes sensory challenges as a result of otolithic deprivation; however, several longitudinal studies have shown that humans reinterpret and adapt their understanding of orientation and spatial surroundings in spaceflight (Pathak et al., 2022). Thus, we wanted to apply noise to sensory modalities that have demonstrated the ability to influence the vestibular, motor, somatosensory, and visual systems as these central nervous system regions are impacted and undergo sensory reweighting in spaceflight (Roy-O'Reilly et al., 2021). Directly influencing these CNS regions, nGVS has been shown to modulate spatial memory and learning in sensorimotor performance tasks (Moore et al., 2015; Hilliard et al., 2019; Putman et al., 2021). Further, nGVS has been shown to improve postural stability and perception in vestibular and visual modalities (Wilkinson et al., 2008; Wuehr et al., 2016; Galvan-Garza, 2018). Indirectly influencing these CNS regions, AWN has been shown to improve memory encoding and learning of auditory and visual stimuli (Othman et al., 2019; Sayed Daud and Sudirman, 2023). Further, AWN may influence locomotion and perception performance in visual, tactile, and somatosensory modalities (Manjarrez et al., 2007; Lugo et al., 2008; Carey et al., 2023). These two modalities have demonstrated the ability to modulate learning and improve performance in perception and key CNS regions, lending themselves as ideal neuromodulation candidates if they also improve performance in complex, operational tasks.

Thus, we chose to investigate acoustically stimulating the auditory system using AWN and electrically stimulating the vestibular system using nGVS. Additionally, these two modalities as we believed they were the least intrusive to interface design or to astronaut mobility, being ideal candidates for operating in the spaceflight environment. However, to assess this we measured the acceptability opinion of users in all groups to see whether sensory noise stimulation impacted their perceived level of ability.

Methods

Subjects

Twenty-four subjects (12F/12M), age 26 ± 10 years (range = 18–55 yrs) completed testing in the Bioastronautics Lab at the University of Colorado-Boulder. This research was approved by the University of Colorado-Boulder's Institutional Review Board (protocol #21-0296) and written informed consent was obtained prior to participation. Subjects were pre-screened and excluded if they reported a history of health issues that could impact cognitive abilities, such as severe head trauma or disorders associated with thinking impairment. They were also excluded if they reported health issues that could impact auditory or vestibular processing, such as language impairment or vestibular dysfunction. Eight willing participants were excluded from being in this study for not meeting pre-screening eligibility. Additionally, subjects underwent auditory screening to verify healthy and unobstructed ear canals (via otoscopy), normal tympanometry, and normal hearing (audiometric thresholds ≤25 dB HL up to 8 kHz). No subjects that passed pre-screening eligibility were excluded as a result of this auditory screening. Twenty subjects reported their occupation as undergraduate or graduate students in technological majors and four subjects reported their occupation as engineers.

Study design and timeline

A between-subject longitudinal experimental design was implemented to evaluate the lasting operational and behavioral health effects of repeated noise exposure. Four groups ($n = 6$ in each group, 3F/3M) were assigned a noise stimulation treatment that was used for the duration of the experiment. Subjects were assigned to treatments using a covariate randomization technique to ensure equal sex grouping in each treatment. These treatments included a no noise sham (3F/3M, age 25.3 ± 6.1 years, range = 21–34), AWN with an intensity of 55 dB SPL (3F/3M, age 27 ± 11.5 years, range = 20–50), nGVS with an intensity of 0.5 mA (3F/3M, age 22.2 ± 5.1 years, range = 18–32), and the combination of the AWN and nGVS treatments, termed multi-modal SR (MMSR) (3F/3M, age 30.5 ± 16 years, range = 19–55). These noise levels (55 dB SPL and 0.5 mA) were selected as our previous work showed they near optimal in terms of inducing SR for a majority of subjects we had tested (Sherman et al., 2023a,b). It should be noted that for within modality perception improvement (i.e., auditory noise to improve auditory signal detection) that low signal-to-noise ratios are required (Zeng et al., 2000; Moss et al., 2004). However, cross-modal perception improvement and cognitive enhancement paradigms using noise have required high levels of noise (~55–70 dB SPL) (Manan et al., 2012; Othman et al., 2019). For AWN stimulation, broadband AWN (20 Hz–20,000 Hz) was administered to subjects through ear buds (Essential Earphones HD) and a Samsung Tablet A; the auditory profiles were developed and calibrated by Creare LLC (Hanover, NH). For nGVS stimulation, broadband, unipolar, zero-mean white noise

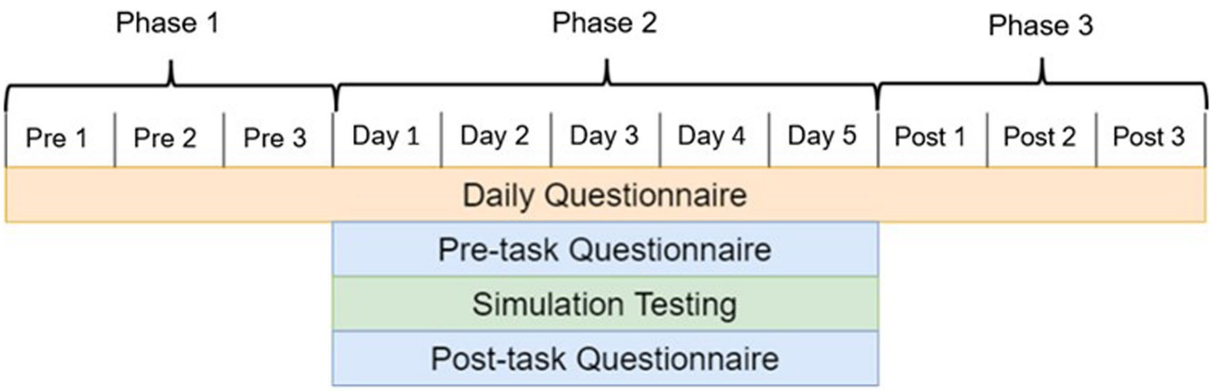

FIGURE 1
Experimental timeline split up into three distinct testing phases. The first phase is a three-day behavioral health metric collection period to serve as a baseline. The second phase consists of five days of simulation testing under treatment stimulation. The third phase is a three-day collection period to observe after-effects of treatment stimulation.

TABLE 1 Experimental questionnaires and their associated assessment tools.

Questionnaire	Metric	Assessment tool	Reference
Daily Questionnaire	Stress	Stress in General (SIG)	Fuller et al. (2003)
	Mood	Profile of Mood States – Short Form (POMS-SF)	Terry et al. (2003)
	Sleep	Consensus Sleep Diary (CSD)	Carney et al. (2012)
Pre-task Questionnaire	Stress	Short Stress State Questionnaire (SSSQ)	Helton (2004)
Post-task Questionnaire	Stress	SSSQ	Helton (2004)
	Mood	POMS-SF	Terry et al. (2003)
	Acceptability	SR Acceptability Questionnaire (SRAQ)	In house

(0 Hz–100,000 Hz) was bilaterally administered to subject mastoids through the Galvanic Vestibular Oscillating Stimulator (model 0810, Soterix Medical, Woodbridge, NJ) using electrodes with a contact area of 2 cm^2 (Voros et al., 2021). Traditionally, nGVS frequency profiles have used 640 Hz or less as the high frequency cutoff (Inukai et al., 2018); however, our group has found success in inducing cross-modal perception improvements using this profile (Voros et al., 2021). In the sham treatment, no sensory noise was administered, but subjects were equipped with electrodes and earbuds. Subjects in all treatment groups were fit with AWN and nGVS hardware, independent of whether they actually received sensory noise stimulation.

In their initial visit, subjects watched an 8 minute tutorial video to orient them to the lunar rover simulation environment (see below for details on rover simulation). They then completed one run of the simulation to become familiar with the motives and controls of the simulation. This was done under the guidance of a test operator, which helped explain the rules of the simulation, while avoiding telling them how to do well in the simulation or giving them an opportunity to practice and thus reduce our ability to assess learning.

For this time-longitudinal experiment, all subjects followed a strict, 11 day timeline, which is displayed in Figure 1. This 11 day timeline is comprised of three phases. Phase 1 served as a three-day baseline assessment of behavioral health prior to any treatment stimulation being applied. Phase 2 was the five-day simulation testing period where subjects completed lunar rover simulations under the influence of one of the stimulation treatments. Phase 3 was a post treatment stimulation assessment that allowed us to identify aftereffects as a result of repetitive treatment stimulation. Across all 11 days, an online daily questionnaire was completed in the morning. In addition, subjects completed a questionnaire before and after simulation testing in phase 2.

Metrics of mood, stress, and sleep were collected over the course of the experiment to analyze behavioral health effects of repeated noise exposure. An additional metric of SR acceptability was collected to analyze the acceptability of the noise treatments (Supplementary Data Sheet 1). This was administered after each day's test session, and then once at the end of the five-day simulation testing period in reference to overall final acceptability. This day 5 questionnaire asked the same questions as the first 4 days but asked subjects to report their overall opinion across the 5 days rather than that specific day. Table 1 details the assessment tools that were used to assess these behavioral health effects.

Lunar rover simulation

The Lunar Rover Simulation (LRS) is a complex, operational task that allows for the assessment of learning through daily use. Subjects interact with the LRS using an HTC Vive Pro head mounted display to view the lunar landscape and a Logitech X-52 Pro HOTAS joystick to operate the rover. The LRS environment was developed and

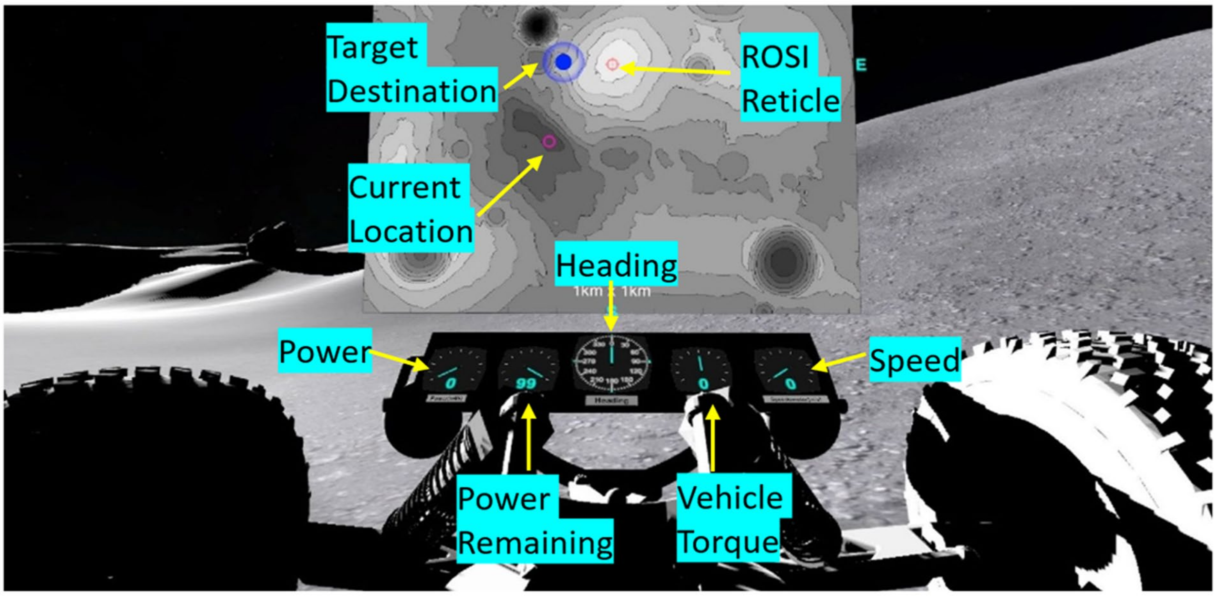

FIGURE 2
Rover display tools that were provided to the subject. Subjects could pull up a geo-fixed 2-D topographical map of the landscape (shown in this example, top middle), where their location was represented as a magenta circle and the destination waypoint was a blue animated marker. Additional dashboard elements that were continuously available to subjects included current power consumption, battery power remaining, torque, vehicle speed, and body-centered heading. A red reticle could be moved along the topographical map for subjects to tag Rock of Scientific Interest (ROSI) locations.

modified in Unity pulling existing assets from another lunar rover simulation our broader group developed (McGuire et al., 2018). This simulation was designed to feature aspects of the lunar environment, such as; realistic terrain, varied crater sizes, representative lunar lighting and lunar gravity. The LRS is comprised of two operational sub-tasks: path optimization and object identification.

For the path optimization subtask, subjects navigated their rover to several waypoint target destinations along the lunar surface with the goal of minimizing their battery consumption between each waypoint. Power consumption used the specific energy rate equations defined by Carr (2001), where the total power was the sum of the power consumed while moving on a level plane or slope, and a constant power drain (Eq. (1)).

$$W_{\text{Total}} = W_{\text{level}} + W_{\text{slope}} + P_{\text{e}} \qquad (1)$$

Battery power consumption was a factor of speed, slope angle, and time (either driving or remaining still, due to constant power drain) across the total distance traveled. Subjects had to learn to weigh each of these factors in optimizing their navigation paths. Subjects were given a variety of tools to help them plan a power-efficient traverse. The first was a 2D topographical contour map of the lunar environment which displayed the waypoint they were navigating to using a blue animated marker with their current location being represented with a magenta circle (see Figure 2, top middle). Subjects could use this tool to plan their traverse trajectory through terrain to optimize power consumption, but they could not move the vehicle while the map was open. Subjects had autonomy on when they looked at and put away the map (selected by button press on the joystick). Subjects were also given a vehicle dashboard which displayed active state information on current power consumption, battery remaining, torque, vehicle speed, and body-centered heading. Figure 2 shows the map and dashboard presented to subjects.

Along with the animated blue marker on the 2D map, subjects knew they had reached their target destination via a stationary 3D robotic rover on the lunar terrain. Once subjects reached their target destination, a new waypoint was presented on the map and their battery was recharged. Each simulation had five waypoints which created a loop; therefore, subjects end where they started. Their starting position in the loop was randomized, but all subjects experienced the same waypoint target destinations. If subjects placed their rover in an unrecoverable position (e.g., overturned in the bottom of a steep crater) or they ran out of battery, the current waypoint trial was considered an "incomplete" and they were teleported to their current target waypoint, which prompted the next traverse.

For the object identification subtask, subjects must tag Rocks of Scientific Interest (ROSIs). Several rocks littered the lunar landscape, some of these rocks blended in with the environment and were ubiquitous (dummies); however, the ROSIs were black in color and contrasted the landscape (Figure 3). Subjects were instructed to be vigilant and tag only ROSIs (and not dummy rocks) during their traverses. Subjects tagged ROSI locations via the 2D contour map, moving the red reticle to their perceived ROSI location and laying down a marker (Figure 2). All rock locations were randomized *a priori* and placed in the terrain during development, ensuring all subjects experienced the same rock placements. Based on map design, subjects were expected to see 2–3 ROSIs for each waypoint trial. A unique lunar terrain was given for each test day, such that strategies, skills, and techniques could be learned, but the exact layouts of the lunar terrain and map were not transferrable. The time to complete the LRS depended on the subjects and their strategy; on average, subjects completed the LRS in 20 minutes per session. Subjects received treatment stimulation over the course of completing the LRS, with stimulation not being applied before or after LRS testing.

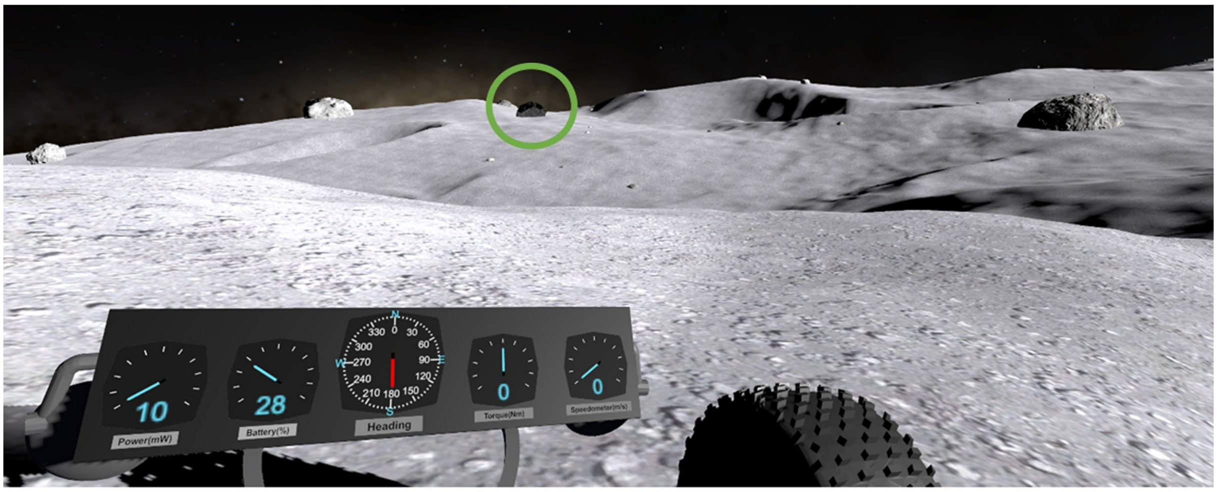

FIGURE 3
Subject point of view in the object identification task. Upon finding a black ROSI (circled green for the reader), subjects would direct the 2-D map's red crosshair on their perceived ROSI location and confirm or "tag" its location.

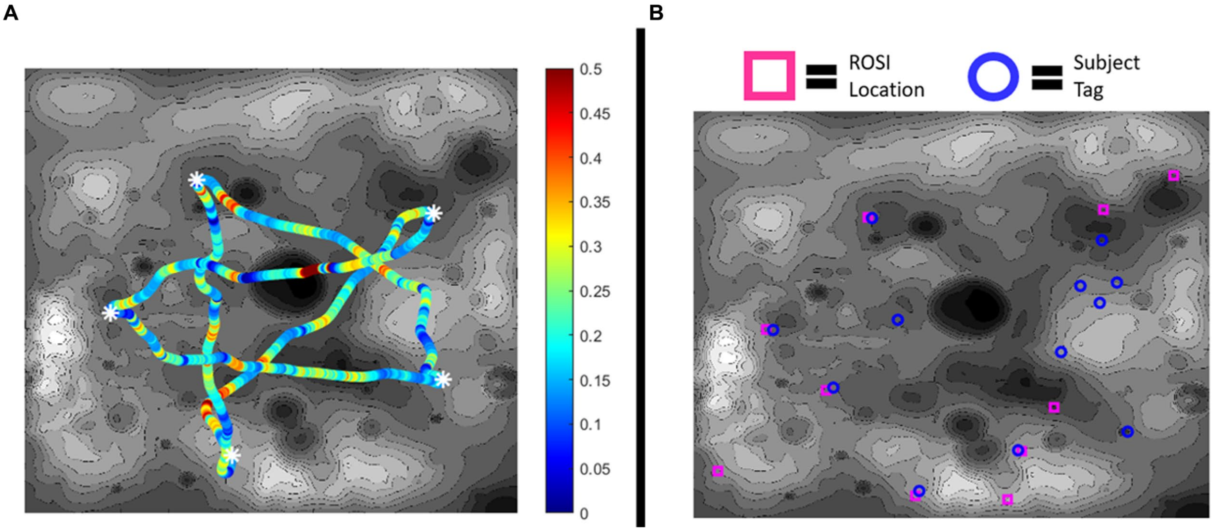

FIGURE 4
(A) Example of subject battery consumption along traverses in the path optimization subtask. White asterisks represent the waypoint locations. Low battery consumption (Watts) is represented by blue in the spectrum and high battery consumption is represented by red. **(B)** Example of subject object identification. Actual ROSI locations are marked in magenta, while subject reported rock tags are marked in blue. In this example, five of the rock tags correspond to ROSI locations but seven do not (i.e., incorrectly identifying a dummy rock as being a ROSI), while five ROSIs were left untagged.

Figure 4 visualizes an example result of one subject's operational performance in a map. Figure 4A represents their performance in the path optimization subtask with power consumption along a traverse being color coded. Figure 4B visualizes their rock tag placements in contrast to the actual ROSI locations.

Analysis

In summary, analysis approaches differed between operational learning performance and behavioral health effects. Learning was assessed as changes in operational performance over the five-day testing phase (Phase 2), whereas, group behavioral health differences were considered across all phases (Figure 1). Several Analysis of Variance (ANOVA) models were applied to analyze the effect of the noise treatments. Assumptions for residual normality in learning were calculated using the Anderson-Darling test ($p > 0.35$) to ensure that parametric statistics were appropriate. Additionally, Bartlett's test was used to test variance homogeneity between groups in the behavioral health analysis ($p > 0.3$). If the omnibus F-test results from the ANOVAs were significant, Tukey HSD multiple pairwise comparisons were used to identify which treatments were different from one another.

Learning analysis

Performance scores in a traverse for the path optimization subtask was defined as the "battery needed" to reach the desired waypoint. If a subject reached the waypoint, this was simply the amount of battery consumed since the start of the traverse. If a subject failed to reach the waypoint as a result of an "incomplete," the battery needed term was calculated as 100 (the total amount of battery allotted) plus the battery that would be used to traverse the distance remaining to waypoint (at full speed with no sloped terrain). While this additional term may not accurately reflect subject driving behavior, it prevents the performance ceiling effects of incomplete traverses (if they all remain at 100) and weighs incomplete traverses that made it closer to the waypoint target more favorably than those further away. The performance (P) used in our statistical model (Eq. (3)) for each day was the summation of the five "battery needed" traverse scores for the single LRS divided by five (i.e., a value of 100 corresponded to the full battery consumed on each of the 5 traverses, while lower values corresponded to better performance since less battery was consumed, and higher values were the result of some incomplete traverses and thus worse performance).

Performance scores in the object identification subtask relied on the total number of correct ROSI identifications on a given map. This was done by identifying which rock (ROSI or dummy) was closest to the user's tagged location. Correct identifications (c) were selected if a ROSI was the closest rock to this tagged location and incorrect identifications (i) were marked if a dummy rock was closest. Identification scores (ID_{P}) for a given map were calculated using Eq. (2) to reward correct tags and penalize incorrect tags. This was standardized by dividing the result by 10, as there were only 10 ROSIs in each map. The performance (P) used in our statistical model (Eq. (3)) for each day was this ID_{P} score.

$$\mathrm{ID}_{\mathrm{P}} = \left(c - i\right) / 10 \tag{2}$$

To observe between subject differences in path optimization or object identification performance (P), a mixed effects model was utilized with day (D) was a continuous covariate. Map (M, as a categorical variable) was also included as a covariate to capture variations simply due to the difficulty of the map. A fixed effect of noise treatment (NT) was included to evaluate whether treatment influenced operational performance independent of learning. Finally, to assess differences in learning between the four groups, an interaction term between treatment and day was included in the model. The interaction accounts for the slope of performance improvement between treatment groups. The final analytical model for the two operational subtasks is given in Eq. (3).

$$P \sim \mathrm{NT} + M + D + \mathrm{NT} * D \tag{3}$$

Behavioral health analysis

Following the guidance of previous studies that validated the assessment tools from Table 1, quantifiable metrics of behavioral health were defined. Stress and mood were considered when assessing immediate behavioral health effects from noise stimulation. For mood, the total mood disturbance (TMD) metric was calculated by adding the raw score responses of tension, depression, anger, fatigue, and confusion and then subtracting the vigor score (Terry et al., 2003); thus, lower scores indicate more stable mood profiles. Stress metrics of engagement, distress, and worry were calculated by adding the raw score response of the questions associated with that metric (Helton, 2004). We cared about deviations in behavioral health after task completion and stimulation; thus, the final metric scores being statistically assessed were the behavioral health metric post testing minus the behavioral health metric pretesting.

Following our objectives, we wanted to know whether repeated noise exposure over time impacted behavioral health (B); thus, behavioral health metrics were observed across the 5-day simulation testing period. A two-way ANOVA was used to observe between differences in mood and stress. For this, categorical variables of treatment, day, and their interaction were used, allowing us to understand changes in behavioral health state. The final analytical model used for these behavioral health states is given in Eq. (4).

$$B \sim \mathrm{NT} + D + \mathrm{NT} * D \tag{4}$$

Expanding on this, we wanted to understand longitudinal behavioral health effects, seeing whether repetitive noise administration affected behavioral health in the long term (during or afterwards). With respect to the daily questionnaires which loaded questions related to mood, strain, and sleep, we completed two-way ANOVAs to assess differences between the three testing phases (Figure 1). This allowed us to understand how the treatments impacted behavioral health during and after the stimulation testing period, which could suggest long-term after-effects. The categorical testing phases (TP) assessed were the 3 days prior to testing, the 5 days of testing, and the 3 days after testing. Categorical variables of treatment, test phase, and their interaction were used, allowing us to understand changes in behavioral health state across the three test phases. Longitudinal behavioral health measures were standardized by subtracting the average in each subject's baseline measures. The means were calculated for each test phase in each subject and compared to reduce the weighting of the second test phase (as there were separate measures in this period compared to the three measures collected in the other periods). The final analytical model used for these behavioral health states is given in Eq. (5).

$$B \sim \mathrm{NT} + \mathrm{TP} + \mathrm{NT} * \mathrm{TP} \tag{5}$$

Finally, based on the structure of the acceptability questionnaire (Supplementary Data Sheet 1), raw scores at the conclusion of stimulation were assessed in each of the six questions. A one-way ANOVA was used to understand general acceptability of the stimulation treatments.

Results

The results are presented in terms of first the operational performance improvement (i.e., learning effects) and second the behavioral health impacts.

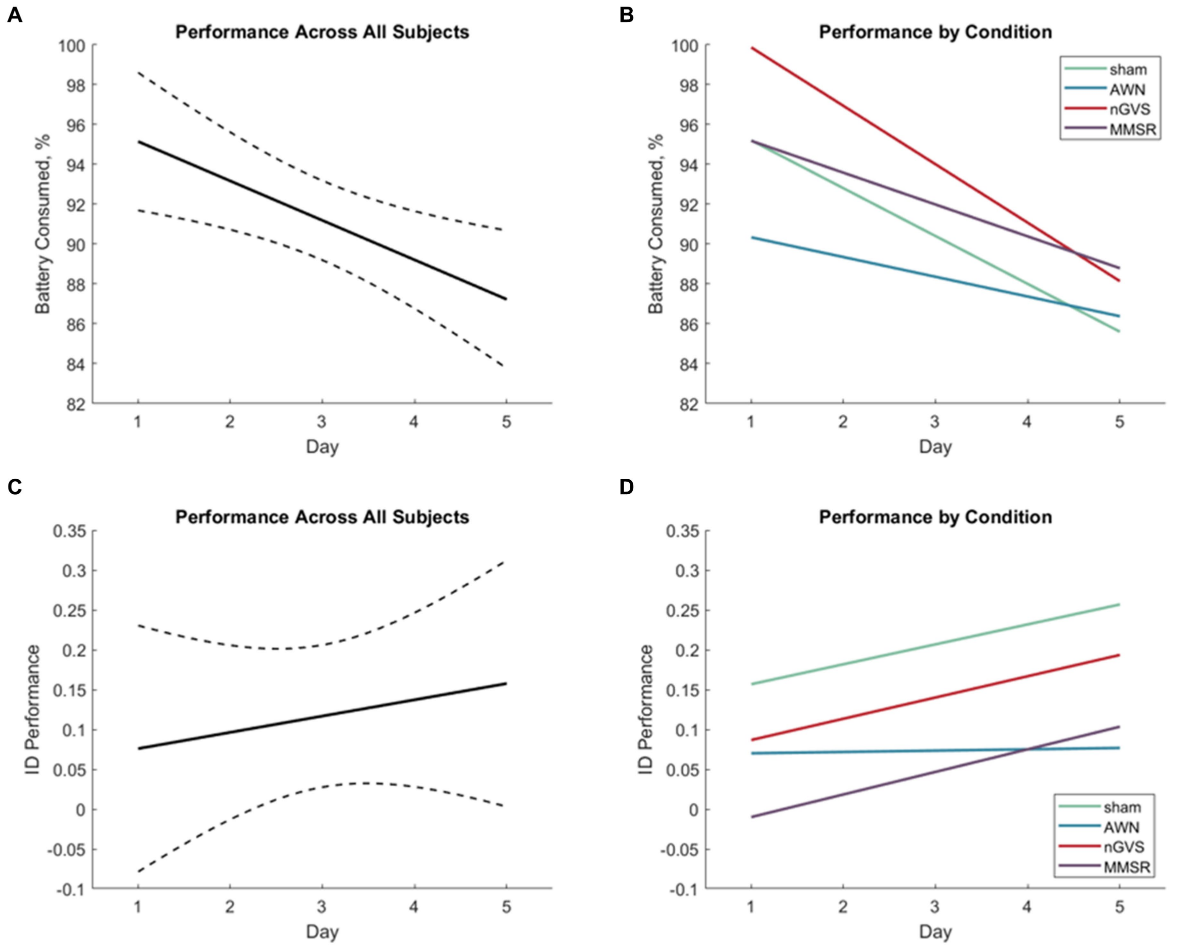

FIGURE 5
(A) Linear regression of path optimization performance improvement across the five test sessions for all subjects. Dashed lines indicate the 95% confidence interval of the modeled fit. **(B)** Linear regressions of path optimization performance improvement across the five test sessions for each treatment group. **(C)** Linear regression of object identification performance improvement across the five test sessions for all subjects. Dashed lines indicate the 95% confidence interval of the modeled fit. **(D)** Linear regressions of object identification performance improvement across the five test sessions for each treatment group.

TABLE 2 Mixed effect model results for operational learning performance, for each operational sub-task of path optimization and object identification.

Factor	Path optimization			Object identification		
	F (dof)	*p*-value	η_p^2	F (dof)	*p*-value	η_p^2
Noise Treatment	1.74 (3, 108)	0.16	0.046	0.23 (3, 108)	0.87	0.006
Map	0.94 (4, 108)	0.44	0.034	5.98 (4, 108)	<0.005*	0.181
Day	13.98 (1, 108)	<0.005*	0.115	3.86 (1, 108)	0.05*	0.035
Noise Treatment*Day	0.66 (3, 108)	0.58	0.018	0.15 (3, 108)	0.93	0.004

Asterisks represent metrics that met a statistical significance below $\alpha = 0.05$.

Learning results

These results explore learning through changes in operational performance over time in the path optimization and object identification subtasks. Overall needed battery consumption was the metric of performance in path optimization and ID performance (Eq. (2)) was the metric for rock identification. Figure 5 shows the rates of operational performance change in these metrics for all subjects (Figures 5A,C) and by treatment group (Figures 5B,D). Table 2 shows the results of the statistical tests produced by Eq. (3). Significant effects of day were identified in each learning subtask (indicating learning across all subjects); however, the interaction effects were not significant (indicating no difference in learning between treatment groups).

For the path optimization task, since map appeared to not be a statistically significant factor in the model, we followed up with a simplified model without the map factor to add extra statistical power to the other factors considered. However, this removal did not induce

TABLE 3 Two-way ANOVA results for behavioral health effects following stimulation, split between mood and the three metrics of stress.

Factor	F (dof)	*p*-value	η_p^2	F (dof)	*p*-value	η_p^2
	TMD			Engagement		
Noise Treatment	2.23 (3, 100)	0.09	0.063	1.6 (3, 100)	0.19	0.046
Day	0.4 (4, 100)	0.81	0.016	0.84 (4, 100)	0.5	0.033
Noise Treatment*Day	1.22 (12, 100)	0.28	0.128	2.1 (12, 100)	0.02*	0.202
	Distress			Worry		
Noise Treatment	1 (3, 100)	0.39	0.029	0.5 (3, 100)	0.68	0.015
Day	0.73 (4, 100)	0.57	0.029	0.5 (4, 100)	0.74	0.02
Noise Treatment*Day	1.42 (12, 100)	0.17	0.145	1.42 (12, 100)	0.17	0.146

Asterisks represent metrics that met a statistical significance below 0.05.

TABLE 4 Two-way ANOVA results for longitudinal behavioral health effects between treatments, split between mood, strain (three metrics), and sleep (three metrics).

Factor	F (dof)	*p*-value	η_p^2	F (dof)	*p*-value	η_p^2
	TMD			Relaxed and Calm		
Noise Treatment	0.02 (3, 60)	0.99	0.001	1.51 (3, 60)	0.22	0.07
Period	0 (2, 60)	0.99	<0.001	0.49 (2, 60)	0.61	0.016
Noise Treatment*Period	0.19 (6, 60)	0.98	0.019	0.48 (6, 60)	0.82	0.046
	Comfort and Smooth			Pushed and Stressed		
Noise Treatment	2.65 (3, 60)	0.06	0.117	1.09 (3, 60)	0.36	0.052
Period	2.18 (2, 60)	0.12	0.068	0.2 (2, 60)	0.82	0.007
Noise Treatment*Period	0.88 (6, 60)	0.51	0.081	0.77 (6, 60)	0.6	0.071
	Total Sleep			Sleep Quality		
Noise Treatment	0.89 (3, 60)	0.45	0.042	1.38 (3, 60)	0.26	0.064
Period	0.21 (2, 60)	0.81	0.007	0.01 (2, 60)	0.99	<0.001
Noise Treatment*Period	0.52 (6, 60)	0.79	0.049	0.42 (6, 60)	0.86	0.041
	Feeling Refreshed					
Noise Treatment	5.16 (3, 60)	<0.005*	0.205			
Period	1.13 (2, 60)	0.33	0.036			
Noise Treatment*Period	1.34 (6, 60)	0.24	0.118			

Asterisks represent metrics that met a statistical significance below $\alpha = 0.05$.

significance in the other factors ($p > 0.19$). This was not applied to the object identification data as map was a significant factor. This technique was not applied to the behavioral health data as it was important to understand the factor effects of treatment and day to identify time longitudinal changes in behavioral health. Contrary to our hypothesis, we did not observe improvements in learning for the noise stimulation treatments, for either path optimization or objective identification performance. Further visualizations of these results, separated by group with representative variance, can be found in Supplementary Image 1.

Behavioral health results

Immediate behavioral health results

We explored the differences in mood and stress prior to and after completing the task with treatment stimulation. Table 3 show the statistical test results given by Eq. (4). Visualizations of these results can be found in Supplementary Image 2.

We identified a significant interaction between noise treatment and day for the stress metric of engagement (Supplementary Image 2); however, no other factors were significant. Contrary to our hypothesis, it appears there are no strongly influential effects of stimulation on immediate behavioral health.

Longitudinal behavioral health results

We wanted to observe differences in behavioral health between the three time periods; pre-testing baseline, testing with stimulation, and post-testing aftereffects. Table 4 show the statistical test results given by Eq. (5). Visualizations of these results can be found in Supplementary Image 3.

We identified a significant effect of noise treatment for the sleep metric of "feeling refreshed"; however, no other factors were

TABLE 5 One-way ANOVA results for the six metrics of treatment acceptability.

Metric	F (dof)	*p*-value	η_p^2
Felt the equipment did not inhibit performance	2.43 (3,116)	0.07	0.059
Felt that the AWN was comfortable	5.55 (3,116)	<0.005*	0.126
Felt that the nGVS was comfortable	0.93 (3,116)	0.43	0.023
Felt that they were able to maintain focus	2.31 (3,116)	0.08	0.056
Found the treatment stimulation was distracting	5.07 (3,116)	<0.005*	0.116
Found the treatment stimulation fatigued them	2.52 (3,116)	0.06	0.061

Asterisks represent metrics that met a statistical significance below $\alpha = 0.05$.

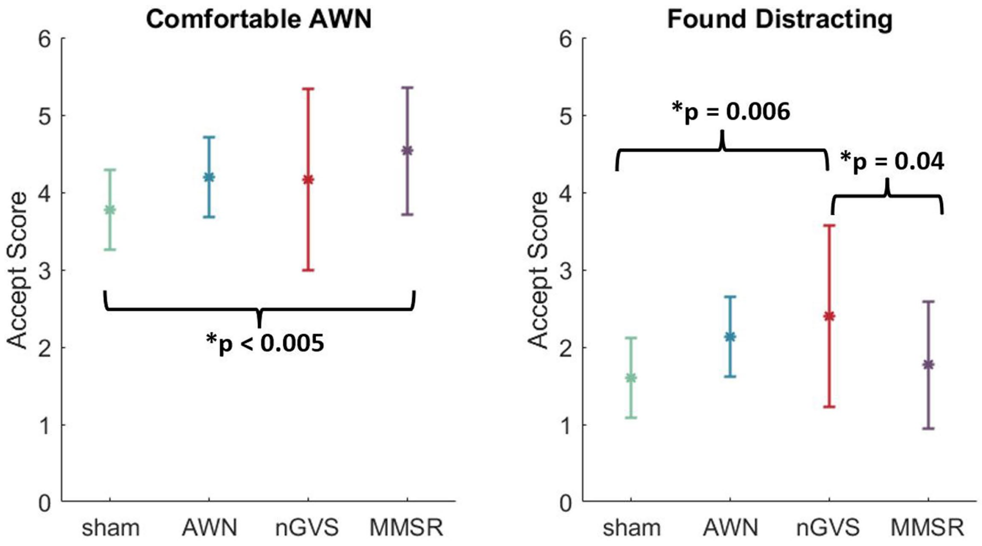

FIGURE 6
Multiple comparisons in the two significantly different acceptability metrics. Error bars indicate the standard deviation of the data point. Brackets indicate the treatments that were identified to be different from one another.

significant. Multiple comparisons showed that the AWN treatment group was significantly more refreshed than the sham group ($p < 0.005$). Contrary to our hypothesis, it appears there are no strongly influential effects of stimulation on longitudinal behavioral health since only this difference was identified.

Acceptability results

We developed an acceptability questionnaire (Supplementary Data Sheet 1) to assess differences in stimulation acceptability between treatment groups. Table 5 show the statistical test results for the resulting one-way ANOVAs. Visualizations of these results can be found in Supplementary Image 4.

We identified a significant effect of noise treatment for the acceptability metrics of "AWN was comfortable" and "stimulation was distracting." No other acceptability questionnaire metrics were significant. For the first significant metric, a multiple comparison analysis showed that the MMSR treatment group believed the AWN stimulation was significantly more comfortable than the sham group ($p < 0.005$). For the second significant metric, a multiple comparison analysis showed that the nGVS treatment group believed the nGVS stimulation was significantly more distracting than the sham group ($p = 0.006$) and the MMSR group ($p = 0.04$). These results are visualized in Figure 6. Independent of these two metrics, it appears that sensory noise stimulation is generally deemed to be acceptable between the treatment groups.

Discussion

This research investigated for the first time the effects of repetitive sensory noise stimulation on operational learning, as well as its long-term effects on behavioral health. This was done by having subjects complete a lunar rover simulation once daily, for 5 days, under treatment stimulation. While we found subjects broadly performed better in the operational task across days, there were no differences in the rate of task improvement between groups (i.e. no differences in learning). Prior, post, and during this period, subjective questionnaires related to behavioral health metrics of mood, stress, and sleep were collected. We found no significant differences in behavioral health or acceptability between treatment groups except in a few specific metrics.

Previous sensory noise literature related to memory found that nGVS can improve spatial memory and AWN can improve auditory working memory (Hilliard et al., 2019; Othman et al., 2019); however, the study presented here was not able to find significance. Focusing on the study conducted by Hilliard et al. (2019), subjects completed a within-subject cross-over design with a virtual spatial memory task under the influence of nGVS stimulation (tailored to 80% of their sensation threshold) in one of two sessions that were separated by 2 weeks. During testing subjects were tasked to explore a virtual arena, learn the location of objects, and then mark their location when they were removed. They completed three of these runs. This study found improved accuracy of object location across the learning run. It should be noted that Hilliard et al. (2019) tested more subjects than ours, but we want to call into question the use of nGVS for declarative vs. non-declarative memory formation, where procedural memory tasks are non-declarative in nature (Brem et al., 2013). The task completed in this study was procedural, whereas Hilliard et al. (2019) object location task can be argued as declarative. It is possible that the memory formation paradigm that SR targets is semantic and declarative in nature, but further investigations into procedural memory formation paradigms are needed.

The closest procedural paradigm similar to the experiment presented here was found for alternative forms of neuromodulation which had observed that neural stimulation from tDCS applied to the right dorsolateral prefrontal cortex can lead to improved learning rates in complex operational tasks as opposed to receiving no stimulation (Choe et al., 2016). Choe et al. (2016) investigated operational learning in an aviation landing simulation across 4 days. In this task subjects aimed to replicate a landing that was similar to an autopilot demonstration that was presented to them before their simulation began. To do this, subjects used instrumentation cues during the autopilot demonstration to guide their landing. For the simulation paradigm we investigated, this type of replication scenario was not represented, as our task was a self-guided learning paradigm. Results compiled across all subjects suggest that performance in the operational task significantly improved across all subjects over time, but there was no difference between stimulation treatments and sham. This indicates the lunar rover simulation paradigm could still capture effects of learning. This could suggest that our results imply that additive sensory noise is not an appropriate neuromodulation technique for learning enhancement within this group or that the noise treatment produces sufficiently low effect sizes that this experiment is not sensitive to. Yet, it is entirely possible that we are assessing the incorrect learning task mode to demonstrate SR improvements as the tDCS study referenced in this paper used a replication paradigm.

While sensory noise may not improve learning within this experimental paradigm for this population, it has been shown that noise can lead to broad performance enhancement within specific use cases. Multiple studies have shown that SR is broadly exhibited in perception, both within and across separate sensory modalities (Lugo et al., 2008; Galvan-Garza, 2018; Voros et al., 2021). This implies that certain attributes of information processing can be enhanced by sensory noise for a broad population. However, when it comes to inducing cognitive enhancements, the results appear to be inter-individually driven. Wilkinson et al. (2008) found that nGVS improves facial recognition recall in healthy, neurotypical participants, but Söderlund et al. (2010) and Chen et al. (2022) found auditory noise improves cognitive processing in only inattentive children, worsening cognition in attentive children. This is furthered by a recent investigation which observed mixed results for AWN and cognition in neurotypical subjects (Awada et al., 2022). Further, research conducted by our lab found no broad cognitive enhancements under sensory noise, but found that subject interactions were significant, with subjects that self-reported being able to work better with background noise showing cognitive enhancement as a result of sensory noise treatment (Sherman et al., 2023a). This implies that applying sensory noise for cognitive processing may only be beneficial for certain individuals. Our study used a novel operationally complex learning paradigm with a neurotypical population, which shows mixed results for noise affecting cognitive influence. Additional investigations are necessary to determine if there are separate paradigms or specific individuals would see learning enhancement due to noise.

However, it is useful to understand whether sensory noise has secondary effects to behavioral health which would undermine the usage of sensory noise in these specific use cases or individuals.

Alternative neuromodulation techniques, specifically tDCS and TMS, have been shown to create immediate, lasting effects on neuronal excitability and long-term behavioral health (Mantovani et al., 2012; Medeiros et al., 2012). A suitable neuromodulation technique for repeated administration would not negatively affect behavioral health, especially on a long-duration space mission. Since sensory noise effects on behavioral health have not been observed in the literature, we aimed to address this gap. Behavioral health questionnaires following stimulation and testing allowed us to assess immediate behavioral impacts. The longitudinal daily collection of behavioral health questionnaires related to mood, strain, and sleep allowed us to assess sensory noise effects on general behavioral health and potential aftereffects. In general, our results do not suggest that sensory noise impacts behavioral health. While you cannot prove a null result, the effect sizes related to most of our metrics suggest that you would need extremely high subject numbers to identify significant differences. For example, a retrospective power analysis for immediate mood changes with a $\eta_p^2 = 0.063$ (Table 3) showed that 104 subjects are required to identify treatment group differences. With such a small effect size from these validated and sensitive questionnaires, we feel confident that many of the measures related to behavioral health would not result in meaningful impacts from sensory noise stimulation. Inferring from these results and our findings which suggest noise stimulation is generally acceptable (Table 5), we believe that repetitive administration of AWN and nGVS have no effects on behavioral health and is generally acceptable for repeated use in situations and individuals that necessitate its usage.

There are a few limitations to this study that are worth noting. First, previous research conducted for perceptual and cognitive SR have identified that there is a subject and task specific optimal noise level to induce performance enhancement (Ries, 2007; Voros et al., 2021; Sherman et al., 2023a). Since this task is a learning paradigm, there was no efficient way of identifying a subject's specific optimal noise level. We tried to navigate this problem by choosing the noise levels that were most commonly represented as near optimal in previous cognition investigations completed within this lab (Sherman et al., 2023a,b), which we believed would allow us to produce potential SR effects for a majority of participants in this study. However, it is possible that these levels would not induce SR benefits in terms of improved learning for some or many of our subjects, but that had we applied different levels (or individualized levels) SR benefits may have been observed. Second, our subject number per group ($n = 6$) is relatively low. That being said, we have included effect sizes for future research and meta-analyses. The effect sizes related to operational learning are sufficiently low enough for the interaction terms of our statistical analysis (Table 2) that a few more subjects within each treatment group would probably not yield significant changes. However, this low subject number may explain significant differences in certain ordinal measures. For example, sham subjects believed the AWN stimulation was more uncomfortable than the MMSR group which did receive AWN stimulation (as well as nGVS); the AWN treatment group was not significantly different from either. While is possible that the simultaneous application of nGVS and AWN caused the experience of AWN to be more comfortable, it could suggest that this result is a false positive. Greater sensitivity in the acceptability questionnaire or greater subject numbers may have prevented this result. However, the significant acceptability result of nGVS being more distracting than sham follows with preconceived notions. Finally, it is difficult to speculate on how nGVS effects in an Earth gravity environment translate to similar performance in microgravity. Microgravity induces otolithic deprivation which induces sensory reweighting, especially in the vestibular system (Pathak et al., 2022). While the otoliths are still functional in microgravity and continue to transduce linear acceleration, this could cause an interaction that changes the effects of GVS stimulation in spaceflight. While Lajoie et al. (2021) provide an in-depth review on the potential promise of nGVS for spaceflight human performance and vestibular enhancement, the interaction effects of nGVS with the microgravity-affected vestibular system are still unknown as no spaceflight studies using GVS have occurred to date.

Conclusion

This investigation evaluates the long-term effects of repetitive sensory noise administration on operational learning and behavioral health. We conclude that applying AWN and nGVS repeatedly does not affect the rate of learning of an operational task for a neurotypical population. Additionally, there appears to be no effects of sensory noise exposure on behavioral health, either immediately or on a longitudinal timescale. We also found that AWN and nGVS stimulation is perceived to be acceptable by subjects. Thus, repeated sensory noise exposure to elicit SR in specific use cases or individuals may be utilized with little side effects.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the University of Colorado-Boulder's Institutional Review Board (protocol #21-0296). The patients/participants provided their written informed consent to participate in this study.

Author contributions

SS is the first author responsible for analyzing the data, developing the experimental design, and drafting the manuscript. AJ, QL, and MS are co-authors responsible for developing experimental hardware/software and subject testing. DS is a co-author that helped consult on this project and guidance for the original rover simulation environment. TC and AA are co-authors and co-PIs on this research. They helped guide and provide feedback on experimental design, data analysis, and manuscript writing. All authors contributed to the article and approved the submitted version.

Funding

This study was funded by the Translational Research Institute for Space Health (TRISH) through NASA Cooperative Agreement NNX16AO69A (award number T0402).

Acknowledgments

We acknowledge Daniel Gutierrez-Mendoza for their testing efforts on this project.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2023.1180314/full#supplementary-material

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Frontiers in Neural Circuits

TYPE Original Research
PUBLISHED 13 July 2023
DOI 10.3389/fncir.2023.1197278

OPEN ACCESS

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RECEIVED 30 March 2023
ACCEPTED 28 June 2023
PUBLISHED 13 July 2023

CITATION
Gammeri R, Salatino A, Pyasik M, Cirillo E, Zavattaro C, Serra H, Pia L, Roberts DR, Berti A and Ricci R (2023) Modulation of vestibular input by short-term head-down bed rest affects somatosensory perception: implications for space missions.
Front. Neural Circuits 17:1197278.
doi: 10.3389/fncir.2023.1197278

Modulation of vestibular input by short-term head-down bed rest affects somatosensory perception: implications for space missions

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Introduction: On Earth, self-produced somatosensory stimuli are typically perceived as less intense than externally generated stimuli of the same intensity, a phenomenon referred to as somatosensory attenuation (SA). Although this phenomenon arises from the integration of multisensory signals, the specific contribution of the vestibular system and the sense of gravity to somatosensory cognition underlying distinction between self-generated and externally generated sensations remains largely unknown. Here, we investigated whether temporary modulation of the gravitational input by head-down tilt bed rest (HDBR)–a well-known Earth-based analog of microgravity—might significantly affect somatosensory perception of self- and externally generated stimuli.

Methods: In this study, 40 healthy participants were tested using short-term HDBR. Participants received a total of 40 non-painful self- and others generated electrical stimuli (20 self- and 20 other-generated stimuli) in an upright and HDBR position while blindfolded. After each stimulus, they were asked to rate the perceived intensity of the stimulation on a Likert scale.

Results: Somatosensory stimulations were perceived as significantly less intense during HDBR compared to upright position, regardless of the agent administering the stimulus. In addition, the magnitude of SA in upright position was negatively correlated with the participants' somatosensory threshold. Based on the direction of SA in the upright position, participants were divided in two subgroups. In the subgroup experiencing SA, the intensity rating of stimulations generated by others decreased significantly during HDBR, leading to the disappearance of the phenomenon of SA. In the second subgroup, on the other hand, reversed SA was not affected by HDBR.

Conclusion: Modulation of the gravitational input by HDBR produced underestimation of somatosensory stimuli. Furthermore, in participants experiencing SA, the reduction of vestibular inputs by HDBR led to the disappearance of the SA phenomenon. These findings provide new insights into the role of the gravitational input in somatosensory perception and have important implications for astronauts who are exposed to weightlessness during space missions.

KEYWORDS

vestibular system, sensory attenuation, somatosensory perception, head-down bed rest, tactile perception

Introduction

Somatosensory processes enable us to detect, localize, and perceive the quality and intensity of sensory stimuli on our bodies, and to distinguish self-generated from externally generated stimuli (Schafer and Marcus, 1973; Blakemore et al., 1998). On Earth, it has been shown that self-produced somatosensory stimuli (i.e., stimuli related to the execution of a voluntary action) are generally perceived as less intense than those externally generated (i.e., stimuli unrelated to one's own action) of the same intensity (Blakemore et al., 1998; Burin et al., 2017). This phenomenon, named somatosensory attenuation (SA), has been suggested to underlie the distinction between self and non-self, which has a crucial role in detecting and promptly responding to external stimuli that are potentially relevant for survival (Kilteni and Ehrsson, 2017; Pyasik et al., 2021). SA is thought to be rooted in the construction of an internal model, built on the integration of afferent and efferent multisensory signals. Among afferent signals, a relevant role must be played by the vestibular signal which encodes head/body position with respect to gravity. Nevertheless, the specific contribution of the vestibular system and the sense of gravity to somatosensory cognition underlying distinction of self-generated and externally generated sensations is still unknown. To address this issue, we investigated whether temporary modulation of the gravitational input by head-down tilt bed rest (HDBR)–a well-known Earth-based analog of microgravity–might significantly influence perception of a self-generated stimulus produced by one's own intended movements, compared to an identical externally generated stimulus.

Somatosensory attenuation phenomenon is thought to arise when the sensory consequence of a voluntary action matches the consequence predicted by an internal forward model (Miall and Wolpert, 1996), in which duplicates of the motor commands of voluntary actions are used to predict and suppress the sensory consequences of that specific action (Waszak et al., 2012). In particular, in a self-generated movement, the descending motor command is accompanied by an internal representation of that command, named efference copy, which is then used to predict the sensory feedback of the movement. This sensory prediction is compared with the actual sensory feedback from the sensory receptors or "reafference." If the prediction matches the actual sensory feedback, sensory attenuation of self-generated stimuli is likely to occur (Blakemore et al., 1998; Borhani et al., 2017; Burin et al., 2017). On Earth, the expectation of the constant force of gravity is an inherent component of this internal model (Carriot et al., 2015). By integrating information from multiple modalities into its internal model, the brain can detect and anticipate the effects of gravity on both self-generated actions and compensatory reflexes (McIntyre et al., 1998; Zupan et al., 2002). As a result, the constructed neural representation of the body and its parts, as well as their movements are normally preserved (Carriot et al., 2015).

In space, the vestibular system is abruptly deprived of the sense of gravity (Demir and Aydın, 2021). This hampered peripheral input may in turn affect vestibular cortical projections to areas where the integration of sensory inputs takes place, such as the parieto-insular cortex, the thalamus, and the temporoparietal cortex (Demertzi et al., 2016; Van Ombergen et al., 2017). Indeed, during spaceflight altered integration of the vestibular input with somatosensory, proprioceptive, and visual signals misinforms the brain with respect to its existing (i.e., Earth-based) internal model of the expected sensory consequences of the movements (Freeman, 2000). The conflict between the brain's expectation of the sensory feedback and the actual sensory experience is also thought to underlie motion sickness in the early stages of the spaceflight (Carriot et al., 2021). Thus, a correct internal model is crucial to build an adequate representation of our own movements and is fundamental for veridical somatosensory processing of self-generated and externally generated stimuli (Kilteni and Ehrsson, 2020).

In recent years, the SA phenomenon has been widely studied in different sensory modalities, using behavioral and psychophysical methods (Kearney and Brittain, 2021; Kiepe et al., 2021). Some studies suggested the importance of vestibular information both in the construction of a coherent internal model of a movement (Green et al., 2005) and in the modulation of somatosensory perception (Ferrè et al., 2013a,b, 2015; Moro and Harris, 2018), but the specific contribution of a modulation of vestibular signals to the SA phenomenon has never been investigated. Previous studies investigating the effects of temporary postural changes or short period of HDBR of up to 2 h on brain activity reported decreases in EEG power of the alpha, beta, and gamma bands (Schneider et al., 2008; Chang et al., 2011; Spironelli and Angrilli, 2017) and increased cerebral oxygenation in the prefrontal cortex associated with a slight improvement of executive functioning (Mekari et al., 2022). Long-term HDBR is used by space agencies to study changes associated with long-term spaceflight and consists in placing healthy subjects in −6° head-down tilt bed rest. Long-term HDBR is indeed an accepted Earth-based model of the microgravity and represents both physiologically and perceptually the ground position best resembling weightlessness in space environment (Pavy-Le Traon et al., 2007). In these models (Roberts et al., 2010, 2015), as in microgravity (Karmali and Shelhamer, 2008;

Clément et al., 2020; Salatino et al., 2021), the weight of vestibular inputs is greatly reduced. However, although the effects of sustained HDBR on different domains of spatial cognition have been investigated (Clément et al., 2008, 2013; Roberts et al., 2019), it is still unclear whether long-term or temporary modulations of vestibular inputs by HDBR may affect the emergence of the SA phenomenon.

With the present study we aimed to investigate whether a modulation of the vestibular signals by short-period HDBR might influence (i) the general perception of somatosensory stimulations and, more specifically, (ii) the intensity rating of self-generated stimuli compared to identical but externally generated stimuli. We hypothesized that short-period HDBR could differentially affect somatosensory perception of self- and externally generated stimuli. Specifically, we expected that HDBR conditions, by reducing the weight of vestibular information, might affect somatosensory perception and the ability to distinguish between self-generated and externally generated sensations as measured by the SA phenomenon.

Materials and methods

Participants

Forty healthy volunteers (23 females; age range: 22–27 years old) were recruited for this study. Participants had no history of neurological or psychiatric disease. All participants were classified as right-handed according to the Edinburgh Handedness Inventory (Oldfield, 1971).

All participants gave their written consent after being informed about the experimental procedure of the study, which was approved by the Bioethics Committee of the University of Turin. Participants were volunteers and received no remuneration.

Sensory attenuation (SA)

During the experiment, the lateral digital nerve of the participants' dominant index finger was stimulated using 5-mm-diameter Ag/AgCl classical bipolar surface electrodes attached at the lateral side of the tip and base of the finger. The stimulator (Digitimer DS7A) delivered non-painful electrical stimuli. To determine individual somatosensory threshold, participants were instructed to close their eyes and report verbally when they felt stimulation on their right index finger. The threshold was determined by an ascending-descending-ascending staircase method and set at an intensity at which the participant reported feeling a stimulus on 50% of trials (3 out of 6). The stimulation intensity (2.5 times the subjective threshold + 4 mA with 300 V voltage) was the same for each trial and it was chosen according to the results of a preliminary experiment that tested the effect of different intensities (Burin et al., 2017). Two buttons were connected to the electrical stimulator to trigger the stimulation: one was placed under the participant's index finger and the other one under the experimenter's index finger [see also (Pyasik et al., 2019)].

Participants were instructed to press the button when they heard "You" (*Self condition*) or to stay still while the experimenter pressed the button when they heard "Me" (*Other condition*). A total of 40 stimuli were administered (20 self-generated and 20 generated by the experimenter). Eight catch trials (i.e., a trial without stimulation) were also included in a random order to avoid response biases and to control for phantom sensations (i.e., false detection of the somatosensory stimuli). The order of the 48 trials was randomized across participants. In order to avoid habituation, every 20 stimulations the experimenter slightly shifted the position of the stimulating electrode. At the end of each trial, participants were asked to rate the perceived intensity of the stimulus (i.e., intensity rating) delivered to their right hand on a 0–7 Likert scale, with 0 indicating "absence of stimulation" and 7 indicating "highest intensity." Note that participants were instructed that the intensity of the stimuli would never reach the level of pain and that three "familiarization" stimuli were administered by the experimenter before the main experiment to present the participants with the approximate intensity of the stimuli and to avoid disproportionately high ratings for the first stimuli of the main experiment.

Procedure

Participants were blindfolded to avoid the influence of visual cues on somatosensory perception. The SA paradigm was administered under two different experimental conditions according to the position of participants: (1) *Upright*, where participants were seated on a chair and with both arms and hands on the table (2) *HDBR*, where participants were lying supine on the bed with their heads tilted six degrees downward and their arms at their sides (**Figure 1**). The order of the two conditions was randomized across participants and the somatosensory threshold was calculated twice, i.e., before starting to administer the SA paradigm in each condition. The entire experiment lasted about 1 h; 20 min for each condition with a 10-min break. HDBR was performed in accordance with the international guidelines for the standardization of bed rest studies in the spaceflight context.

Data analysis

SPSS Statistics software (IBM, version 28.0) was used for data analysis. Self-ranking scores were intra-subject normalized using z-score transformations (i.e., for each participant, each rating value was subtracted by the mean rating and then divided by the standard deviation) in order to obtain comparable measures among the participants (Romano et al., 2014; Burin et al., 2017). The Shapiro-Wilk test, performed on the z-transformed values, indicated that all variables were normally distributed ($p > 0.05$). In order to detect modulations of somatosensory thresholds by HBDR, a paired t-test was performed to compare mean values of the two positions. To explore bedrest modulation of sensory attenuation phenomenon, a repeated measures ANOVA with Agent (*Self*, *Other*) and Position (*Upright*, *HDBR*) as within-subject factors was performed on intensity rating. Since SA may not be present in all individuals (Reznik et al., 2015; Burin et al., 2017; Majchrowicz and Wierzchoń, 2021), in order to specifically investigate putative modulation of sensory attenuation by HDBR, we also conducted the same analysis

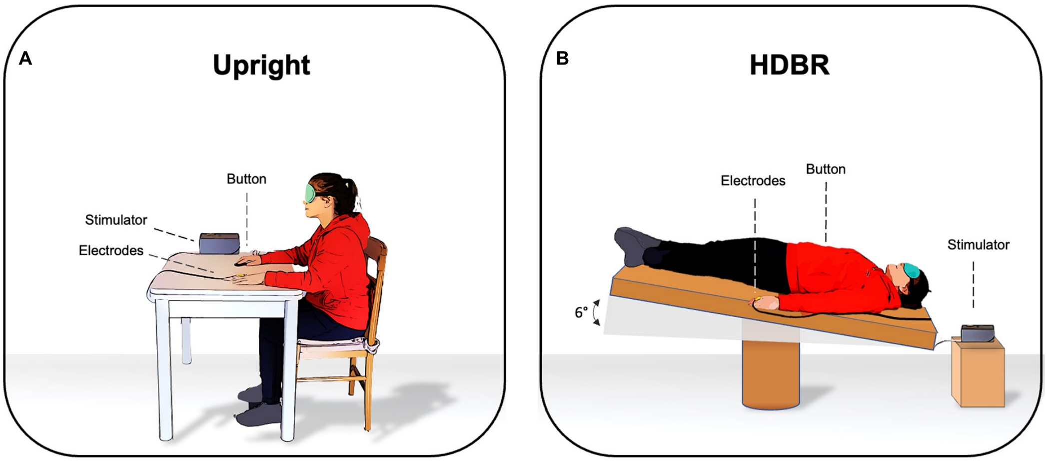

FIGURE 1
Experimental setting in **(A)** upright position and in **(B)** six degrees head-down tilt bed rest (HDBR).

separately in participants who showed sensory attenuation in upright position (i.e., positive difference between other-generated stimuli and self-generated stimuli). *Post hoc* comparisons were performed using the Student–Newman–Keuls test. Correlations between somatosensory thresholds and the amount of sensory attenuation (calculated as the difference between the ratios of Self and Other conditions for each position) were also calculated using Pearson's correlation. Statistical significance of $p < 0.05$ was assumed.

Results

Somatosensory perception

Based on the individual somatosensory threshold, the average stimulation intensity was 8.9 ± 1.24 mA. No statistical difference was found between somatosensory thresholds in the two different positions [t(39) = −0.168; p = 0.868]. The repeated-measures ANOVA showed a main effect of Agent [$F_{(1,39)} = 6.629$; $p = 0.014$; $\eta_p^2 = 0.709$] and Position [$F_{(1,39)} = 4.812$; $p = 0.034$; $\eta_p^2 = 0.571$] while the interaction Agent by Position was not significant [$F_{(1,39)} = 1.760$; $p = 0.192$; $\eta_p^2 = 0.253$]. Surprisingly, the significant effect of the factor Agent showed that self-generated stimulations were perceived as more intense than those generated by others (*Self*: Median = 4.5, MAD = 1; *Other*: Median = 4.25, MAD = 1) regardless of the participant's position (Figure 2A). In addition, the factor position showed that somatosensory stimulation was perceived as more intense during upright than in HDBR condition (*Upright*: Median = 4.75, MAD = 0.75; *HDBR*: Median = 4, MAD = 0.75) regardless of Agent (Figure 2B).

Sensory attenuation

SA + subgroup

In order to investigate putative modulation of sensory suppression phenomenon by HDBR, we selected individuals showing, in the upright position, the sensory attenuation phenomenon (i.e., sensory attenuation for self-generated stimuli). A total of 14 participants (35% of the sample) were identified and their performance as a group was analyzed as before for the entire sample. Also in this group, the *t*-test comparing somatosensory thresholds in the two positions was not significant [t(13) = −0.436; p = 0.670]. On the other hand, the repeated measures ANOVA analyzing the effects of Position on sensory attenuation showed a main effect of Agent [$F_{(1,13)} = 5.619$; $p = 0.034$; $\eta_p^2 = 0.592$] and a significant interaction Agent by Position [$F_{(1,13)} = 9.230$; $p = 0.010$; $\eta_p^2 = 0.802$]. Newman–Keuls *post hoc* analyses showed that while the factor Agent was statistically significant in the Upright condition ($p = 0.003$), it was not significant in the HDBR condition ($p = 0.907$). Specifically, SA attenuation was present in the Upright condition (*Self*: Median = 4, MAD = 1; *Other*: Median = 5, MAD = 1) but not during HDBR (*Self*: Median = 4, MAD = 0.5; *Other*: Median = 4, MAD = 0.75). Moreover, other stimulations in the Upright condition were rated as significantly more intense than those produced by Self ($p = 0.003$) and Other ($p = 0.001$) in HDBR (Figure 2C).

rSA subgroup

A total of 26 participants showed reversed sensory attenuation (rSA) at Upright, as self-generated stimulations were rated as more intense than those generated by others. As for previous analyses, no statistical differences of somatosensory threshold were observed between the two positions [t(25) = 0.128; p = 0.899]. A repeated measures ANOVA showed an effect of Agent [$F_{(1,25)} = 59.058$; $p < 0.001$; $\eta p2 = 0.703$], but not Position [$F_{(1,25)} = 3.165$; $p = 0.087$] nor the interaction of Agent by Position [$F_{(1,25)} = 0.395$; $p = 0.536$]. More specifically, Self-stimulations were rated as more intense than those produced by Others (*Self*: Median = 5, MAD = 1; *Other*: Median = 4, MAD = 1.25), regardless of the position (Figure 2D).

Correlation analysis

We computed a series of Pearson correlations in the whole group (N = 40) between somatosensory threshold and

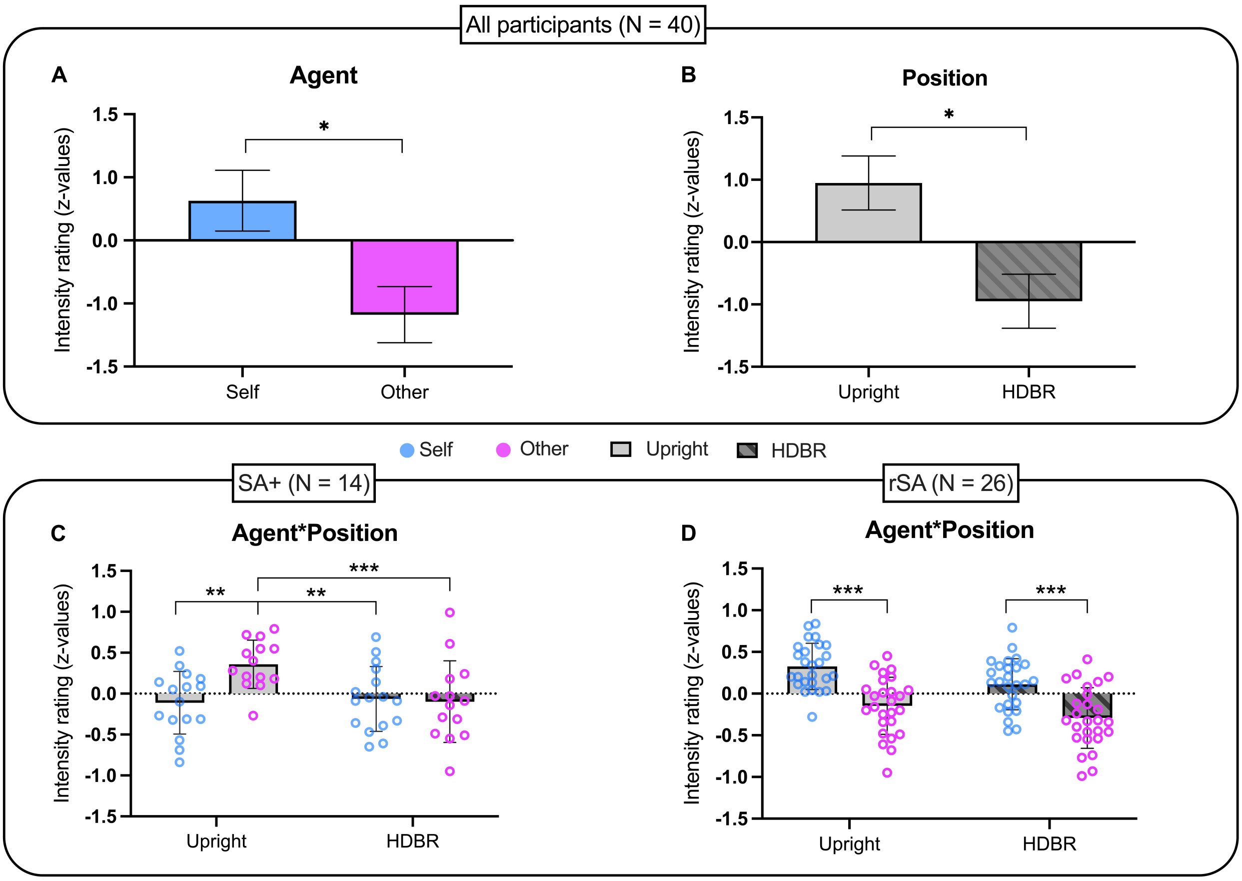

FIGURE 2
Intensity rating of somatosensory stimulations in: **(A,B)** the whole group (n = 40); **(C)** the sub-group of participants showing sensory attenuation in upright position (n = 14); **(D)** the sub-group of participants showing reversed sensory attenuation in upright position (n = 26). Data have been transformed into z-scores and presented as mean and standard error of the mean (SEM). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p \leq 0.001$.

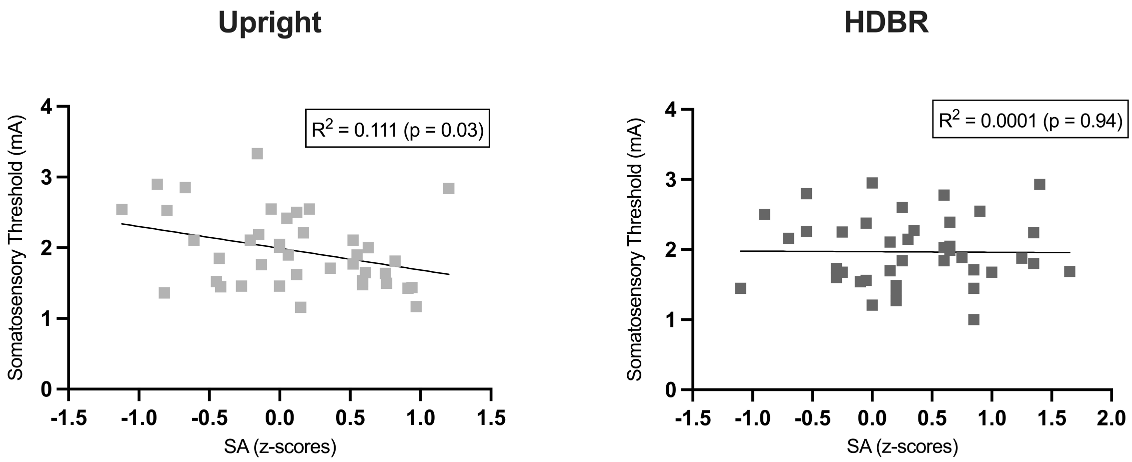

FIGURE 3
Pearson's correlation between individual somatosensory thresholds and sensory attenuation (SA) index (i.e., difference between the z-transformed subjective ratings for self-stimulation and other-stimulation).

the sensory attenuation index (i.e., subjective rating for Self-stimulation minus Other-stimulation) for each position (*Upright*, *HDBR*). A significant negative correlation was observed in the Upright condition between the somatosensory threshold and the amount of sensory attenuation ($r = -0.34$, $p = 0.029$). In other words, individuals with lower somatosensory thresholds also had a greater sensory attenuation phenomenon (Figure 3). Interestingly, this correlation was not significant in the HDBR position ($r = -0.10$, $p = 0.94$). No other comparison resulted to be significant.

Discussion

We investigated the impact of short-period Head-Down Bedrest (HDBR) on the somatosensory perception of self-generated and other-generated stimuli, as measured by the sensory attenuation (SA) phenomenon, whereby self-generated stimuli are perceived as less intense than stimuli generated by others. In all participants, an influence of HDBR on the perception of the intensity of somatosensory stimuli was observed independently of the agent producing the stimulation and in absence of changes of somatosensory threshold. Moreover, a significant modulation of SA by HDBR was found in a subgroup of participants.

Somatosensory perception

Overall, somatosensory stimuli during HDBR were perceived as less intense than in the upright position, regardless of the agent administering the stimulus. In other words, participants underestimated the intensity of somatosensory stimuli when lying in the head-down position. This change occurred in absence of somatosensory threshold changes, indicating modulation of higher-level somatosensory processes by the HDBR.

To our knowledge no data exist on the putative influence of Earth-based models of microgravity on estimation of the intensity of somatosensory stimuli. However, our results are in line with various experimental studies showing tactile perception modulation induced by vestibular stimulation. For example, left-cold caloric vestibular stimulation (CVS), which activates cortical vestibular regions (Bottini et al., 2005), has been shown to increase tactile sensitivity of both hands in healthy individuals (Ferrè et al., 2011a,b) and improve somatosensory disorders in right (Vallar et al., 1990, 1993) and left brain-damaged patients (Bottini et al., 2005). An improvement of somatosensation has also been induced by subliminal galvanic vestibular stimulation (GVS). In fact, left GVS has been shown to bilaterally increase both tactile sensitivity (Ferrè et al., 2013b) and localization of tactile stimuli (Ferrè et al., 2013c), and both right and left subliminal GVS improved tactile extinction, with lasting effects even after a small number of sessions (Kerkhoff et al., 2011; Schmidt et al., 2013).

On the other hand, our results also seem to be in line with previous studies that have shown that experimental modulations of vestibular input can influence somatosensory processing of noxious stimuli. For example, an overall decrease in pain sensitivity and altered EEG activity of the pain network were observed after 2 h of HDBR (Spironelli and Angrilli, 2011). Notably, the stimulation intensity of our study (i.e., 8.9 ± 1.24 mA) was higher than in previous studies using the same stimulator to investigate non-painful stimuli [3.65 ± 1.09 mA, (Fossataro et al., 2018)] and pain thresholds [4.59 ± 2.44 mA; (Boggio et al., 2008)], but lower than the intensity of stimuli perceived as painful [34.82 ± 10.63 mA, (Fossataro et al., 2018)], suggesting that participants may have perceived the electrical stimulation as moderately painful. In line with these findings, CVS has been found to increase tactile sensitivity but decrease both the perception of pain intensity (Ferrè et al., 2013a) and EEG early cortical responses in somatosensory areas (Ferrè et al., 2015). Consistently, also in clinical populations, CVS has been found to reduce pain perception in patients with central post-stroke pain (Ramachandran et al., 2007; McGeoch et al., 2008, 2009; Spitoni et al., 2016), persistent pain and allodynia (Ngo et al., 2015) and headaches (Wilkinson et al., 2017). However, we did not control for subjective pain experience in our sample, preventing us from drawing firm conclusions on the subjective quality of somatosensory sensations.

The above findings may reflect the complex and multidimensional nature of the somatosensory system, supporting the hypothesis that vestibular signals may have dissociable effects on the various different channels within this system (Ferrè et al., 2015). Pain perception is a complex process that involves the integration of sensory, emotional, and cognitive factors. The perception of painful stimuli is indeed very heterogeneous and may be affected by top-down cognitive processes (Torta et al., 2020), trait personality (Grouper et al., 2021), the intensity of stimulation and anxiety-dependent pain expectancy (Fossataro et al., 2018). Also tactile perception, besides relying on elementary somatosensory processing, involves higher level cognition (Vaishnavi et al., 2000; Ricci et al., 2019, 2021). Thus, it is possible that in our study the vestibular modulation mainly affected high level somatosensory processing (i.e., magnitude estimation of the sensation elicited by electrical stimulation), rather than elementary levels of stimulus processing, as suggested by the unvaried somatosensory threshold during HDBR.

Consistent with the observed behavioral modulation, several neuroimaging investigations over the years have corroborated the evidence of anatomical overlap between vestibular cortical projections and areas involved not only in primary somatosensory processing but also in higher level cognition [for a review see: (Lopez et al., 2012)]. Specifically, fMRI and PET studies in vestibular patients and healthy participants undergoing vestibular stimulation have revealed a distributed vestibular network involving, in addition to the somatosensory cortices, multisensory areas such as the posterior and anterior insula, temporoparietal junction, superior temporal gyrus and the inferior parietal lobule (Lopez and Blanke, 2011; zu Eulenburg et al., 2012). Interestingly, with regard to microgravity analog-models, recent fMRI studies show that HDBR leads to changes in the functional connectivity of vestibular, sensorimotor and somatosensory regions (Cassady et al., 2016). Increased functional connectivity was found between motor and somatosensory areas after long-term HDBR, while decreased functional connectivity was observed in other areas of the vestibular network, such as temporoparietal regions, after both short-term and long-term HDBR (Liao et al., 2015; Cassady et al., 2016). It is important to note that, although these brain areas have been shown to respond differently to intensity-matched tactile and painful stimuli (Su et al., 2019), they responded to both modalities, suggesting that a modulation of their activity may have occurred also in our study. We can hypothesize that, in our study, the temporary reduction of vestibular input by HDBR may have primarily affected the activity of areas involved in higher level processes, such as, for example, magnitude estimation which mainly engages the right posterior parietal cortex (Walsh, 2003; Mennemeier et al., 2005), rather than areas involved in primary somatosensory processing.

In conclusion, our results provide evidence that short-term HDBR induces a general subjective underestimation of the intensity of somatosensory stimuli. Although there are several lines of evidence supporting the hypothesis that this effect can be attributed to decreased vestibular afferents and altered activity within regions contributing to somatosensory cognition, the present study does not directly assess the neural correlates of behavioral changes. Future studies are needed to investigate the neural mechanisms underlying the observed effects.

Sensory attenuation (SA)

Unexpectedly, in our sample, only 35% of the participants showed, at individual level, *sensory attenuation* for self-produced stimuli in the upright position (SA +), while the other participants showed *reversed SA* (rSA), i.e., self-generated stimuli were rated as more intense than those generated by others (Reznik et al., 2015; Majchrowicz and Wierzchoń, 2021). Interestingly, SA + was modulated by HDBR while rSA was not, suggesting that different processes may be activated.

According to Reznik and collaborators (Reznik et al., 2015), the magnitude and the direction of SA phenomena may depend on the intensity of stimulation, as SA + would occur when active self-generated actions result in supra-threshold stimuli. Here, we only used supra-threshold stimuli but rSA was found in the majority of the participants, therefore other factors need to be considered. For example, other studies suggest that the amplitude of SA is modulated also by the action-effect contingency [i.e., the temporal proximity between actions and their sensory consequences, (Baess et al., 2011; Dogge et al., 2019; Han et al., 2022)] or the strength of the agent's prior beliefs (Desantis et al., 2012). In our study the contingency and the predictability of the outcomes were kept constant across conditions, while the participants' beliefs were not controlled.

Interestingly, our data suggest that the individual somatosensory threshold may play a relevant role in the sensory attenuation of self-generated stimuli. Indeed, in the upright position, a negative correlation was found between somatosensory thresholds and SA scores, indexing that lower somatosensory thresholds facilitate the emergence of the SA phenomenon. Furthermore, empirical evidence suggests that both somatosensory perception and the extent of SA are significantly modulated by the subjective feeling of body ownership (Pia et al., 2013; Kilteni and Ehrsson, 2017; Burin et al., 2018; Pyasik et al., 2019, 2021; Ataka et al., 2022). Specifically, a decrease in somatosensory sensitivity has been linked to increased hand-disownership (Ataka et al., 2022) and a greater sense of ownership over one's body leads to greater sensory attenuation phenomenon (Kilteni and Ehrsson, 2017). Consequently, we speculate that the observed individual heterogeneity of SA scores may be attributed to individual differences in somatosensory threshold, which could indicate higher body ownership (BO) in SA + group compared to rSA.

Consistently, a different modulation of the subjective intensity for self- and external-generated stimulations was observed in the two groups. Indeed, in the SA + group the intensity rating of stimuli generated by others strongly decreased in the HDBR position, leading to the disappearance of the SA phenomenon. On the contrary, the reversed SA (rSA) observed in the majority of participants was not modulated by HDBR. As previously discussed, SA + group demonstrated higher SA magnitude and lower somatosensory threshold, while the rSA group showed reversed sensory attenuation and higher somatosensory threshold. Interestingly, previous evidence also suggests that an alteration of vestibular inputs can result in a decreased sense of BO and in a reduced reliability in external references during tactile localization (Pavlidou et al., 2018; Ponzo et al., 2018; Unwalla et al., 2021; Gammeri et al., 2022).

Thus, if SA + group is more sensitive to bodily information as suggested by the lower somatosensory threshold, the observed disappearance of SA during HDBR may be attributed to the reduction of vestibular input generated by the head-down tilt position. In contrast, if the rSA group rely less on bodily information as suggested by the higher somatosensory threshold, the reversed sensory attenuation may be not affected by the vestibular signals' reduction. These interpretations support the hypothesis that vestibular signals play a key role in self-other distinction (Deroualle and Lopez, 2014; Lenggenhager and Lopez, 2015; Lopez et al., 2015), suggesting that in simulated microgravity the boundaries between self- and externally generated stimuli can be lost. Further investigations should explore the relationship between somatosensory perception and body ownership, as well as its interaction with the vestibular system, in order to elucidate the mechanisms underlying the disappearance of sensory attenuation in the HDBR-other stimulations condition.

Implications for space research

Taken together, these findings suggest that modulation of vestibular input by short-period HDBR has an impact on how we process somatosensory information, particularly when sensory attenuation occurs. In space, the neurosensory response to microgravity leads to complex disorientation and motion sickness [i.e., Space Adaptation Syndrome and Space Motion Sickness; (Clément and Reschke, 2008; Wood et al., 2011; Clément et al., 2013)] in the early stages of spaceflight. Within a few days, most sensorimotor impairments resolve, but may reappear upon return to Earth, both after long and shorter space missions (Reschke, 1990; Paloski et al., 1993; Wood et al., 2015; Reschke et al., 2018). Importantly, subtle disturbances in somatosensory cognition may still be present in the later stages of the spaceflight, which, if unrecognized, could significantly impair the crew performance. In particular, during space missions, altered somatosensory perception of externally generated stimuli due to reduced vestibular inputs could result in reduced perception of one's body boundaries, affecting dexterity, motor performance, and ultimately increasing the risk of accidents and errors during critical operations. Given the technical limitation of medical interventions in space environments, undetected somatosensory signaling impairment in astronauts could delay the detection of illnesses and interfere with ambitious long-term space missions. Although the evidence on how microgravity or simulated microgravity might affect somatosensory functions is still scant and controversial, our data may provide new insight into the putative effects of microgravity on somatosensory cognition of self- and other-generated stimuli.

Limitations and future directions

Despite the interesting findings reported in this study, there are several limitations that must be acknowledged. Firstly, most of the published studies on the effects of vestibular input modulation on somatosensory processing have been conducted using different techniques other than microgravity or simulated microgravity, which might affect the vestibular system in different ways. In addition, most HDBR studies have used long-term protocols, lasting more than 7 days, in sharp contrast to our study, which employed a short-term protocol lasting approximately 30 min. Although there is evidence suggesting that electrocortical activity is relatively unaffected by protocol duration (Brauns et al., 2021), it is worth noting that no prior research has specifically examined the influence of HDBR duration on somatosensory perception using behavioral tasks. Therefore, to validate the current findings and support their generalization to spaceflight conditions, future long-term HDBR studies need to be conducted. Secondly, we did not control for the individual degree of body ownership and explicit pain perception, which may have influenced the observed outcomes. In fact, although there is evidence on the relationship between somatosensory threshold, the extent of body ownership, somatosensory sensation, and the magnitude of sensory attenuation, this interaction was not controlled for in the current study. Furthermore, it is crucial to consider that in our study all participants were blindfolded and we cannot dismiss the possibility of an additional effect resulting from visual deprivation. On one hand, previous research indicates that the absence of vision may have an impact on somatosensory perception, generating increased activation of vestibular and somatosensory areas (Marx et al., 2003, 2004). On the other hand, the enrichment of multisensory processing by adding visual information, may facilitate the distinction between self-generated stimuli and stimuli generated by others. Consequently, the precise extent to which these variables influenced the observed outcomes remains to be determined. Finally, the lack of neuroimaging data to support our interpretations is another limitation of this study. Although we interpreted the observed modulation of somatosensory perception in response to HDBR based on prior neurophysiological evidence, it is crucial to emphasize that the existing evidence comes from studies employing techniques and protocols different from those used in this specific investigation. Future research should aim to address these limitations and provide more comprehensive insights into the neurofunctional mechanisms underlying the modulation of somatosensory processing in microgravity environments.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by the Bioethics Committee of the University of Turin. The patients/participants provided their written informed consent to participate in this study.

Author contributions

RG: investigation, data curation, formal analysis, writing, reviewing, and visualization. AS and MP: definition, conceptualization, methodology, resources, software, and validation. EC, CZ, and HS: writing, reviewing, and visualization. LP, DR, and AB: writing and reviewing. RR: definition, conceptualization, writing and reviewing, supervision, and project administration. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by the Ministero dell'Istruzione, dell'Università e della Ricerca (grant number RICR_RILO_17_01, RICR_RILO_18_02) and by CRT Foundation (grant number 2020.0748).

Acknowledgments

We would like to thank all participants who participated in this study. Our special thanks to Prof. Rosalba Rosato for her assistance with data analysis and Elisabetta Zanin, Giulia Mete, and Alessia Calcagni for their support with data collection.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Neural Circuits

TYPE Hypothesis and Theory
PUBLISHED 20 July 2023
DOI 10.3389/fncir.2023.1190582

Modeling orientation perception adaptation to altered gravity environments with memory of past sensorimotor states

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Transitioning between gravitational environments results in a central reinterpretation of sensory information, producing an adapted sensorimotor state suitable for motor actions and perceptions in the new environment. Critically, this central adaptation is not instantaneous, and complete adaptation may require weeks of prolonged exposure to novel environments. To mitigate risks associated with the lagging time course of adaptation (e.g., spatial orientation misperceptions, alterations in locomotor and postural control, and motion sickness), it is critical that we better understand sensorimotor states during adaptation. Recently, efforts have emerged to model human perception of orientation and self-motion during sensorimotor adaptation to new gravity stimuli. While these nascent computational frameworks are well suited for modeling exposure to novel gravitational stimuli, they have yet to distinguish how the central nervous system (CNS) reinterprets sensory information from familiar environmental stimuli (i.e., readaptation). Here, we present a theoretical framework and resulting computational model of vestibular adaptation to gravity transitions which captures the role of implicit memory. This advancement enables faster readaptation to familiar gravitational stimuli, which has been observed in repeat flyers, by considering vestibular signals dependent on the new gravity environment, through Bayesian inference. The evolution and weighting of hypotheses considered by the CNS is modeled via a Rao-Blackwellized particle filter algorithm. Sensorimotor adaptation learning is facilitated by retaining a memory of past harmonious states, represented by a conditional state transition probability density function, which allows the model to consider previously experienced gravity levels (while also dynamically learning new states) when formulating new alternative hypotheses of gravity. In order to demonstrate our theoretical framework and motivate future experiments, we perform a variety of simulations. These simulations demonstrate the effectiveness of this model and its potential to advance our understanding of transitory states during which central reinterpretation occurs, ultimately mitigating the risks associated with the lagging time course of adaptation to gravitational environments.

KEYWORDS

vestibular, otolith, multisensory integration (MSI), internal model (IM), Bayesian, astronaut

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RECEIVED 21 March 2023
ACCEPTED 29 June 2023
PUBLISHED 20 July 2023

CITATION
Allred AR, Kravets VG, Ahmed N and Clark TK (2023) Modeling orientation perception adaptation to altered gravity environments with memory of past sensorimotor states. *Front. Neural Circuits* 17:1190582. doi: 10.3389/fncir.2023.1190582

1. Introduction

In humans, exposure to a new gravity environment results in a central reinterpretation of information from multiple sensory sources, producing an adapted sensorimotor state appropriate for motor actions and spatial orientation perceptions in the new environment (Clark, 2019). However, the temporal evolution of this central adaptation is not instantaneous, and it can take weeks of prolonged exposure to novel environments for adaptation to complete (Roll et al., 1993; Mulavara et al., 2010; Wood et al., 2015).

In the case of astronauts newly exposed to microgravity, the lagging time course of adaptation results in perceptual and functional deficits, including spatial orientation misperceptions and alterations in locomotor and postural control (Clément and Reschke, 2008). This sensorimotor impairment can impact crewmembers' ability to perform mission-critical operational tasks such as piloting vehicles and operating other complex systems (Paloski et al., 2008). Further, it is thought that space motion sickness (SMS) is largely driven by an adapting central nervous system (CNS) incorrectly expecting self-orientation sensory information for vestibular signals of self-motion (Oman, 1982; Lackner and DiZio, 2006). Concerning SMS, symptoms often exceed mere discomfort (Oman, 1987; Davis et al., 1988; Heer and Paloski, 2006), and the risk of nausea and emesis dictates operational schedules and extravehicular activity timelines (Jennings, 1998). Further, sensorimotor adaptation to changing gravitational stimuli also occurs when exiting the microgravity environment [e.g., transitioning to the Earth, Lunar (Clark, 2022), and Martian surfaces], leaving crewmembers once again maladapted and presenting an expected hinderance to future space exploration missions.

To mitigate these risks, it is critical that we better understand transitory central states during which central reinterpretation occurs. With only a conceptual understanding of this adaptation process, we cannot make the operational decisions (e.g., timing of extravehicular activities) necessary to ensure the safety and performance of the crew. To this end, a computational model of human perceptions of self-motion emulating sensorimotor adaptation to new gravity stimuli is needed. Such a model of the CNS enables evaluating perceptual changes, assessing operational risks, and ultimately implementing appropriate countermeasures. Recently we developed a computational model of the neural mechanisms that may be necessary to adapt to altered gravity environment. As detailed below, this approach used fixed parallel alternative hypotheses for the magnitude of gravity, the resulting sensory conflict for each, and Bayesian updates to drive adaptation but did not include a means to develop, update, or retain alternative hypotheses for the magnitude of gravity (Kravets et al., 2021). As an initial step to address this limitation, we have since enhanced the modeling framework to include the ability to dynamically learn new hypotheses of gravity (Kravets et al., 2022). However, this initial implementation was naïve to any prior internal estimate history. The work presented here extends the computational means by which the CNS may dynamically learn and consider alternative hypotheses of gravity by modeling learned states consolidated into implicit memory from prior adaptations.

1.1. Background

Our perception of orientation in three-dimensional space is the result of the complex interaction between our body's real-world dynamics and our central estimation of these dynamics. Our inertial orientation and self-motion are primarily sensed by noisy sensors in the inner ear (i.e., semi-circular canals and otolith organs), which generate sensory afference. To make sense of these noisy, sometimes ambiguous measurements, our brain relies on internal models of sensory dynamics that generate expected afference (Merfeld et al., 1993, 1999; Merfeld and Zupan, 2002; Tin and Poon, 2005). When there are disparities between actual and expected afference, vestibular "sensory conflict" arises, which is thought to drive dynamic updates of the states in the internal model (Oman, 1982; Oman and Cullen, 2014). Studies by Roy and Cullen (2004), Brooks and Cullen (2009), and Jamali et al. (2009) have identified neurons which differentially respond to passive vs. active (i.e., where the brain can generate appropriate expected afference) self-motion (specifically the behavior of "Vestibular Only" neurons) in the vestibular nuclei and cerebellum. These responses are analogous to the hypothesized sensory conflict signal within the observer framework. Apart from the vestibular sense, sensory conflict is also thought to reside in other sensory systems [e.g., "residual error" signals found in the visual cortex within the "predictive coding" framework (Srinivasan et al., 1982; Rao and Ballard, 1999; Huang and Rao, 2011)].

To formalize and quantitatively describe these theories, computational models such as the "observer" model of spatial orientation perception have been developed (Merfeld et al., 1993; Merfeld and Zupan, 2002; Karmali and Merfeld, 2012; Clark et al., 2019). Observer uses sensory conflict signals to drive central estimates of orientation perception by comparing noisy sensory measurements to expected afference signals, based on internal model computations (Brooks et al., 2015; Carriot et al., 2015). Observer has been experimentally shown to predict self-orientation and motion perceptions in a variety of Earth 1 g (Merfeld et al., 1993; Haslwanter et al., 2000; Zupan et al., 2000; Newman, 2009), hyper-gravity (Clark et al., 2015b,c), and hypo-gravity (Clark and Young, 2017; Galvan-Garza et al., 2018) motion paradigms. However, the observer model does not treat the magnitude of gravity as a dynamic parameter but instead as a fixed one. In general, these model parameters represent neural circuitry of spatial orientation perception in a static 1 g environment where adaptation is not necessary.

However, if the environment changes (e.g., hyper-gravity), within the framework of the model, one might expect the model's parameters to evolve. Following a gravity transition a gravity transition, sensory information is altered, rendering existing internal models inappropriate: primarily, the models used to disambiguate forces due to linear acceleration and gravity within the gravito-inertial force (GIF) vector which is sensed by the otolith organs (since the vestibular system, by Einstein's equivalence principle, cannot directly sense gravity). The sensory conflict resulting from inappropriate internal models (for the new environment) is thought to drive a dynamic reinterpretation of vestibular signals, or "adaptation" of the internal models, appropriate for the new gravity environment. Because we still have a limited understanding of the neural computations involved in this process, modeling this neurovestibular adaptation to altered gravity continues to be an active area of scientific interest.

1.1.1. Existing models

Since the late 1990s, computational models of humans adapting to changing gravity stimuli have emerged. A series of works found human disambiguation of the sensed GIF to likely be achieved through internal models that help track the gravity vector's direction (for a static magnitude of gravity) using cues from the semicircular canals (Merfeld et al., 1999, 2001; Zupan et al., 2000; Merfeld and Zupan, 2002); this theory is referred to as the GIF resolution hypothesis. The implementation of this theory, however, does not enable the CNS to update the magnitude of gravity (or other learned parameter model constants e.g., model gains and time constants). Another prominent hypothesis utilized to model this disambiguation is the frequency segregation hypothesis; Bos and Bles (1998) proposed the subjective vertical conflict (SVC) model which utilizes a low-pass filter to estimate both the magnitude and direction of gravity by the CNS in conjunction with Mayne's (1974) principle to track the head's position in an exocentric coordinate system. While the SVC model provides the additional flexibility of a dynamically estimated magnitude of gravity [compared to models built on the GIF resolution hypothesis (Groen et al., 2022), such as the observer model, which nominally assume a constant internal magnitude of gravity], the internally estimated magnitude of gravity adapts in approximately tens of seconds [which is likely unrepresentative of the central reinterpretations involved during altered gravity adaptation, which spans hours to days (Clark, 2019)]. Furthermore, the SVC model offers no framework updating learned parameters or modeling memory of previously experienced environments. While a fundamentally different modeling effort, we note that Wada (2021) aims to capture how the brain might learn exogenous motion dynamics, modifying the expected sensory feedback.

To circumvent these issues, it has been hypothesized that the CNS relies on Bayesian inference to update internal model parameters (Körding and Wolpert, 2004; Darlington et al., 2018), a theory that broadly explains how the CNS uses evidence to reorganize synaptic connections (e.g., reinterpret sensory signals after acute damage to vestibular sensors or downstream afferent nerves, update forward models (i.e., motor memory) after efferent central nervous damage, etc.). Applying this hypothesis to how the CNS may update the magnitude of gravity, an internal model parameter that is rarely stimulated on Earth, multiple iterations of Bayesian models have emerged: first a Bayesian-based computational framework for explaining how the CNS can utilize sensory conflict from the observer model to achieve this update (Kravets et al., 2021), and later a particle filter implementation of this framework to explain how the CNS can achieve this update while considering a finite, dynamic set of alternative hypotheses (Kravets et al., 2022).

While these models of vestibular adaptation to changing gravitational stimuli are well suited for exposure to novel stimuli not-yet experienced by the individual, they have yet to distinguish how the CNS reinterprets sensory information from familiar environmental stimuli (i.e., readaptation). As detailed in the next section, spanning both aerospace and terrestrial applications, there exists evidence that readaptation back to a "learned state," acquired through long-term memory (LTM), enables more rapid readaptation in humans.

1.1.2. Evidence of learned states for readaptation and neuroplasticity

Historically for shuttle astronauts transitioning from microgravity to Earth gravity, postural performance, signaling readaptation to Earth gravity, has been found to be better in repeat flyers than first-time flyers (Reschke et al., 1998; Paloski et al., 1999) suggesting that exposure to familiar gravitational stimuli results in faster adaptation rates. Because Paloski et al. (1999) found significantly better performance in repeated flyers compared to first-time flyers post-flight (with no differences in pre-flight performance) on the sensory organization balance tests 5 and 6 (with no differences on tests 1–4), they suggest that repeat flyers may be "dual adapted and able to more readily transition from one set of internal models to the other." Additionally, deconditioning of the neural circuitry comprising the vestibulo-ocular reflex pathway (measured via ocular counter-roll) shortly after transitioning from microgravity to Earth gravity (1–3 days) has been found to be negatively associated with the number of prior flights in crewmembers (Schoenmaekers et al., 2022). This finding may also be indicative of more flight experience resulting in faster readaptation, and Schoenmaekers et al. hypothesize that experienced flyers acquire a central adaptation from previous space flight missions. Supporting this idea, Gonshor and Jones (1976) found more rapid readaptation of this reflex following a prolonged (2–4 weeks) adaptation to a novel vision reversal stimulus.

Together, these findings support the conceptual idea that the CNS relies on learned states (i.e., a memory of internal circuitry / parameters) to achieve faster readaptation to a familiar gravitational stimulus. However, this evidence could be alternatively interpreted as the CNS becoming more adept at searching for new states (i.e., exhibiting faster adaptation to all stimuli, novel or familiar- that is, learning-to-learn) with repeated adaptations. Further supporting the notion of learned states, long-term postural control adaptation (with consolidated motor strategies) in the presence of artificial perturbations has been found to be isolated to the specific test conditions facilitating adaptation (Tjernström et al., 2002). Regarding adaptation to multiple novel altered-gravity environments, there is evidence that recent exposure to one novel gravity (1.5 or 2 g) results in more rapid adaptive adjustments to baseline performance in a second novel gravity (2 or 1.5 g, respectively) (Clark et al., 2015a). However, Clark et al. (2015a) hypothesizes that this effect is likely cognitive/strategic vs. a restructuring of neural circuitry due to the relatively short time course of adaptation.

Despite this evidence of sensorimotor learning and memory, we do not currently know the neural mechanisms by which parameters involved with learned environments are stored. In the more specific case of motor learning, short-term motor memory is thought to arise in cerebellar Purkinje neurons, and through the consolidation process, short-term adapted strategies are eventually stored as long-term motor programs that can be recalled via neural circuits in the vestibular nuclei [in the case of the horizontal optokinetic response (Shutoh et al., 2006)] and basal ganglia [in the case of stimulus-response associations and motor habits (Packard and Knowlton, 2002)]. However, long-term storage of parameters in the self-orientation perception model, such as a magnitude of gravity, may occur elsewhere, likely distributed across brain regions (i.e., the multiple memory systems theory). For instance, cortical changes associated with central adaptation in F-16 pilots (Radstake et al., 2023), who are repeatedly exposed to altered gravity environments, may provide additional insight.

1.2. Objectives

Based on these findings, we aim to enhance existing models by providing multiple theoretical additions to existing works. These additions provide phenomenological mechanisms the CNS can utilize to achieve faster sensorimotor readaptation through the consideration of learned states. We aim to model these mechanisms by building on the recent work of Kravets et al. (2022), an implementation of the COMPASS framework (Kravets et al., 2021) where the CNS does not consider a static set of potential gravity magnitude hypotheses. Instead, the evolution of hypotheses considered by the CNS is modeled via an indirect sampling approach, employing a Rao-Blackwellized particle filter algorithm.

2. Proposed theory

Bolstering the findings of others in our field, we propose that the CNS is capable of consolidating internal model information describing the current gravitational environment into long-term memory, provided the state is harmonious (i.e., produces low levels of vestibular sensory conflict). Following this storage, the CNS then leverages information about these past states to more readily readapt in the presence of previously experienced stimuli. Using only vestibular sensory conflict, without additional sensory modality (e.g., vision, somatosensory) or ground truth information, we build our theory on the fundamental idea that the CNS considers alternative hypotheses and weighs their likelihoods to formulate an estimate (i.e., uses Bayesian inference) for updating internal models. We give form to this proposed theory through the model framework presented in this section.

In summary, this framework provides a new form of the hypothesis sample distribution (set to be the state transition probability) that is influenced by prior learned internal state parameters. This addition enables faster readaptation to familiar environmental stimuli. Secondarily, we include a formulation for the temporal evolution of learned internal state parameters, enabling the emergence, prioritization, and cessation of learned states within the CNS.

2.1. Model framework overview

Dynamic state estimation during gravity adaptation can be modeled using a particle filter, which uses Monte Carlo methods to estimate a state space over time. In contrast to a broad, static (pre-defined) set of alternative hypotheses, a particle filter relies on a smaller, dynamic set that spans different regions of the state space over time. Such an approach provides the CNS a more computationally efficient means to generate an estimate (no longer having to consider unlikely hypotheses) and additionally enables considering new hypotheses outside the domain of what has previously been considered. However, any sensory learning process will involve a complex, multidimensional state space, and estimates driven entirely by Monte-Carlo simulations are likely still too computationally expensive and inefficient to be utilized for the entire state space during such scenarios. Critically, "vanilla" particle filter algorithms (i.e., where sampling of all states is just performed in a Monte-Carlo fashion) fail to leverage the well-validated observer model, in which perceived states (e.g., angular velocity, gravity, linear acceleration) are produced via sensory conflict and internal models. Alternatively, a Rao-Blackwellized Particle filter (RBPF) makes use of these known relationships, analytically estimating "easy" state variables and conditioning those computations on Monte Carlo estimates of "hard" variables (Ristic et al., 2003; Doucet et al., 2013). We propose that the CNS relies on a similar partitioning approach of the state space.

Using the RBPF framework, we represent the CNS adaptation to altered gravity through indirect sampling of potential alternative hypotheses for the magnitude of gravity ($|\vec{g}|$, a "hard" variable, a model parameter representing neural circuitry), while estimating the remaining "easy" state variables (e.g., the perception of angular velocity, linear motion, and the direction of gravity). The full estimation of self-orientation perception as a posterior probability distribution is conditionally factorized as the following:

$$p\left(\boldsymbol{X_k}|Y_{1:k}\right) \quad = p\left(x_k|Y_{1:k}\right)\cdot p(\boldsymbol{X_k}\backslash\{x_k\}|x_k, Y_{1:k})$$

Here, $\boldsymbol{X_k}$ is the full state space vector at time step k, and in the case of vestibular-driven gravity adaptation, the observer framework is used to estimate the x, y, and z components of linear acceleration and angular velocity, $\boldsymbol{X_k}\backslash\{x_k\}$ (the full set of state parameters excluding the internal estimate of the magnitude of gravity), and each observer solution is conditioned on the sampled parameter, x_k, the internal hypothesis of the magnitude of gravity. $Y_{1:k}$is the complete set of sensory measurements (e.g., from the otoliths and semicircular canals) up to time step k ($Y_{1:k} \quad = \{y_1, \ldots, y_k\}$).

Conceptually, the algorithm can be visualized by **Figure 1**. As proposed in Kravets et al. (2021), at each time step, the algorithm considers multiple hypotheses for the magnitude of gravity, or "particles," in parallel, and conditions an observer model on the internal estimate from each of these hypotheses. Using its hypothesis of the magnitude of gravity, each observer generates expected afferent signals (i.e., for the semicircular canals and otoliths). Each expected afferent signal is compared to the actual afferent measurement (which is the same for each of the parallel observers), and the difference between the two (actual and expected) is captured in a set of multidimensional sensory conflict signals [$\boldsymbol{e}_a$, $\boldsymbol{e}_f$, $\boldsymbol{e}_\omega$, using the standard convention for conflicts associated with linear acceleration, GIF, and angular velocity, see Clark et al. (2019)].

The sensory conflict signals from each observer are combined into a unidimensional Normalized Innovation Squared (NIS) Statistic (Bar-Shalom et al., 2001; Chen et al., 2018):

$$\epsilon_k^j \quad = (\boldsymbol{e}_k^j)^T\,(\mathbf{S})^{-1}\,\boldsymbol{e}_k^j$$

Here $\boldsymbol{e}_k^j \quad = \left[\,||\boldsymbol{e}_{k,a}^j||\ ||\boldsymbol{e}_{k,f}^j||\ ||\boldsymbol{e}_{k,\omega}^j||\,\right]^T$ is the innovation (i.e., sensory conflict) vector for hypothesis j and $\mathbf{S}$ is the scaled biological noise covariance (see **Supplementary Table 1** for specific values of all parameters, and Kravets et al. (2021) for further discussion).

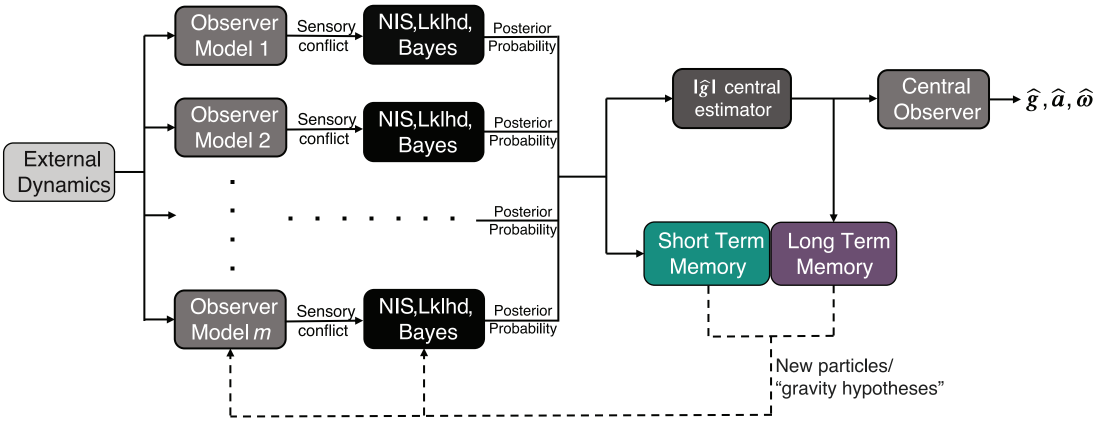

FIGURE 1
Model Framework for adaptation to altered gravity incorporating short term memory (STM) and long-term memory (LTM). The inputs to the model are a time history of body/world dynamics [x, y, and z components of linear acceleration ($\boldsymbol{a}$) and angular velocity ($\boldsymbol{\omega}$)], and the outputs are the perceived gravity ($\hat{\boldsymbol{g}}$), acceleration ($\hat{\boldsymbol{a}}$), and angular velocity ($\hat{\boldsymbol{\omega}}$). Here and throughout the text, bold denotes a 3D vector.

The NIS statistic informs the likelihoods of the incoming measurements, y_k, given the *jth* gravity hypothesis, x_k^j, as follows:

$$p\left(y_k|x_k^j\right) = \mathcal{N}(\boldsymbol{e}_{\boldsymbol{k}}^j;0;\boldsymbol{S}) = \frac{1}{\sqrt{(2\pi)^n|\boldsymbol{S}|}}e^{-\frac{1}{2}\epsilon_k^j}$$

where $\mathcal{N}(\boldsymbol{e}_{\boldsymbol{k}}^j;0;\boldsymbol{S})$is a Gaussian probability distribution function evaluated at $\boldsymbol{e}_{\boldsymbol{k}}^j$ and n is the length of $\boldsymbol{e}_{\boldsymbol{k}}^j$. The set of likelihoods is then used to calculate the Bayesian posterior probability of each gravity hypothesis:

$$p\left(x_k^j|Y_{1:k}\right) = \frac{p\left(y_k|x_k^j\right)\ p\left(x_k^j\right)}{p\left(y_k\right)}$$

where $p\left(x_k^j\right)$ is the prior probability density for the *jth* hypothesis of gravity at timestep k (the posterior of the previous time step), and $p\left(y_k\right)$ is the marginal likelihood that the measurement y_k was observed. Using the posterior probability densities of each gravity hypothesis in the current time step, a central estimate of the magnitude of gravity is calculated. A variety of summary statistics can be utilized for this calculation, but we present results based on the maximum *a posteriori* (MAP) estimator,

$$\hat{x}_{k,\mathrm{MAP}} = argmax\left[p\left(x_k|Y_{1:k}\right)\right]$$

We denote the estimate of the magnitude of gravity as $|\hat{\boldsymbol{g}}|$. A "central observer" is then conditioned on the estimate, generating the overall model's current estimate of linear acceleration, angular velocity, and the full gravity vector (i.e., tilt perception). The central observer represents an individual's current model of self-orientation perception.

In Kravets et al. (2021), a static set of hypotheses for the magnitude of gravity were pre-defined and maintained. While this was sufficient to enable adaptation of the central estimate of the magnitude of gravity by Bayesian updates of the posterior probabilities, it fails to define a mechanism for the brain to produce, maintain, or remove potential alternative hypotheses. Here we employ a novel approach for how the set of alternative hypotheses (particles) for the magnitude of gravity evolve. In preparation for the next time step, a new set of hypotheses (for the magnitude of gravity) is sampled from a dynamic state transition probability density function. We propose that this state transition function is comprised of (1) a short-term memory, sensory conflict driven component and (2) a long-term memory component, which can be dynamically updated. This state transition probability is conveyed here in a general form and is fully defined in in the following sections:

$$x_{k+1}^j \sim p\left(x_{k+1}^j|x_{1:k}^j\right)$$

Because we have set the particle sample distribution to be equivalent to the state transition probability, the recursive particle weight calculation (Ristic et al., 2003) becomes the following at each time step:

$$\tilde{w}_k^j = p\left(y_k|x_k^j\right)\ w_{k-1}^j$$

After which, all particles are normalized so that cumulative probability is unity:

$$w_k^j = \frac{\tilde{w}_k^j}{\sum_{j=1}^{N_s}\tilde{w}_k^j}$$

2.2. Short-term memory search

Similar to the methods described in Kravets et al. (2022), we begin by recognizing that the CNS achieves adaptation to environmental stimuli, transitioning from a state of exploitation (i.e., using high probability hypotheses for the internal estimate of the magnitude of gravity) to a state of exploration (i.e., aggressively considering a wider range of alternative hypotheses), and eventually back to a state of exploitation. To mathematically capture this, we first define a "short-term memory" (STM) search capability of expanding and contracting the search domain in the presence of changing environmental stimuli (**Figure 2**). We define the STM search in general terms as the following Gaussian probability density function:

$$p_{STM}\left(x_{k+1}|x_k;\sigma_{Jitter}\right) = \mathcal{N}(x_k,\sigma_{Jitter})$$

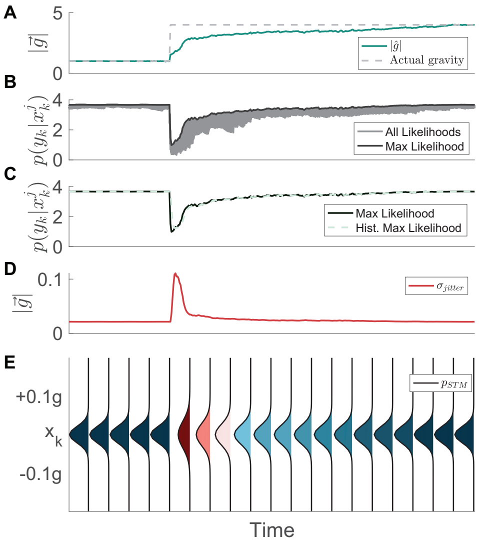

FIGURE 2
Example evolution of the STM mechanism over time, as proposed by Kravets et al. (2022). **(A)** The neural estimate of the magnitude of gravity (MAP) initially is identical to the actual magnitude of gravity (1 g). However, when the actual gravity instantly changes to 4 g in this simulation, the internal estimate gradually updates and converges to the proper value. **(B)** All particle computed likelihoods (gray) as well as the max computed likelihood (black). When the actual magnitude of gravity suddenly changes to 4 g, all of the particles produce low likelihoods. **(C)** The max likelihood (black) is used to compute a history of max likelihood (HML). **(D)** The evolution of the standard deviation of the STM function over time. **(E)** The STM probability density evolving over time. In instances where the history of the max likelihood drops the standard deviation of the probability density function increases. As we have done previously (Kravets et al., 2021), in this figure and throughout, the "Time" on the *x*-axis does not include units, as it depends on parameters in the model that can be tuned and fit to empirical data in the future.

Where x_k is the hypothesis of the magnitude of gravity at time step k. The short-term search is defined by a normal distribution with its mean chosen from the cumulative probability distribution of gravity hypotheses from the previous time step. The standard deviation of this normal distribution, σ_{Jitter}, serves to provide "jitter" to the probabilistic sampling distribution. The value for σ_{Jitter} is defined to be inversely proportional to the maximum likelihood of the alternative hypotheses within a short-term history prior to the present time step, termed *HML*:

$$\sigma_{Jitter,\ k} \propto \frac{1}{(HML_k)^{\chi_1}}$$

When calculating σ_{Jitter}, we use the exponent χ_1 to modulate the sensitivity of the algorithm to changes in maximum likelihood, such that a higher χ_1 will lead to a more drastic increase in jitter when the maximum likelihood drops. The history of maximum likelihoods (HML) at time step k is calculated as an exponentially weighted average of the time history of maximum likelihoods:

$$HML_k \ = (1 - \frac{1}{1+f})\left(HML_{k-1}\right) + \frac{1}{1+f} max[p\left(y_k|x_k\right)]$$

Where $p\left(y_k|x_k\right)$ is the set of likelihoods at time step k and f is the "forgetting factor," which can range from 0 to 1. With this formula, the magnitude of the weighting factors on each historical maximum likelihood decreases exponentially as the age of the data increases. The forgetting factor determines the rate at which historical data is "forgotten," with an f closer to 1 attributing more weight to past data. As the likelihoods are a function of sensory conflict, this averaging method prevents the model from becoming unstable with single unexpected measurements, and instead requires a buildup of sensory conflict before entering an "exploration" phase.

This formulation of jitter is not to be confused with the regularized particle filter (Ristic et al., 2003), and its original implementation comes from Kravets et al. (2022), utilized as a sample distribution. Functionally, the standard deviation of the short-term search increases when the history of the max likelihood decreases. Conversely, the standard deviation decreases when the likelihood function increases. This fluctuation represents a tradeoff between exploration and exploitation, respectively. Specifically, when the maximum likelihood of the alternative hypotheses for the magnitude of gravity has recently been high (i.e., the brain has been certain about the magnitude of gravity), it samples new hypotheses very near to the current ones (exploitation). An example of this process is provided in **Figure 2**.

2.3. Long-term memory search

In order to model CNS memory of learned sensorimotor states, we hypothesize that the CNS considers past, learned parameters comprising these states when formulating hypotheses. Regarding gravity transitions, we expect that an extended exposure to a certain gravity environment would eventually comprise a learned state of internal model parameters, and the CNS will consider these parameters when a substantial amount of sensory conflict (and by extension, substantial NIS) is present. A natural expression of this memory is through the state transition probability density function, similar to the STM search. Rather than just considering a localized (now called STM) search, as was the case in Kravets et al. (2022), a "long-term memory" search, $p_{LTM}\left(x_{k+1};\,H_k\right)$, is now also considered.

Defining the long-term memory, H_k is the sequence of estimated states up to the current (*kth*) iteration that are *harmonious*. We definite the set of harmonious state estimates affecting long-term memory as those which produce a resultant NIS (i.e., central NIS estimate) beneath a threshold, ν :

$$H_k \ = \{h_i,\ i \ = 0, \ldots, k\}$$

where h_i satisfy:

$$\epsilon_i(h_i) \ < \nu$$

Enabling the dynamic evolution of learned states, we model the long-term portion of the state transition probability as a function of the time spent in harmonious states. The continuous time representation is the following:

$$p_{LTM}\left(x_{k+1};\,H_k\right) \ = \frac{1}{T_{wind}} \int_{t-T_{wind}}^{t} \delta\left(x_{k+1} - h\left(\tau\right)\right) d\tau$$

Here, T_{wind} is the temporal window of which the CNS considers past harmonious states (presumably only considering a finite amount of information). In discrete time form, considering a discrete set of harmonious states, this evolution becomes the following:

$$p_{LTM}\left(x_{k+1}; H_k\right) = \frac{1}{N_{wind}} \sum_{i=k-N_{wind}}^{k} \delta(x_{k+1} - h_i)$$

$$N_{wind} = \frac{T_{wind}}{\Delta_k}$$

For the long-term (and short-term) memory, there is an implicit reliance on past parameters ($x_{1:k} = \{x_1, \ldots x_k\}$) and measurements ($Y_{1:k}$) since H_k (and σ_{Jitter}) are dependent on both of these sets. With this mathematical framework, we can model the evolution of learned states considered by the CNS when evolving hypotheses without making prior assumptions about what the learned states are, and these learned states construct themselves from states with sub-threshold sensory conflict without access to ground truth information. An example of this process is provided in Figure 3.

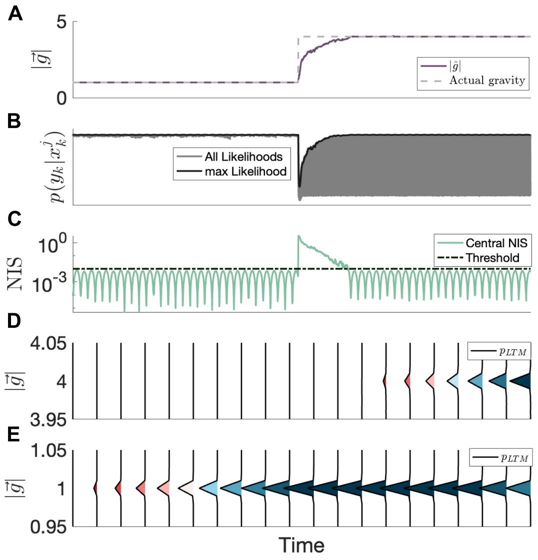

FIGURE 3
Example evolution of the proposed LTM mechanism over time. **(A)** The neural estimate of the magnitude of gravity (MAP) is shown, along-side the actual magnitude of gravity. **(B)** All particle likelihoods (gray) as well as the max likelihood (black). In contrast to the likelihoods at 1 g, the likelihoods following the transition to 4 g span a wider range, as the CNS considers a learned state at 1 g. **(C)** The central observer's NIS statistic, which determines whether or not the current estimate is harmonious (i.e., beneath an internal threshold; dashed line). **(D)** The LTM probability density evolving over time around 4 g. **(E)** The LTM probability density evolving over time around 1 g. Note that the LTM probability density between 1.05 and 3.95 is negligible (i.e., is 0) and not shown, so between panels **(D,E)**, the entirety of the LTM probability density function is shown. In instances where the current estimate is harmonious, the long-term memory portion of the state transition probability density function (shown here evolving over time) is updated, storing the state information at the current estimate. Probability densities are colored by peak densities to demonstrate emergence and cessation of learned states.

2.4. The state transition probability density function

We represent the full state transition probability as a combination of both short-term and long-term conditional state transition probabilities, expressed as the following mixture model:

$$p\left(x_{k+1}|x_k; \sigma_{Jitter}, H_k, W\right) = \frac{p_{STM}\left(x_{k+1}|x_k; \sigma_{Jitter}\right) * (1-W) + p_{LTM}\left(x_{k+1}; H_k\right) * W}{\int_{-\infty}^{\infty}[p_{STM}\left(x_{k+1}|x_k; \sigma_{Jitter}\right) * (1-W) + p_{LTM}\left(x_{k+1}; H_k\right) * W]dx}$$

Here, W is a parameter that defines the prioritization of long-term over short-term memory (the impact of this parameter is conveyed in Figure 4A). We choose to model this weighting parameter as a function of the jitter (and as a result, related to both likelihood and sensory conflict) via a sigmoid function, lending weight to STM when in an exploitative state and more equally weighting both STM and LTM while in an exploratory state:

$$W_k = \frac{1}{1+e^{-\sigma_{jitter}\cdot\chi_2}} - \frac{1}{2}$$

and now, $W \in (0, \frac{1}{2})$. How the full state transition probability function varies based on this parameter is conveyed in Figures 4B, C.

3. Example model simulations

3.1. Model implementation

The theoretical framework described above is implemented herein both with and without LTM, using the MAP estimate for the estimate of the magnitude of gravity ($|\hat{g}|$), in order to demonstrate the effect of modeling memory on various adaptation profiles. The central observer includes the recent enhancement to the observer model that incorporates differential weighting of components of otolith stimulation (Clark et al., 2015c), allowing for prediction of roll tilt over- or underestimation in hyper- and hypo- gravity scenarios. As was the case in prior models (Kravets et al., 2021), units of time on the x-axis are excluded until free parameters can be determined through future controlled experiments. However, all model parameters are held constant across model simulations to enable comparisons between adaptation profiles.

The motion profile influencing adaptation in each of the example simulations is a passive sinusoidal roll tilt at 1 rad/s (0.159 Hz) angular frequency with a peak angular velocity of 10°C. Because the observer model is implemented in Simulink, full re-run of the Simulink model from the beginning of the simulation time is required every time a particle's estimate of gravity changes (i.e., at every time step). To circumvent the computational expense associated with this process, all potential gravity levels (on a grid with a coarseness of 1/100 g) and their associated sensory conflicts were pre-computed to be pulled from a bank during the particle filter simulations. To reduce the variability in the simulations for the purpose of comparison, we chose to use $N_s = 100$ particles within the particle filter (but adaptation can be achieved with only a few particles). Additionally, similar to the design considerations of a Sequential Importance Resampling (e.g., "Bootstrap") Particle Filter (Ristic et al., 2003), we chose to resample particles from the

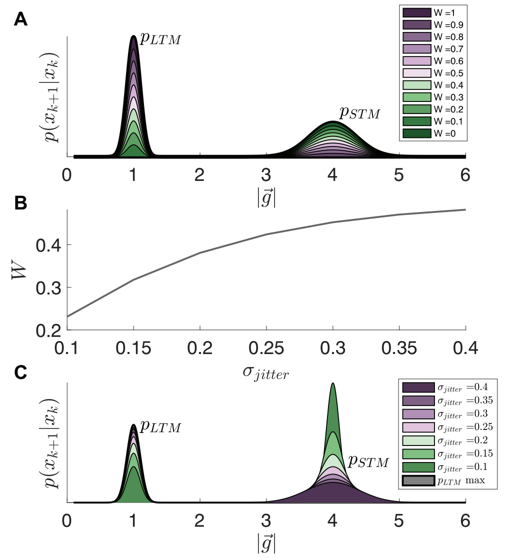

FIGURE 4

(A) Impact of weighting parameter, W, on prioritization of long-term over short-term memory. **(B)** Modeling W as the solution to a logistic function, dependent on σ_{Jitter}. **(C)** The resultant state transition probabilities due to varying levels of jitter, displayed in panel **(B)**.

posterior distribution at every iteration. This reduces the recursive particle weight calculation to be proportional to their likelihoods.

We also introduced sensory noise into the vestibular sensory signals similarly to Kravets et al. (2021). Currently, the exact form of actual sensory vestibular noise is unknown. Multiple works have theorized that increased vestibular stimuli, particularly to the otolith organs in the presence of hyper-gravity, results in an increased signal to noise ratio (and decreased ratio in hypo-gravity) (Clark et al., 2015a; Rosenberg et al., 2018). Other works suggest that vestibular sensory noise increases non-linearly with vestibular stimuli (Vingerhoets et al., 2009). We implemented vestibular noise similarly to prior works (Kravets et al., 2021, 2022) where a constant noise power (1e-8) is applied to the vestibular sensory signals (noise power is the height of the power spectral density of the white noise added to the system). A comparison of noise power to adaptation time can be found in Kravets et al. (2021; see Figure 7).

3.2. Simulation results

In **Figure 5**, our simulations demonstrate how this framework, incorporating LTM, is able to achieve faster readaptation to familiar stimuli than the prior framework with only the jitter (implemented as STM here) component from Kravets et al. (2022). The relative performance of these two frameworks is compared across multiple adaptation scenarios. At timepoint T2, readaptation to 1 g differs when implementing LTM due to the learned 1 g state prior to timepoint T1. In **Figure 5A**, readaptation to 4 g at T3 occurs at an accelerated rate due to the learned 4 g state between T1 and T2. The formation of the internal magnitude of gravity estimate is accelerated at T3 only in **Figure 5A**, and prior gravity transitions to other magnitudes of gravity (staying at 1 g, transitioning to 2 g, and transitioning to 0.5 g in **Figures 5B–D**, respectively) do not affect the adaptation rate to 4 g.

To further demonstrate the inner workings of our framework incorporating LTM, we examine the evolution of individual hypotheses (particles) considered by the CNS over time. Both their dynamic evolution and the posterior weighting of these hypotheses are compared with and without LTM in **Figure 6**, an enhanced view of timepoint T2 from **Figure 5A**. Without LTM (**Figure 6A**), just prior to timepoint T2, the gravity hypothesis particles are exclusively focused around the actual gravity level of 4 g. However, with LTM (**Figure 6B**), because 1 g is a previously learned state, a few of the gravity hypothesis particles continue to be sampled at 1 g. This enables a very different time course of adaptation of the internal magnitude of gravity. Without LTM, the RBPF has to gradually resample the hypotheses. Those gravity hypotheses that are lower magnitude (closer to 1 g) produce higher likelihoods, which encourages subsequent sampling of lower gravity magnitudes, but it is still a gradual process. In contrast, with LTM (**Figure 6B**), the internally estimated gravity level corrects to 1 g very rapidly after the actual gravity magnitude transitions from 4 to 1 g at timepoint T2. This is because gravity hypothesis particles are already being intermittently sampled at 1 g (as a learned state), such that when the actual gravity changes to 1 g the likelihood of the particle near 1 g is very high. It takes a little time after T2 for the majority of the particles near 4 g to transition to being centered around 1 g, but the central estimate of the gravity magnitude converges nearly immediately. Further, with LTM, the learned state of 4 g continues to be intermittently sampled by the gravity hypothesis particles after T2.

Finally, we simulate human perception of roll tilt (**Figure 7**) during the central adaptation occurring at T1 in **Figure 5A**. This simulation was conducted to demonstrate how the framework presented enables a better understanding of transitory perceptions during central adaptation, much like in Kravets et al. (2021). At timepoint B, when $|\hat{g}|$ correctly matches the actual gravity (prior to the gravity transition at T1), the perceived tilt accurately matches actual tilt (i.e., no misperception). However, following the gravity transition at T1, and before the model has time to fully adapt to the new gravity level, the model predicts an overestimation of tilt, which is evident at timepoint C. This is consistent with the "G-Excess" illusion, in which upon initial exposure to hyper-gravity, humans misperceive self-tilt as being larger than it actually is (Schöne, 1964; Correia et al., 1968; Clark et al., 2015b). The misperception decreases by timepoint D, as $|\hat{g}|$ more closely matches the actual gravity level. By timepoint E, the model has correctly learned the new gravity level, and once again the predicted perception matches the actual tilt.

4. Discussion

4.1. Summary of theoretical contributions

The overarching computational model provided herein of vestibular adaptation to gravity transitions enables modeling

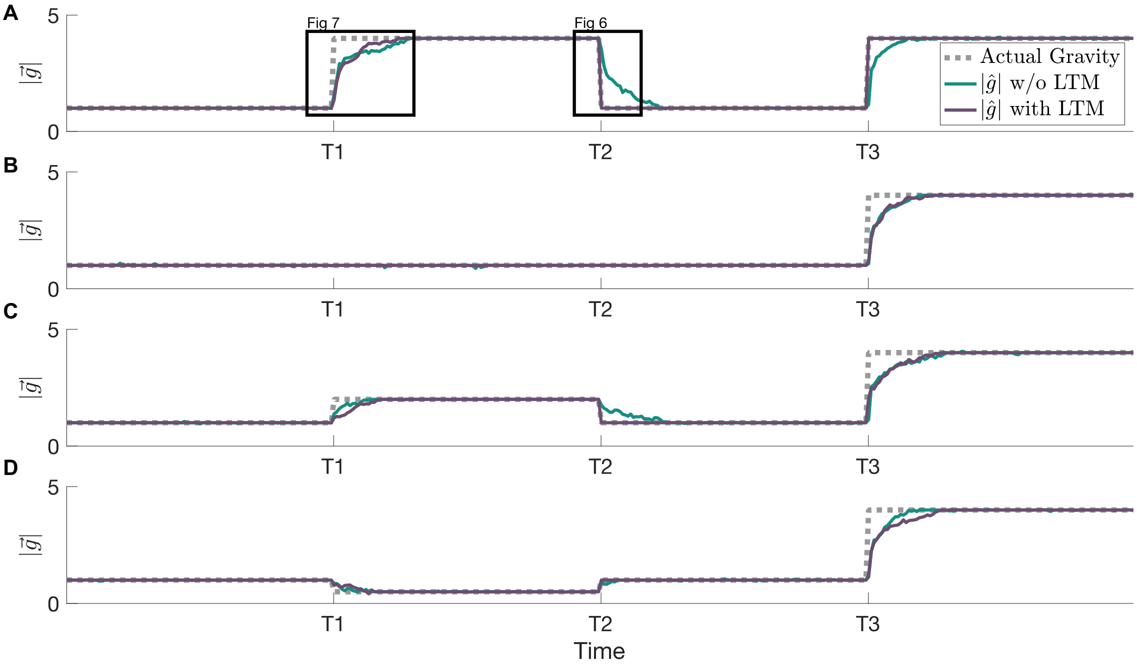

FIGURE 5
Example simulations showing various adaptation profiles and resulting MAP estimates, both with and without the LTM component of the state transition probability. All simulations begin with an actual gravity level of 1 Earth gravity, and all *x*-axes are linked to the same timescale. **(A)** An adaptation to 4 g (see **Figure 7**), readaptation to 1 g (see **Figure 6**), and readaptation to 4 g. **(B)** An adaptation to 4 g after a prolonged stint in 1 g. **(C)** An adaptation to 2 g, readaptation to 1 g, and an adaptation to 4 g (a second novel hyper-gravity stimulus). **(D)** An adaptation to 0.5 g, readaptation to 1 g, and an adaptation to 4 g (a second novel gravity stimulus, but where the first was hypo-gravity, and the second is hyper-gravity).

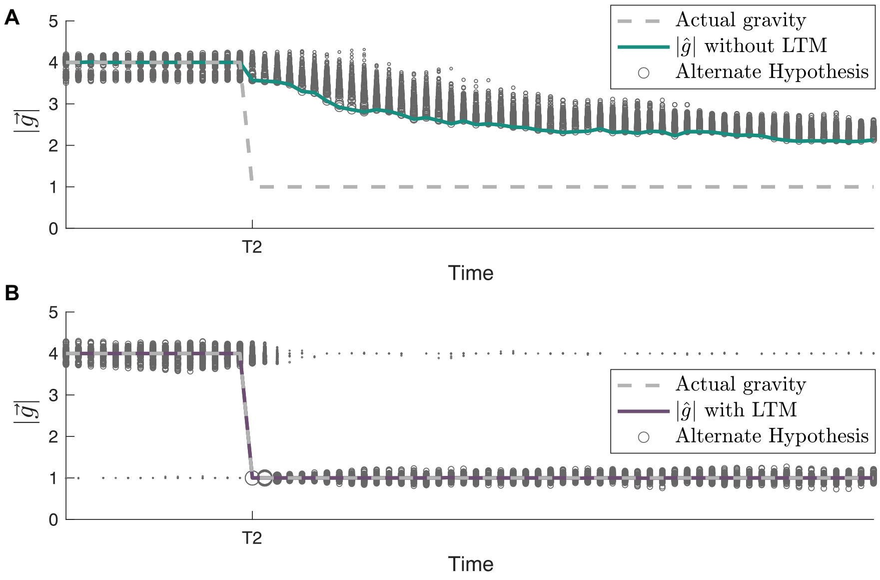

FIGURE 6
Gravity hypothesis generation with and without long-term memory (LTM). The path of gravity adaptation differs between simulations **(A)** without LTM incorporated and **(B)** with LTM incorporated, as shown by the small particles/alternate hypotheses at 1 g prior to T2 (see **Figure 5A** for full gravity transition history). In both panels **(A,B)**, the sizes of the particles are proportional to the posterior probability of each hypothesis at that timestep.

transient states of sensorimotor impairment due to changing gravitational stimuli. Our framework is dependent on vestibular sensory stimuli alone, without access to other channels of sensory information or direct information about the true magnitude of gravity. This model CNS recursively estimates gravity's magnitude through Bayesian inference, as previously proposed in Kravets et al. (2021). However we differ from the Kravets et al. (2021) implementation (which considered a static set of gravity hypotheses at each time step), and instead utilize methods proposed in Kravets et al. (2022) by modeling the evolution of potential

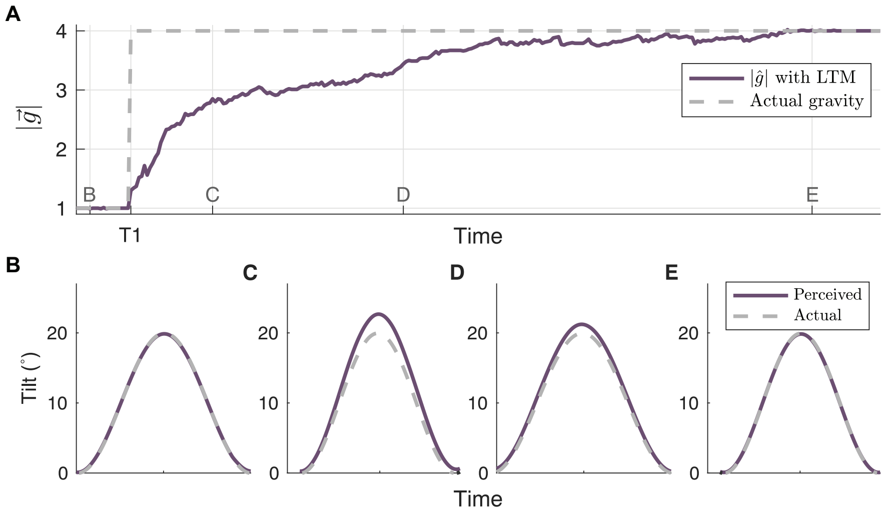

FIGURE 7
Model simulation of tilt perceptions associated with adaptation to gravity transition. **(A)** highlights the adaptation trajectory surrounding the gravity transition from 1 to 4 g at timepoint T1 in **Figure 5**, with a roll tilt motion profile. The associated tilt perceptions (or misperceptions) generated by the central observer at time points **(B–E)** are shown in their respective panels.

hypotheses via an indirect sampling approach, characterized by a Rao-Blackwellized particle filter algorithm.

As a novel improvement to these previous implementations, the model framework presented here emulates sensorimotor adaptation while retaining a memory of past harmonious states, allowing the model to consider previously experienced gravity levels (while also dynamically learning new states) when formulating new parallel alternative hypotheses of gravity. This framework's contributions include both modeling the influence of learned internal state parameters on the CNS's evolution of hypotheses and a model of the temporal evolution of learned internal state parameters (corresponding to implicit memory). Together, this framework enables the consolidation of harmonious states into long-term memory, in turn enabling faster readaptation. Notably, the computations involved with learning and storing internal state parameters do so without any ground-truth knowledge of the actual magnitude of gravity at any point in time. Further, this long-term memory functionality is beneficial toward readapting to a previously experienced magnitude of gravity, but does not have any substantial downside (i.e., it helps when useful, but does not hurt when the learned state is not relevant). While we propose this framework specifically for adaptation to a changing gravitational stimulus by learning magnitudes of gravity, this framework can be applied more broadly to other model parameters (e.g., other observer model gains and / or time constants) and other forms of implicit memory (e.g., consolidating descriptive parameters within internal models describing motor control).

4.2. Insight from model simulations

Compared to modeling STM alone, the LTM framework enables exploitation of information from past learned states to achieve faster readaptation. This effect is best demonstrated in Figure 5A at T2, when readaptation to 4 g from 1 g occurs. When considering new hypotheses of gravity, the STM search is restricted to a domain (represented here by a Gaussian distribution) centered around the current hypotheses. However, the LTM framework retains a finite memory of previously experienced harmonious states to additionally consider when in the CNS is in a state of exploration. This effect is demonstrated in **Figure 6**, readaptation to 1 g from 4 g. The rate of adaptation to learned states can be modulated through the parameter W and additionally through the free parameter χ_2. If W is sufficiently low, the adaptation trajectories with and without LTM are indistinguishable. Further, because LTM is modeled with a finite retention window, learned states are down-weighted (i.e., reduced probability of being considered by the CNS), taking longer for readaptation occur, and eventually unlearned entirely if enough time is spent outside the learned state.

Despite the more rapid readaptation enabled by the LTM framework when memory of a harmonious state exists, the time course of adaptation to novel gravity environments remains the same both with and without LTM in the simulations shown. This is consistent with evidence that sensorimotor learning is restricted to specific conditions (Tjernström et al., 2002). However, the LTM framework has the potential to facilitate quicker adaptation to unfamiliar gravity conditions that closely approximate a previously learned gravity environment. For example, if the model has a history of adaptation to 3 g, it may adapt more rapidly when transitioning from 1 to 3.2 g because it will start "exploring" new particles surrounding 3 g (which will have higher likelihoods that the existing particles at 1 g) instantly. While this hypothesis would need to be tested experimentally, it highlights one of the benefits of a computational model of gravity adaptation, as it provides specific quantitative theories that can inspire experimental work.

Finally, this framework provides the utility of computationally generating self-orientation perceptions in humans during the period of time where adaptation occurs, dependent on previous exposure to gravitational environments. It has previously been shown that tilt is overestimated following a transition to hyper-gravity from 1 g before adaptation is fully achieved (Clark et al., 2015b). Similar to Kravets et al. (2021), the internal estimate of gravity driven by this framework results in an overestimation of tilt during adaptation to a greater magnitude of gravity (shown in **Figure 7**), and the LTM framework presented herein enables computational assessments of self-orientation perception that are affected by memory of past states. By using this model's predicted perceptions in response to a controlled physical stimulus, the results can be mapped to experimental results and operational concerns. In the current model implementation, the central observer produces predictions of spatial orientation perception using the central estimate of the magnitude of gravity. One alternative approach would be to have each parallel, alternative observer predict spatial orientation perceptions, which could then be weighted and merged. This approach would allow for the quantification of bimodal orientation perceptions as have been reported for some motion paradigms (Vingerhoets et al., 2008).

4.3. Limitations and future work

Once again, this model exists as an untuned and unvalidated theory. As a result, the time course of adaptation remains undetermined. While relative comparisons can be made between simulations, there exists a need to obtain empirical data describing the time course of adaptation. For transitions from 1 g to microgravity, recent work has provided some (while limited) insight. In an attempt to quantify in-flight adaptive changes, performance in a bimanual coordination task in-flight was not found to be correlated to mission duration exceeding 4 months (spanning 4 to 11 months) (Tays et al., 2021). This finding reinforces the concept that sensorimotor adaptation reaches an exploitation state following an exploration state once the CNS achieves some desirable level of adaptation. Additionally, this finding of no differences after 4 months may provide some upper-bound time course of functional adaptation to microgravity. However, future work measuring perceptions during adaptation is recommended to quantify the time course of adaptation.

The simulation results presented here focus on gravity transitions between 1 g, hyper-gravity, and hypo-gravity, and intentionally do not address a transition to or from microgravity (i.e., 0 g). Modeling adaptation to microgravity is a unique challenge that likely involves more than just a reinterpretation of the internal magnitude of gravity. Evidence suggests that the CNS may reinterpret all otolith stimulation as translation (Young et al., 1984; Parker et al., 1985), or that there may be a degradation of the internal model of how rotational cues affect tilt perception (Merfeld, 2003). Notably when utilizing this framework for a transition to microgravity, as the internal estimate of gravity approaches zero, the central observer begins to interpret otolith stimulation as linear acceleration, and upon reaching zero, all otolith stimulation is interpreted as linear acceleration. When transitioning back to a 1 g environment, when the estimate of gravity $\in (0, 1g)$, the central observer predicts linear acceleration perceptions opposite that of physical tilt, similar to those predicted by the rotation otolith tilt-translation reinterpretation hypothesis. Despite these promising effects, it is possible that additional model parameters associated with the GIF [such as the K_f and $K_{f\omega}$ gains in the observer model, see Clark et al., 2019 for details] also change. Alternatively, the observer framework may fundamentally change upon transitioning to microgravity in a way that cannot be reflected through updating values of model parameters, and it is possible that these changes differ between individuals. While the implementation of our model does not address these unique challenges associated with microgravity, this modeling framework is not limited to just a dynamic adjustment of the magnitude of gravity and could be used to include adaptation of additional parameters that may be involved in transitions to microgravity. Future works should thoroughly explore the extension of this framework to microgravity.

It is also important to emphasize that the implementation of the model we have presented is limited to vestibular cues resulting from passive motion. However, when undergoing a gravity transition, the CNS is likely to use all sources of sensory information, such as visual and somatosensory cues, to adapt to the new environment. In fact, there is evidence that the CNS may reweight the sensory information it receives based on the reliability of the cues it is receiving (Fetsch et al., 2009; Hupfeld et al., 2022). While this is a limitation of the current implementation of the proposed framework, the model could be adjusted to include these cues and preferential weightings between sensory systems. Versions of the observer model have been developed to include visual cues (Newman, 2009; Clark et al., 2019), and other adjustments to the sensory dynamics process could be incorporated.

Sensory reweighting can be modeled by modulating the gains in the observer model contributing to perception from different sensory channels [e.g., the visual channel K_{v_v} and K_{ω_v} gains in the visual observer model, see both (Newman, 2009; Clark et al., 2019) for details]. Similar to our demonstration of updates to the magnitude of gravity parameter over time, these parameters may be updated through indirect sampling and Bayesian inference, driven by sensory conflict. Our LTM framework can also be leveraged for modeling learned states comprising different sensory weighting schemes over time. Moreover, the sensory conflict from this additional sensory channel can be incorporated into the NIS statistic formulation. To garner a full picture of sensory adaptation, the addition of somatosensory pathways and variable weighting should also be modeled. Providing more reliable sensory cues may affect the rate of adaptation predicted by the model.

As theories and evidence surrounding specific adaptation scenarios and multisensory integration mature, our proposed modeling implementation can be modified accordingly. Building up the framework presented here (through empirical validation, multisensory modeling, and reweighting of sensory channels) may eventually result in a means of improving training, operational scheduling, and countermeasure development accompanying planned gravity transitions. This framework represents a foundational stepping stone toward these goals.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

AA, VK, and TC contributed to the theoretical framework and wrote sections of the manuscript. AA, VK, TC, and NA contributed to the functionality of the computational model and the reviewing of simulation results. AA and VK implemented the model. All authors contributed to manuscript revision, read, and approved the submitted version.

Funding

This work was supported by a NASA Space Technology Graduate Research Opportunities Award.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fncir.2023.1190582/full#supplementary-material

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frontiers | Frontiers in Physiology

TYPE Original Research
PUBLISHED 31 July 2023
DOI 10.3389/fphys.2023.1201253

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RECEIVED 06 April 2023
ACCEPTED 21 July 2023
PUBLISHED 31 July 2023

CITATION
Keime M, Chomienne L, Goulon C, Sainton P, Lapole T, Casanova R, Bossard M, Nicol C, Martha C, Bolmont B, Hays A, Vercruyssen F, Chavet P and Bringoux L (2023), How about running on Mars? Influence of sensorimotor coherence on running and spatial perception in simulated reduced gravity. *Front. Physiol.* 14:1201253.
doi: 10.3389/fphys.2023.1201253

How about running on Mars? Influence of sensorimotor coherence on running and spatial perception in simulated reduced gravity

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Motor control, including locomotion, strongly depends on the gravitational field. Recent developments such as lower-body positive pressure treadmills (LBPPT) have enabled studies on Earth about the effects of reduced body weight (BW) on walking and running, up to 60% BW. The present experiment was set up to further investigate adaptations to a more naturalistic simulated hypogravity, mimicking a Martian environment with additional visual information during running sessions on LBPPT. Twenty-nine participants performed three sessions of four successive five-min runs at preferred speed, alternating Earth- or simulated Mars-like gravity (100% vs. 38% BW). They were displayed visual scenes using a virtual reality headset to assess the effects of coherent visual flow while running. Running performance was characterized by normal ground reaction force and pelvic accelerations. The perceived upright and vection (visually-induced self-motion sensation)in dynamic visual environments were also investigated at the end of the different sessions. We found that BW reduction induced biomechanical adaptations independently of the visual context. Active peak force and stance time decreased, while flight time increased. Strong inter-individual differences in braking and push-off times appeared at 38% BW, which were not systematically observed in our previous studies at 80% and 60% BW. Additionally, the importance given to dynamic visual cues in the perceived upright diminished at 38% BW, suggesting an increased reliance on the egocentric body axis as a reference for verticality when the visual context is fully coherent with the previous locomotor activity. Also, while vection was found to decrease in case of a coherent visuomotor coupling at 100% BW (i.e., post-exposure influence), it remained unaffected by the visual context at 38% BW. Overall, our findings suggested that locomotor and perceptual adaptations were not similarly impacted, depending on the -simulated- gravity condition and visual context.

KEYWORDS

motor adaptation, gravity, space analog, locomotion, sensory integration, spatial perception, unweighting

1 Introduction

"That's one small step for man, one giant leap for mankind," stated Neil Armstrong when he set foot on the Moon in 1969. Fifty years later, the goal of space exploration remains similar: land, walk and ultimately, settle, on another planet. With this purpose in mind, future missions will have to take into account the adaptive abilities of the astronauts to keep them in optimal conditions during the journey and settlement on a novel environment, Mars being the current target.

So far, human adaptation to space missions has mostly been evaluated in microgravity during parabolic flights and on the International Space Station (ISS). Some studies (see White et al., 2020 for a review) focused on sensorimotor skills, i.e., motor production based on sensory state estimates and feedback, mainly examined through reaching movements (Bringoux et al., 2012; Bringoux et al., 2020; Gaveau et al., 2016; Macaluso et al., 2017), grasping tasks (Crevecoeur et al., 2010; Giard et al., 2015) or more complex tasks such as "reach to lift" (Patron et al., 2002) or bouncing series (Ritzmann et al., 2016). All the aforementioned studies have highlighted specific sensorimotor adaptations to microgravity. Among these previous works, some quantified adaptive effects of exposure to different visual flow patterns during and after walking (e.g., Mulavara et al., 2005; Nomura et al., 2005; Richards et al., 2007), but not running. It was reported that heading direction and locomotor trajectory were notably affected. Surprisingly however, while running or skipping may constitute a mechanically fitting pattern of locomotion when the level of gravity is reduced (Cavagna et al., 1972; Pavei et al., 2015), there is, to our knowledge, no corresponding study which tested running adaptation. In fact, the effects of a reduced level of gravity on locomotion have been scarcely investigated, be it on trained astronauts or on novice participants, partly because of the lack of adapted experimental analogs. Among recent technologies, the LBPP treadmill (LBPPT) provides body weight (BW) support (i.e., partial unweighting) as the air pressure increases within the associated flexible chamber, hence creating a lifting force from the pelvic level (Whalen and Hargens, 1992). Such analog appears thus promising as it gives the possibility, on Earth, to study locomotion under simulated hypogravity conditions (Fazzari et al., 2023).

A primary consequence of unweighting on locomotion, specifically during running, is the previously reported adoption of a longer flight duration combined with a reduced duration of the contact phase leading to the slowing of stride frequency (Grabowski and Kram, 2008; Sainton et al., 2015; Farina et al., 2017). Such a pattern recalls skipping adopted by Neil Armstrong on the Moon. Our previous studies precisely characterized the running pattern at 80% and 60% BW on a LBPPT, bringing forth that biomechanical adaptations to hypogravity are specific to both the unweighting level and the running phase (Sainton et al., 2015). However the presence of after-effects on the reloading phase reveals that the temporal adaptations of the running pattern are not optimal (Sainton et al., 2015). A potential explanation for these discrepancies could be the lack of visual information often reported as a factor favouring a default pattern (Liebermann and Goodman, 1991; Müller et al., 2014).

The aim of the present study was to test the influence of visual information, notably through the manipulation of visual cues in terms of sensorimotor coupling, on running adaptation in a realistic Mars-like environment. Besides, we also questioned how spatial perception evolves in response to these various sensory contexts. Until now, only 80% and 60% BW levels have been studied using a LBPPT, while studies about spatial perception were mostly performed on the ISS and on parabolic flights. It is yet unknown whether adaptations are comparable under Martian gravity (around 38% BW) which might be experienced in the near future.

In the following experiment, we studied locomotor adaptations and related spatial perception following manipulation of the multisensory context during running. By multisensory context, we consider two BW levels mimicking Earth and Mars gravity (100% or 38% BW respectively) and different related visual information. We hypothesized that visual context would influence locomotor adaptations to simulated hypogravity, such that a coherent visual scene, which traduces the natural head oscillations and forward translations when running in hypogravity, might induce more noticeable adaptations of the running pattern. Our second hypothesis was that spatial perception in simulated hypogravity would also be influenced by visual context. The latter was manipulated during running along the vertical axis to subsequently study its impact on upright orientation, and along the anteroposterior axis, to evaluate the effects on visually-induced forward self-motion perception (i.e., vection). We expected that simulated hypogravity would decrease the reliance on visual cues for upright perception and suppress post-exposure effect on vection in case of a coherent visuo-locomotor activity.

2 Methods

2.1 Participants

Twenty-seven healthy male recreational runners (mean age 19.6 ± 1.8 years) volunteered for this study. Individuals with counter-indications to running, with medical/surgical antecedents (motor and sensory issues) or any illness/injury not compatible with the study (affecting lower limbs, spine, and sensory inputs) were automatically excluded. For technical reasons, a participant was unable to perform the spatial tests following his running sessions. This study received approval by the ethics committee of the ethical national instance CERSTAPS (IRB00012476-2021-31-03-96). In accordance with the Declaration of Helsinki, all participants provided written informed consent to take part in the experiment.

2.2 Materials

The experiments were conducted at the Institute of Movement Science in Marseille (France). Each volunteer ran on a LBPPT

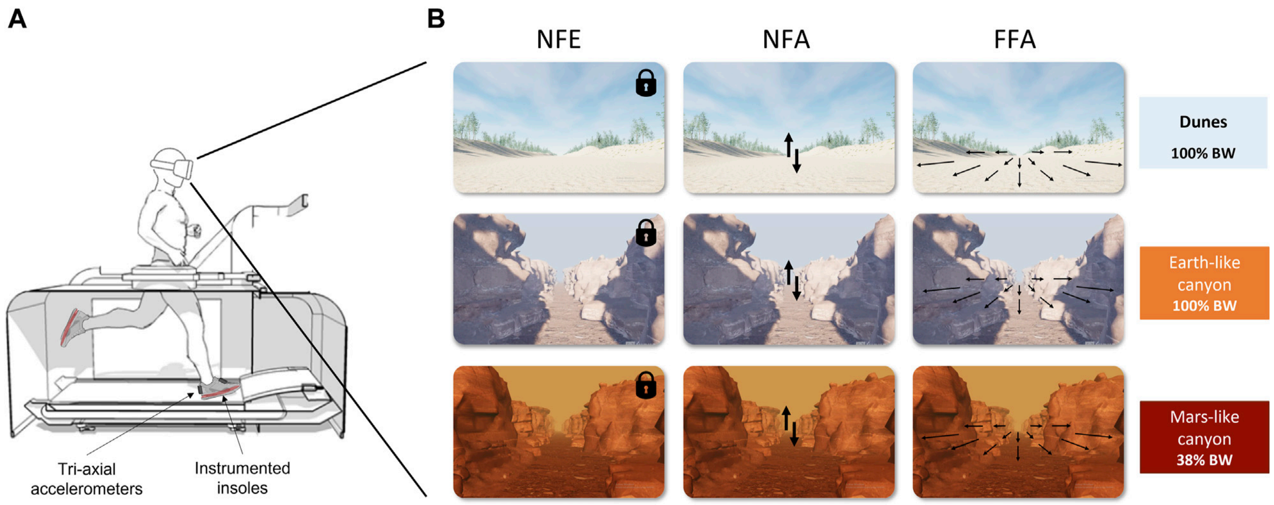

FIGURE 1
(A) Sketch of the experimental setup including the LBPPT used for the experiment. The differential air pressure technology allowed for controllable unweighting of the runner on the treadmill. Participants were equipped with accelerometers and wore shoes with specific insoles to collect information about the running pattern. They wore a VR headset displaying different visual scenes along the experiment. **(B)** illustration of the visual scenes displayed when running 1) in PRE and POST sessions (upper panel); 2) in PER session at 100% Body Weight (middle panel); 3) in PER session at 38% Body Weight (lower panel). The different visual conditions manipulating the reference frames/optic flow presented to the participants (NFE, NFA, and FFA) were displayed from the left to right respectively.

(VIA400X AlterG®, Fremont, CA, United States; Figure 1A) wearing neoprene shorts zipped to the flexible chamber of the treadmill, at the height of the greater trochanter. Initial inside chamber air (100% BW) was pressurized to reach 38% BW, simulating hypogravity (0.38 g). 100% BW thus corresponded to normogravity (1 g).

2.2.1 Biomechanical measurements

Two tri-axial accelerometers (Pico Cometa systems®, Milan, Italy, ±8 G, F = 2 kHz) were positioned on the right foot, one on the posterior aspect of the heel, one medially (navicular), and a third one was placed at the sacrum level. Data was recorded through the software EMGandMotionTools®. Instrumented insoles (Loadsol, Novel®, Munich, Germany; F = 100 Hz) were inserted in each running shoe (Run active, Kalenji®) to record the normal ground reaction force (GRF) on posterior, antero-medial and antero-lateral surface of the foot. Data was acquired using the Loadsol application software. Head position was acquired through the sensors of the HP Reverb G2 virtual reality (VR) headset (F = 90 Hz, 2160 × 2160 pixels per eye). The VR headset was also used to display the different visual scenes during the running sessions and to perform spatial tests.

2.2.2 Visual conditions

2.2.2.1 Visual scenes and flows

To display the different visual scenes, the participants wore a HP Reverb G2 VR headset controlled by a laptop (Windows Mixed Reality, Steam VR, using Unreal Engine to develop the scenes). The onsets of both accelerometer acquisition and visual scenes were synchronized with the help of an external controller (Leo Bodnar Electronics, BU0836A 12-Bit Joystick Controller). Throughout a test session, participants were successively presented with three different visual scenes: one that was clearly taking place on Earth, with a visual background different from the others to avoid habituation, and two picturing a canyon, respectively with Earth-like and with Mars-like features (e.g., sky color, pathway texture, see Figure 1B). Prior to each test session, the visual scene was calibrated to the participant's height. Participants ran and went through the whole session with the headset on.

Different visual conditions (i.e., reference frames/visual flow) were presented to each participant, in a pseudo-randomized order over three sessions.

- No Flow Ego (NFE): static viewpoint anchored to the participant (egocentric fixation). The image did not change regardless of participant's head movements.
- No Flow Allo (NFA): static viewpoint anchored to the external environment (allocentric fixation). The participant could look around the scene as if he was standing still in a room.
- Full Flow Allo (FFA): allocentric anchor (same as above) with a dynamic viewpoint and a continuous retinal flow at the same speed as that of the treadmill corresponding to each participant's preferred speed to give a realistic running impression. In this condition, the focus of expansion characterizing the motion direction of the visual scene mimicking a forward displacement was always kept centred at eye level with respect to the external space (ahead of the participant's initial natural orientation on the treadmill).

2.2.2.2 Spatial tests

Two tests were used to evaluate the interplay between visual inputs and locomotor adaptations through the consequences on spatial perception. Visuals of the tests were developed in-house by

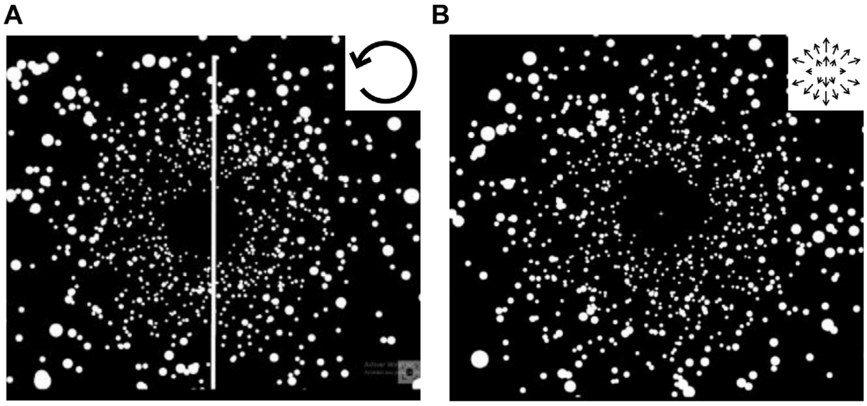

FIGURE 2
(A) Snap of the visual scene displayed between each run session to assess the perceived upright orientation (Rod and Disc Test). Participants were asked to continuously align the rod to their subjective upright (using a joystick) while facing a rotating cloud of dots in the frontal plane during 30 s. **(B)** Snap of the visual scene displayed between each run session to assess vection. Participants were asked to estimate the “quantity” of visually-induced forward self-motion (using a joystick) while facing an expanding cloud of dots at eye level along the sagittal axis during 30 s. The motion direction of the clouds of dots displayed for each test was presented in the top right corner of each panel.

using Unreal Engine 5.0 and displayed using the VR headset, with responses given by the participants using the right joystick (F = 90 Hz). The participants stood still throughout the tests without laying their resting hand on the treadmill. The Rod-and-disk test (RDT) was first presented to evaluate the dynamic visual influence on the perceived upright orientation (Dichgans et al., 1972). The use of VR technology for assessing upright perception has been found valuable in static (RFT: Bringoux et al., 2009) and dynamic (RDT: Zaleski-King et al., 2020) virtual environments. Using the right joystick of the VR set, the participants were asked to continuously adjust a rod to upright in the presence of a rotating visual flow (white points on a black background moving at 30°/s, Figure 2A). The joystick could be pushed to tilt the rod accordingly to the left or right. At the beginning of the test, the rod was upright (i.e., aligned to gravity). The test was designed to give the participants the illusion that the rod was rotating, while only the background was moving. The more influenced the participants were by the rotating background, the more they moved the joystick and re-adjusted the position of the rod. In the second spatial test, the participants had to continuously evaluate their visually-induced forward self-motion perception (i.e., vection) while viewing an antero-posterior visual flow (expanding cloud of points on a black background, 10 $m.s^{-1}$, Figure 2B). Vection was defined to the participants as the sensation of moving forward when facing visual stimuli moving backward while there is no actual physical motion occurring. They were asked to move the joystick along the antero-posterior axis to evaluate how intensely they felt self-motion: the more intense the feeling, the more they pushed the joystick forward.

2.3 Procedure

2.3.1 Familiarization

One week before the main session, each volunteer participated in a familiarization session to get a first experience of the LBPPT and determine their preferred running speed. They first filled in the VIMSSQ questionnaire (Keshavarz et al., 2019) to assess their tolerance to VR and long-time screen exposure, before trying on the VR headset. From this questionnaire, we did not spot any participants too highly susceptible to VR sickness to participate.

2.3.2 Tests

Each selected participant went through three test sessions (each presenting a different visual condition), performed over the same day (4 h). Each session was divided in PRE, PER, and POST phases (Figure 3). The PRE and POST runs were conducted at 100% BW while displaying in the VR headset a common Earth-based scene (dunes) in FFA condition. The PER phase was composed of two runs, at 38% and 100% BW, presented in a counterbalanced manner. They were successively performed under the same visual condition, either NFE, NFA or FFA. The order of the sessions including one of the three visual conditions in the PER phase was pseudo-randomized.

Each session thus presented four consecutive runs of 5-min duration each, performed at the participant’s preferred running speed established during familiarization with the VR headset (on average, 10.5 ± 0.6 km/h). The same running speed per participant was maintained across each run for comparison purpose. Although it is known that the preferred running speed on a treadmill could be impacted by the available visual flow (Prokop et al., 1997), it was found comfortable and natural across the whole experiment.

Each run pre-started with the treadmill being gradually accelerated up to the preferred running speed during approximately 30 s. The visual scene was displayed in the VR headset as soon as the participant started running, thus allowing gradual immersive experience proper to each visual condition before entering each 5-min run at constant speed. Each run was followed by RDT and vection tests. Both tests were successively presented as soon as the participant had stopped running and was stable and ready to enter this perceptual evaluation phase.

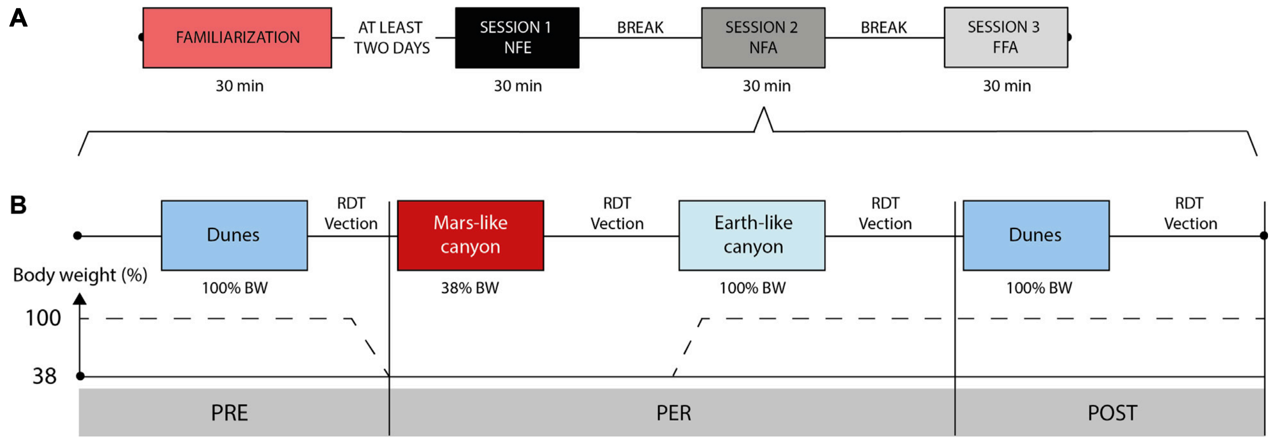

FIGURE 3
(A) Sketch of the protocol with the 3 running sessions preceded by the familiarization session, and example order of visual conditions (here: NFE−NFA−FFA). **(B)** Example of a detailed session presenting a specific visual condition (e.g., NFA). Half the participants began the PER phase with the 38% BW run, as pictured, the other half started with the 100% BW run.

2.4 Data analysis

All data analyses were carried out on Matlab R2021b (MathWorks, Inc.). Acceleration signals were low-pass filtered using a 4th order Butterworth zero-phase filter with a 10 Hz cut-off frequency. The vertical acceleration recorded at the pelvic level was double integrated and band-pass filtered to identify the end of the braking phase, corresponding to the minimum vertical position of the pelvis. Active peak force (APF), contact and toe-off points were determined using the normal component of the GRF, with a force detection threshold set at 50 N. Flight, stride, stance, step frequency, braking and push-off durations were then computed as well as the amplitude of the pelvic vertical displacement during stance (i.e., during braking (ΔH_B) and during push-off (ΔH_P)). Maximum rod deviation during RDT (MaxDev) along the 30 s duration of the test was chosen as the variable of interest for the first spatial test. This variable represents the maximum amount of disturbance on the perceived upright orientation encountered by the participants due to the rotating visual field. Quantity of vection (QVec) was the variable selected for the second spatial test and was obtained by integrating vection intensity recorded over the 30 s duration of the test, after applying a low-pass filter (1 Hz). This variable thus reflects a single perceptual effect combining both magnitude and duration of visually-induced self-motion perception, allowing to test the complex experience of vection in a more holistic way (Kooijman et al., 2023).

2.5 Statistics

Statistical analyses were conducted using JASP software (version 0.16.3) with a level of significance set to $p < 0.05$. Outliers with inconsistent and extremely high results on vection and RDT data were removed from the analysis. For each variable, two repeated measures Analysis of Variances (ANOVAs) were performed. The first specifically compared the different phases (PRE; PER38; PER100; POST) with a repeated single visual condition (FFA) to stress the unweighting effect itself. Also, a 2-BW level [PER100; PER38] × 3 visual conditions [NFE; NFA; FFA] repeated measures ANOVA was performed to focus on the interaction between the visual coherence relative to the sensorimotor activity and the BW condition. A Greenhouse-Geissner sphericity correction was applied to the ANOVA results when necessary. Significant effects were further examined using post-hoc tests with Bonferroni correction. The results were expressed as means and standard deviations.

3 Results

Data analysis focused first on the effects of the simulated gravity condition (i.e., BW influence across experimental phases) independently of the visual conditions, before also considering the latter during PER exposure to bring forward possible interactions between gravitational and visual contexts.

3.1 Effects of body weight reduction on the running pattern

The ANOVA performed over the 4 phases (PRE, PER100, PER38, POST) revealed a significant influence of the BW condition on the running pattern. The results of ANOVAs conducted on each running parameters are synthesized in Table 1.

Unweighting condition (PER38), specifically compared to each other phase, led to longer flight time, shorter stance time and lower step frequency ($p < 0.001$). The relative difference between the parameters at 100% BW (during PRE runs) and at 38% BW (during PER38 runs) led to a decreased stance time that went along with the decreased step frequency, while flight time increased by 147%, consequently enough to stand out of the other values (Figure 4). Interestingly, braking and push-off durations did not significantly differ between phases despite the decreased stance duration.

TABLE 1 Variations of biomechanical parameters between PER (38% BW) and PRE (100% BW) runs.

Variable	Values (PRE - PER38)	% Variation/PRE runs	Statistical significance
Stance Time	0.292 s – 0.250 s	−14%	$F_{(3,26)} = 191.1$; $p < 0.001$; $qp^2 = 0.880$
Step Frequency	2.501 step/s to 2.041 step/s	−18%	$F_{(3,26)} = 265.018$; $p < 0.001$; $qp^2 = 0.911$
Braking time	0.164 s – 0.158 s	−4%	$F_{(3,26)} = 0.621$; $p = 0.573$; $qp^2 = 0.023$ (ns)
Push-off time	0.154 s – 0.139 s	−11%	$F_{(3,26)} = 0.709$; $p = 0.529$; $rip^2 = 0.027$ (ns)
Pelvic vertical displacement during braking (ΔHB)	0.018 m – 0.012 m	−33%	$F_{(3,26)} = 9.865$; $p < 0.001$; $qp^2 = 0.275$
Pelvic vertical displacement during push-off (ΔHP)	0.021 m – 0.011 m	−48%	$F_{(3,26)} = 22.744$; $p < 0.001$; $qp^2 = 0.532$
Active Peak Force	1686 N – 998 N	−41%	$F_{(3,26)} = 550.787$; $p < 0.001$; ripe = 0.957
Flight time	0.088 s – 0.213 s	142%	$F_{(3,26)} = 440.42$; $p < 0.001$; $qp^2 = 0.944$

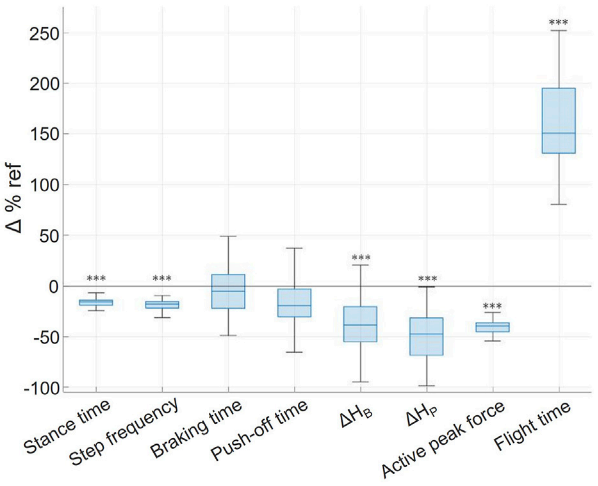

FIGURE 4
Relative unweighting-induced variations (Δ%ref) of the temporal characteristics of the left and right steps. For each variable the individual changes are represented by the median, interquartile range, and extreme values. ***$p < 0.001$ when statistically different from the initial condition values during PRE run.

ΔH_B, ΔH_P, and APF were also reduced by 30–40% at 38% BW compared to 100% BW. In other words, there was less vertical pelvic excursion during braking and push-off and, upon contact, the ground normal reaction force was lessened with unweighting.

3.2 Effects of body weight reduction on upright perception

Body weight reduction not only affected the running pattern as it also tampered with the participants' spatial perception, as shown by the results of the RDT revealing how upright perception is significantly influenced by a dynamic visual environment following each phase ($F_{(3, 25)} = 5.66$; $p < 0.01$; $\eta p^2 = 0.19$). MaxDev decreased significantly in PER38 compared to PRE [−25% (11.3°–8.4°), $p < 0.001$; Figure 5]. Thus, it appears that the maximum deviation recorded during the RDT following a 38% BW run was significantly smaller than when the same test was performed after the very first run at 100% BW.

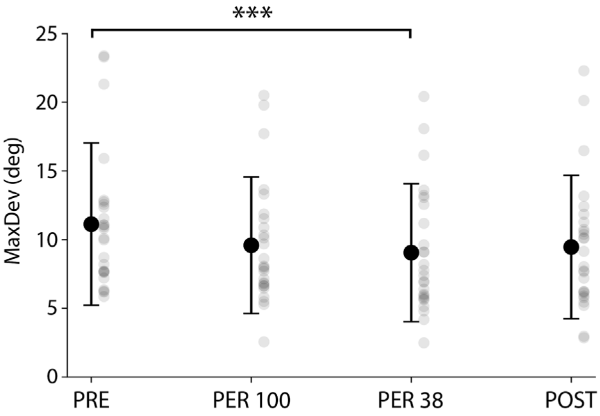

FIGURE 5
MaxDev (Mean maximum deviation of the rod assessed to upright perception) over the 4 phases. ***$p < 0.001$.

3.3 Effects of body weight reduction on vection

Vection (QVec) was barely but not significantly impacted by the BW condition ($F_{(3,25)} = 2.78$; $p = 0.053$; $\eta p^2 = 0.10$, after Greenhouse-Geissner correction). While some participants were immune to any visually-induced motion stimuli throughout the whole experiment, some others presented high responses, particularly when Qvec was evaluated following a run at 38% BW.

3.4 Interaction between gravitational and visual contexts

The previous subsections presented the results pertaining to the experimental phases to stress the effect of body weight reduction

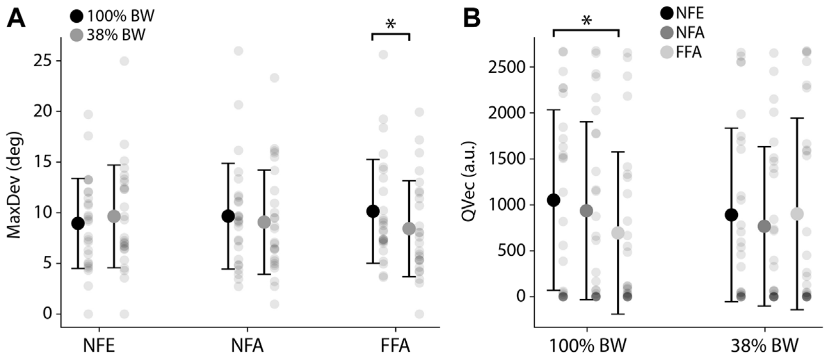

FIGURE 6
(A) MaxDev (Mean maximum deviation of the rod assessed to upright perception) depending on the visual context and the loading condition. *$p <$ 0.05. **(B)** QVec (Mean quantity of vection, i.e., visually-induced forward self-motion perception) depending on the loading condition and the visual context. *$p < 0.05$.

only, yet our study also introduced varying visual contexts during the two PER runs, at 38% and 100% BW. Our goal was here to focus on a possible interaction between the visual context (NFE; NFA; FFA) and the simulated gravity (i.e., loading conditions: PER100; PER38).

We did not observe any significant effect of the visual condition nor any interaction between the visual and loading conditions on the biomechanical parameters ($p > 0.05$ for the eight parameters characterizing the running pattern).

Regarding upright orientation perception, there was no main effect of the visual condition ($F_{(2,25)} = 0.01$; $p = 0.99$; $\eta p^2 = 0.001$) but a significant interaction between PER-loading and the visual conditions ($F_{(2,25)} = 5.77$; $p < 0.01$; $\eta p^2 = 0.19$). MaxDev was found to decrease in PER38×FFA as compared to PER100×FFA [−17% (10.1°–8.4°), $p < 0.05$; Figure 6A]. In other words, participants were less influenced by a moving visual background for upright perception following a run at 38% BW compared to 100% BW when the PER-running session presented a coherent visual stimulation (FFA scene).

Considering vection, there was no main effect of the visual condition ($F_{(2,25)} = 2.81$; $p = 0.09$; $\eta p^2 = 0.10$) but a significant interaction between PER-loading and the visual condition ($F_{(2,25)} = 4.25$; $p < 0.05$; $\eta p^2 = 0.15$). QVec specifically decreased from PER100 × NFE to PER100 × FFA (−34%, $p < 0.05$; Figure 6B). Participants running at 100% BW with a full coherent visual flow (FFA scene) perceived a smaller quantity of self-motion than with no previous visual flow nor head motions allowed (NFE scene). Visuomotor coherence during the PER-runs at 100% BW thus led to a significant decrease of subsequent visually-induced self-motion perception, which is no more apparent at 38% BW.

4 Discussion

The main purpose of this study was to examine the interplay between the visual and gravitational contexts and its influence on the adjustments of the running pattern and related spatial perception. Combining LBPPT running with various VR visual scenes showed that the biomechanical parameters of running were not influenced by the visual context, but were affected by the reduction in body weight. Spatial perception, in terms of gravity-related information processing and self-motion perception, exhibited variations depending on the level of simulated gravity but also on the interaction between the latter and the visual context. We will further discuss these observations in the following parts, focusing first on locomotion and spatial perception separately before considering their interaction.

4.1 Adaptation of the running pattern

The analysis of the gait at 38% BW revealed the same temporal organization as previously shown at lower unweighting levels (Sainton et al., 2015). Stance time decreased, due to a large increase of flight time, leading to reduce the step frequency as well as active peak force. As expected, such characteristics illustrate a gait that gets closer to skipping, as described by Minetti. (1998), in line with the pattern described at 60% BW by Sainton et al. (2015) and previous studies (Grabowski and Kram., 2008; Smoliga et al., 2015). Grabowski and Kram. (2008) even went down to 25% BW, reporting a decrease in active peak force similar to our findings. Interestingly, they also noted a longer stance time, contrary to our results and other studies conducted in similar settings (Raffalt et al., 2013; Neal et al., 2016).

Yet, in our case, no variation appeared on the stance time components, whatever the visual context. Also, neither braking nor push-off times decreased. However, interindividual variability of the braking phase duration reveals an almost equally Grabowski and Kram. (2008) partitioned behaviour. Some participants modified either the braking time or the push-off time, sometimes both, wheareas the others kept the stance phases constant. This differentiation is new as Sainton et al. (2015) reported a specific decrease in braking time associated to a large inter-individual variability at the larger unweighting level (i.e., 60% BW vs. 80% BW). Unweighting at 38% BW would, thus, introduce a forced choice between two slightly different running patterns depending on what is most efficient for each individual. Adjusting either braking or push-off parts of the stance phase may also reveal a specific control performed online. Here, targeted adaptations may allow for the preservation of the overall efficiency despite the unfamiliar gravitational context. Further analyses of the muscles activity are of course mandatory to deeper investigate the underlying neuromuscular control. In addition, as tests were conducted over a short period (5-min runs), adaptations to the running pattern can be assumed to settle quickly, in line with previous experiments (Sainton et al., 2016). This could be actually the expression of a fast integration of the changes in gravitational context. Alternatively, the visual context could require more time to be taken into account in the adaptive process to unweighting affecting running.

4.2 Adaptation of spatial perception

Although visual information did not seem to impact running pattern itself, it did affect spatial perception along with the reduction in body weight. Upright orientation is determined by the importance given to the different available sensory inputs and prior knowledge leading to an estimation of the vertical direction (de Winkel et al., 2018). Following a run at 38% BW, participants were less affected by dynamic visual perturbations during upright estimates than after a run at 100% BW. This points towards a reweighting of sensory inputs required for processing gravity-related information. We suggest here that the importance attributed to sensory inputs involved in graviception is reduced following exposure to simulated Martian gravity, in favor of a higher reliance on the participant's own body axis as a strong reference for upright perception (de Winkel et al., 2012).

Following this idea, Harris et al. (2017) observed that astronauts exhibit an increase in reliance on body longitudinal axis as a main reference for upright orientation after 10 days in microgravity, and an overall decrease in visual reliance. Additionally, Dyde et al. (2009) showed that background orientation is less important for upright perception in microgravity, which could also provide insights as to why the influence of the moving background in RDT decreases in hypogravity. This study, though, was conducted with static participants and no locomotor activity prior to the test. Our findings suggest that a coherent locomotor activity may help induce a comparable although faster perceptual adaptation under simulated hypogravity.

Notably, such a lower influence of dynamic visual perturbation on the perceived upright orientation specifically occurred after the participants were exposed to visual flow and head motions congruent with the locomotor activity (i.e., FFA condition). This strongly supports the idea that visuomotor coherence during prior exposure to Martian hypogravity is necessary for subsequent changes upon gravity-based processing for upright perception to take place.

Visually-induced self-motion perception, probed through the vection test, was also found to be differently affected by the visual condition, depending on the level of simulated gravity. After a run at 100% BW with full visual flow (FFA condition), vection decreased compared to a run with no visual flow and no possible head-related visual motion (NFE condition). Conversely, this "post-exposure" influence following a run in FFA condition disappeared at 38% BW. Thus, exposure to a coherent visual flow during locomotor activity in normogravity seemed to subsequently reduce the visual influence on self-motion perception, which was not the case after being exposed to a simulated reduced gravity. Some pioneer studies reported an increased visually-induced motion sensation during and after long-term microgravity exposure (Young et al., 1984; Young and Shelhamer, 1990; Young et al., 1992; Watt, 1993; Oman et al., 2000). Noticeably here, while we did not find any main effect of the level of simulated gravity upon subsequent vection (although the trend was barely significant), one may speculate that previous coherent sensorimotor exposure (i.e., FFA condition) may help preserve the sensibility to visually-induced self-motion sensation (which is conversely diminished at 100% BW in our experiment). The time course of these visually-driven sensory reweighting processes is still discussed, since Allison et al. (2012) found a reduction of the 'oscillation enhancement effect' on vection sensitivity after short-term microgravity exposure during parabolic flight and a global decrease of visually-induced self-motion perception post flight.

Overall, these fast perceptual adaptations in information processing for upright and self-motion perception following short term locomotor exposure to simulated reduced gravity strongly suggest that prior visual conditions may have a great influence on spatial responses under Mars-like conditions.

4.3 Interactions between perceptual and sensorimotor behavior

While visual context was found to interact with body weight variations on spatial perception, it did not influence the temporal and dynamical characteristics of the running pattern which was merely affected by the body weight condition, indicating that sensorimotor and perceptual adaptations are not similarly driven by a same sensory context. Some pioneer studies of Paillard (see Clarac et al., 2009 for a review) reported possible interactions between two levels of action control: the sensorimotor level, which interacts directly with the environment through motor commands and ultimately movement, and the cognitive level, integrating sensory inputs to constantly update internal representations and reference frames. While these two levels communicate and can be influenced by each other, some degree of independence is maintained, allowing one-sided updates and different levels of shared information to external sensory stimulation (Leclere et al., 2022). Our findings supported that claim, in that spatial information processing was rapidly influenced by coherent visual exposure with respect to the locomotor activity being performed, despite the visual condition having no consequence on the observed neuro-mechanical adjustments.

The literature also emphasize how crucial time is for the adaptation of perceptual and sensorimotor levels. Spatial representations are mostly considered rather robust and immune to short term perturbations (Glasauer and Mittelstaedt, 1992; Glasauer and Mittelstaedt, 1998), while motor adaptations have been found very early in novel gravity-related environments (White et al., 2020). For instance, Harris et al. (2017) mentioned that reweighting of visual cues for spatial perception takes days to settle in astronauts on the International Space Station. Here, we provide evidence for distinct adaptive processes governing locomotor behavior and spatial perception in response to short term exposure to a simulated Martian gravity. Strikingly, visuomotor coherence in such an extreme environment might serve to rapidly update spatial cues, and thus optimize perceptual adaptation.

5 Conclusion

This study reveals that very short-term locomotor exposure to a simulated Martian gravity (i.e., 5-min runs), using the LBPPT technology, led to specific adaptations of the running pattern and spatial perception. While the former exhibited substantial locomotor changes immune to the visual background, spatial perception was also modified when the visual scene was coherent with respect to the novel sensorimotor context. Of course, one should remain cautious when extrapolating our findings to real locomotion on Mars, due to the existing constraints of the LBPPT analog (e.g., Earth-related vestibular cues, LBPPT ring-related information about the body position with respect to the feet . . .). Further experiments including longer periods of exposure may help investigate how the overall sensorimotor context may also differentially affect locomotor activity on Mars, exploring for instance fatigue and the transitions between different unweighting levels on muscular activation and synergies.

Data availability statement

The raw data supporting the conclusion of this article will be made available by the authors, without undue reservation.

Ethics statement

The present study involving human participants was reviewed and approved by the CERSTAPS Commitee (Ethical National Instance) (IRB00012476-2021-31-03-96). The patients/participants provided their written informed consent to participate in this study.

Author contributions

MK, PC, and LB designed and performed the experiment, analyzed data and wrote the paper; LC, PS, RC, MB, and CN designed and performed the experiment, analyzed data and reviewed the paper; CG, CM, BB, AH, FV, and TL designed the experiment and reviewed the paper. All authors contributed to the article and approved the submitted version.

Funding

This work was supported by grants from the French Space Agency (CNES- DAR 4800001107).

Acknowledgments

The authors wish to thank the Mediterranean Virtual Reality Center (CRVM) of Aix-Marseille University for technical support. The authors are also grateful to the students and participants who took part in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphys.2023.1201253/full#supplementary-material

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frontiers | Frontiers in Neural Circuits

TYPE Perspective
PUBLISHED 17 August 2023
DOI 10.3389/fncir.2023.1170395

OPEN ACCESS

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RECEIVED 20 February 2023
ACCEPTED 31 July 2023
PUBLISHED 17 August 2023

CITATION
Pathare NN, Fayet-Moore F, Fogarty JA, Jacka FN, Strandwitz P, Strangman GE and Donoviel DB (2023) Nourishing the brain on deep space missions: nutritional psychiatry in promoting resilience.
Front. Neural Circuits 17:1170395.
doi: 10.3389/fncir.2023.1170395

Nourishing the brain on deep space missions: nutritional psychiatry in promoting resilience

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The grueling psychological demands of a journey into deep space coupled with ever-increasing distances away from home pose a unique problem: how can we best take advantage of the benefits of fresh foods in a place that has none? Here, we consider the biggest challenges associated with our current spaceflight food system, highlight the importance of supporting optimal brain health on missions into deep space, and discuss evidence about food components that impact brain health. We propose a future food system that leverages the gut microbiota that can be individually tailored to best support the brain and mental health of crews on deep space long-duration missions. Working toward this goal, we will also be making investments in sustainable means to nourish the crew that remains here on spaceship Earth.

KEYWORDS

space, astronaut, mental-health, psychiatry, nutrition, food, microbiome, probiotics

Nourishing the brain in deep space

Deep space missions will test crews in unprecedented ways. The hazards of this hostile environment include unshielded ionizing radiation, prolonged isolation from loved ones, extreme physical confinement, a distance from Earth resulting in major communication delays and inability to resupply food and other essentials, physiological challenges of microgravity, and the psychological toll of living in a highly complex spacecraft susceptible to catastrophic engineering or human failures, with the ever-present knowledge that no one from the "outside" can help.

These hazards of deep space human exploration require mitigation if we are to protect the health and performance of the crew, demanding powerful, holistic, and feasible strategies to foster mental and physical resilience. Safeguarding brain health is of paramount importance to ensure cognitive performance and emotional regulation throughout the mission. Scientific consensus linking food and brain health propels our position that the deep space food system should offer a powerful tool for promoting resilience. This includes addressing the gut microbiome composition, which modulates mood, hormonal balance, and brain function and adaptation through neuronal and inflammatory effects (Berding et al., 2021; Shi et al., 2022). One such target is a form of bidirectional communication known as the gut-brain axis that depends on direct nerve firing, the release of hormones, and other bioactive molecules. It also offers a challenge: create bespoke diets contributing to diverse microbiomes, individually tailored to optimize physical and mental health.

In this Perspective, we describe the unique combination of spaceflight-associated challenges to brain health, the evolution of our current spaceflight food system, and the challenges associated with developing a deep-space food system. We then discuss the evidence base for nutritional psychiatry and break down the nutritional and psychoactive components of food. Finally, we review microbiome-based approaches to promote brain health and offer a vision for a future food system that aims at much more than just providing nutritional minimums but instead promotes health and resilience in humans wherever they explore.

The brain in space

Spaceflight's effects on human brain health range from cellular to social, including through neuroinflammation, sleep disruption, impacted cognitive performance, and psychosocial issues including poor team dynamics.

Deep space missions inherently involve dramatic increases in exposure to highly charged and energetic (HZE) ionizing radiation, which affects cellular function. Dose-relevant radiation studies have revealed direct effects on neuronal tissue (Raber et al., 2016; Jandial et al., 2018), functional decrements (Vlkolinsky et al., 2010; Blackwell et al., 2022), as well as oxidative stress and neuroinflammation (Zwart et al., 2021; Holley et al., 2022; Miller et al., 2022; Verma et al., 2022). Neuroinflammation is in turn associated with a wide range of maladies—including neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's diseases (Teleanu et al., 2022).

Astronauts experience a headward fluid shift in zero gravity which has been correlated with a decrease in the sensitivity of aroma perception which could contribute to a reduced daily caloric intake of 80 percent (Taylor et al., 2020). Spaceflight also poses challenges to the human sleep and circadian system, although the exact causes of such sleep disturbances remain unclear. In low-Earth orbit, astronauts sleep an average of 6 h/per night (Barger et al., 2014), which can significantly impair behavioral performance (Jewett et al., 1999). This occurs even though sleep medications are used at a rate approximately ten times higher in space than on Earth (Putcha et al., 1999; Barger et al., 2014; Wotring, 2015). Significant sleep and circadian disruptions have also been observed in space confinement simulations such as Mars520 (Basner et al., 2013), low-/artificial-light settings (Phillips et al., 2019), and ground simulations of a 24.6-h Martian day (Nguyen and Wright, 2010), despite the use of countermeasures (Barger et al., 2012). Inadequate sleep duration or quality has been linked to suboptimal cognitive, behavioral, and physical performance (Van Dongen et al., 2003).

To date, studies have not demonstrated major disruptions in cognitive performance during spaceflight (Strangman et al., 2014), but important caveats remain. Nearly every cognitive performance study in spaceflight has had serious shortcomings; too few subjects, low sensitivity of measures, limited coverage of cognitive processes, as well as task variability that has prevented meta-analysis across studies are all common (Strangman et al., 2014). In one rare mission, a case-controlled human study involving detailed cognitive testing before, during, and after a 340-day spaceflight revealed diminished cognitive performance that extended for at least 6 months post-flight (Garrett-Bakelman et al., 2019). This unique long-duration flight still only represented 35–40% of the anticipated duration of a mission for landing on Mars (at ~900 days). Intact cognitive performance in deep space missions thus remains a critical risk needing surveillance and mitigation.

Psychological health issues have occurred in spaceflight and analogs (Kanas and Manzey, 2008). These have included depression and anxiety (Stuster, 2010), as well as at least one suggestion of an in-flight and potentially behavioral-related emergency leading to an abrupt abort of the Soyuz T14-Salyut 7 mission (Morris, n.d.). Such behavioral health findings parallel reports on isolation studies on Earth (Lugg, 2005; Basner et al., 2013), and point to non-radiation-induced changes in brain health that result in behavioral health issues in settings that are far less resource constrained than spaceflight.

Finally, in addition to the impact on individuals, team performance challenges have arisen during spaceflight missions. In astronaut journals, the number of positive comments about team interaction decreases over the mission (Stuster, 2010). Reductions in team cohesion (e.g., subgrouping) have been reported in various analogs (Kanas et al., 2009; Basner et al., 2013; Tafforin et al., 2015), and communication with ground personnel decreases over time (psychological "closing") (Gushin et al., 2012). A meta-analysis of various mission types indicated that each team had at least one conflict by 90 days into their mission (Bell et al., 2019). The increasing distance from Earth causes communication delays of up to 22 min each way, and a Mars mission will isolate the crew even more, exacerbating many of these challenges.

Various approaches used on the International Space Station (ISS) to avoid or mitigate psychological, behavioral, and team issues are dependent upon real-time communications (calling family/friends, interaction with flight psychologists and psychiatrists, special events with ground personnel), resupply (special foods, surprise deliveries), and free time to gaze and photograph the beauty of Earth (Earth-viewing: a prominent de-stressing activity). Deep space missions will not offer most of these approaches.

The space food system

The US spaceflight food systems initially focused on the basic safety of consuming semi-solid foods. During the Mercury Program, once John Glenn demonstrated that humans could properly swallow applesauce, the focus was on providing engineered foods with appropriate calories and basic nutrients. This approach continued through the Apollo program with the addition of some food variety, but the system was limited to pastes or dehydrated meats, fruits, and vegetables (Perchonok and Bourland, 2002). Based on previous crew feedback regarding the importance of palatability, Skylab further improved the space exploration food system (Kerwin and Seddon, 2002). Research and development of the food system continued during the shuttle and ISS eras, and as missions extended to several months, the food system became more complex. Crews continued to highlight the criticality of the taste and texture of food to the overall success of missions. This criticality is punctuated by the nearly total lack of *in situ* food sources, complete reliance on Earth, and the need for the food system to be implementable in a closed, small, and constrained habitat.

The food requirements for a deep space Mars class exploration mission, 18–36 months, will surpass any experience that is equivalent in resource limitations to date. While there have been expeditions to remote places on Earth, many parameters such as total duration, time in deep space transit, time on a distant planet, number of spacewalks, etc., remain relatively undefined so far and present unique challenges in designing an ideal food system. We need to understand what a diverse crew will need, to endure the extreme spaceflight duration, and meet performance expectations. Even though the space food system has an essential role in the crew's survival, it is also part of an operational environment that has significant competition with other systems for mass, power, and volume. Also, it must not introduce additional risks. This means that the system must accomplish many critical functions with the lowest impact on the overall vehicle and mission architecture. This is incredibly challenging when the humans, vehicle design, and mission operations are only generally described based on experience and models. The food system is then guided only by known and emerging requirements and best practices.

Earth-based human food requirements are adjusted for spaceflight based on the mission parameters and the anticipated environmental impacts on the human. Mission parameters include the duration of the mission, the need to pre-deploy food, the ability to resupply food, to provide fresh foods during the mission timeframe (growing crops, cultured protein sources, etc.), and the crew performance requirements (physical and cognitive). The mission parameters determine the duration of preservation and the need to supplement micronutrients or for augmentation of the food system with freshly grown or cultured components. Each parameter must be assessed for safety and stability. All foods, whether processed and stored, or freshly grown/cultured, need to be safe to eat, nutritionally adequate, and palatable, meeting all the crew's needs. Each component of the food system must be robust so that the crew can rely on it. There is a long history of preserved foods that address reliability, but their lifespan is inadequate for the ∼5-year duration required to support the Mars exploration class mission because of the requirement to pre-deploy food to the planet's surface well in advance of the arrival of the crew. We also know that the preserved food component is inadequate to address micronutrient requirements throughout the period that the food system would be stored, and a Mars crew would consume it (Cooper et al., 2011, 2017; Perchonok et al., 2012; Douglas et al., 2020). Decrements in the food system used today include the degradation of labile vitamins essential for health as well as stability, palatability of the meal components, and adequate variety of food choices. Therefore, investment in the development of the capability to grow fruits and vegetables during spaceflight has increased significantly, as has the emerging capability to culture protein sources for spaceflight, while the technology and acceptability are maturing on Earth. New information on the likely critical components of foods beyond macro and micronutrients (i.e., bioactive compounds, fermentation products, bacteria themselves) is prompting consideration of other forms of augmentation that may yield improvements for nutrition, flavor and texture, and preservation.

While we have learned much about providing a safe, reliable, diverse, and palatable food system for low Earth orbit, there is still much work to be done to explore successful ways to drive a more sustainable food future as well as to enhance the current space food system that is based heavily on preserved foods with fresh and nutrient-rich foods frequently resupplied from Earth. The food system of the future must not only meet the caloric and nutritional needs of the astronauts but also provide psychological resilience and prevent and mitigate the effects of spaceflight stressors.

Food components critical for overall nutrition and brain health

Nutrition is one of the top three lifestyle factors that influence disease initiation and propagation in humans on Earth (Afshin et al., 2019). Its role is particularly paramount in space, where spaceflight hazards challenge the body and mind in unprecedented ways (Zwart et al., 2021). Foods and nutrition components required to maximize brain and cognitive function for astronauts on ISS or private citizens visiting commercial low Earth orbit destinations are likely to significantly differ from those that will be required on deep space missions. An adult's brain consumes significantly more energy from glucose (20%) than expected for its size (2%) for neural functioning, and unlike muscles (which utilize glycogen), the brain does not have stored energy reserves and is always metabolically "on." Hence, a balance of essential brain nutrients that includes long-chain omega-3 fatty acids, antioxidant vitamins (C and E), the b-vitamins including B12, and vitamin D, and the minerals iron, magnesium, and zinc together influence cognitive function and performance, brain development, oxygen transport, brain cell health, neurotransmitter function, brain structure, intercellular connections, and protect against oxidative stress (Tardy et al., 2020).

The impact of food on mental and brain health

Diet is critical to mental as well as physical health and offers new opportunities for the prevention and treatment of mental health problems, as well as for optimizing mental and brain health under particularly challenging conditions such as space missions (Marx et al., 2017).

Diet quality is now understood as a modifiable, independent risk factor for depression, which itself represents the most common and burdensome mental health condition globally (Dash et al., 2016), experienced in both spaceflight and analogs. The associations between diet quality and depression risk are seen across the lifespan (Jacka et al., 2011, 2013a,b; Borge et al., 2017; Lassale et al., 2019). Importantly, evidence from randomized controlled trials shows that dietary interventions can treat even severe depressive illnesses (Jacka et al., 2017; Bayes et al., 2022) as well as improve depressive symptoms in non-clinical populations (Firth et al., 2019). While dietary habits vary across cultures, the fundamentals of what comprises a "healthy diet" associated with less depression are broadly similar (Opie et al., 2017)—plant foods (vegetables, fruits, wholegrain cereals, legumes, nuts, and seeds), healthy fats from seafood and plants, and a reduction in or avoidance of foods high in refined carbohydrates, salt, saturated and trans fats, and other additives, particularly those classified as "ultra-processed foods," which are associated with poorer physical and mental health (Lane et al., 2021).

The multitude of mechanisms that link diet quality to mental health includes immune function, gut microbiota, brain plasticity, neurotransmitter and stress response systems, and gene expression (Marx et al., 2021). The range of mechanistic pathways implicated reflects the understanding that many aspects of mental illness do not just occur in the brain, but rather can be influenced by many bodily systems and processes. However, in adapting and optimizing brain health under extreme conditions such as those in deep space, animal studies suggest poor diet can impact cognition via inflammation and its effects on neurogenesis and hippocampal function is critical (Beilharz et al., 2015). The extensive evidence in this area is now supported by observational data in humans, wherein diet quality (Jacka et al., 2015) and dietary factors are clearly linked to the size of the hippocampus and other brain regions (Akbaraly et al., 2018; Croll et al., 2018). Moreover, intervention studies in humans have shown a rapid impact on cognitive function in young, healthy adults on western-type diets, high in saturated fats and added sugars (Stevenson et al., 2020). Highly relevant is the emerging evidence that a diet is enhanced for long-chain. omega-3 fatty acids and flavonoids via increased quantity and variety of plant foods and seafood led to better cognitive performance, among other parameters, in subjects undergoing closed chamber missions in the NASA Human Exploration Research Analog (HERA) (Douglas et al., 2022).

One of the key areas of investigation and promise relates to the human microbiota, which is now understood to influence all bodily systems and is, in turn, influenced by the brain and behavior. The largest number of microbes reside in the gut, where they break down elements of food that cannot be broken down by human enzymes, particularly plant fiber, and polyphenols. Current evidence links these dietary components, as well as fruits, vegetables, nuts, mono and polyunsaturated fatty acids (MUFA/PUFA), plant-based proteins, and—more widely—plant-focused and Mediterranean-style dietary patterns, to beneficial gut microbiota profiles, while animal proteins, saturated fatty acids, artificial sweeteners, and emulsifiers, as well as western diets more broadly, are linked to gut microbiota profiles associated with poor health outcomes (Berding et al., 2021). We discuss the microbiome further below.

Examples of novel components of a deep space food system

The current food system on ISS relies on mostly prepackaged processed foods and frequent resupply with fresh foods. Resupply will not be an option on deep space missions. A trip to Mars would require some of the food to be prepositioned on the planet's surface for many months in advance of the crew's arrival. There are concerns about the nutritional stability of the food system for that long of a period. If we are to provide a healthy food system to support a Mars mission crew, we must go beyond providing the minimum nutritional and caloric requirements. There are promising new food sources and potentially bespoke approaches to utilizing microbes that can help safeguard health.

Algae, which belong to their own kingdom, and Protista, (neither plant nor animal), may help to meet the needs for long-chain omega-3 fatty acids including DHA (Winwood, 2013), the predominant fatty acid in the brain (Weiser et al., 2016). Further, they can capture and utilize carbon in closed-loop ecosystems and food systems, being an extraordinary carbon sink. There are over 500 species of algae, providing not only DHA, but other key micronutrients not typically found in plants (vitamin B12), and a non-animal source of protein and long-chain omega-3 fatty acids. Further, unlike plants, algae harvests need fewer inputs (i.e., some species such as *Chlorella pyrenoidosa* can obtain all nutrients from air and water) and some can be harvested daily (Han et al., 2017). Algae can grow in a microgravity environment, making them a suitable option in space. Fungi, and specifically edible mushrooms, are the only unfortified and non-animal source of dietary vitamin D and are grown in controlled environments. UVB-exposed mushrooms provide more than 100% of daily vitamin D requirements (Blumfield et al., 2020). Given UVB exposure via the skin is not feasible in deep space, innovation with both fungi and algae foods may allow for the development of nutrient-dense foods that provide a multitude of not only nutrients, but also their corresponding bioactive compounds, possibly combating some of the challenges (Tang et al., 2021) of creating palatable and nutritious food for long duration missions.

It is unreasonable to assume that we can provide astronauts with all the freshly grown foods needed to optimize health and performance in deep space; we will need to rely in a large part on prepackaged foods. There is increasing recognition of the importance of plant bioactive compounds (non-nutrient components) as a primary driver of health benefits beyond just the nutritional and caloric value (Rodriguez-Casado, 2016). About 20 years ago, research showed that flavonoids in apples explained most of their antioxidant properties, whereas vitamin C explained only 0.4% of the antioxidant activity (Liu, 2003). The health benefits associated with eating a rainbow of color (bioactive pigments) were recently proven (Blumfield et al., 2022). Further, color is a natural visual cue for food consumption (Pennock et al., 2023), and added color via bioactive compounds in food may provide further benefits related to food intake and wellbeing in deep space. There are more than 10,000 individual bioactive compounds in plant foods to date (Zhang et al., 2015), and enhancing their preservation in prepackaged foods for consumption in space should be a priority, especially given many have prebiotic properties linked to improved gut health (Plamada and Vodnar, 2021).

The role of microbes in a deep space food system

Our microbiome is an entire second genome, one larger and more variable than our own. At the latest estimate, the human genome contains just under 20,000 protein-coding genes (Piovesan et al., 2019), with greater than 99.5% matching identity across our entire species. The average person's microbiome is estimated to contain roughly one hundred times this number of genes (Qin et al., 2010). This functional power is further revealed by metabolomics, where nearly half of the metabolites found in blood are influenced by microbiome composition (Visconti et al., 2019). Most of our microbes live in our gastrointestinal tract, wherein a given person there typically exists hundreds of unique species of bacteria and lesser numbers of archaea, fungi, and bacteriophage (Huttenhower et al., 2012). These microbes are highly heritable in nature, some of which are passed to us from our mother (Grieneisen et al., 2021). The others reflect the people, experiences, and challenges that define our lives (Valles-Colomer et al., 2023).

Beyond controlling what our microbes are exposed to, programmed in our genome are mechanisms to influence and preserve the composition of our gut microbiome. These include our rich complement of immune cells, secretion of mucin glycans that feed commensal bacteria (Tailford et al., 2015), the release of bile salts (Schubert et al., 2017), lipocalin-2 (Flo et al., 2004), and antimicrobial peptides like beta-defensins (Ostaff et al., 2013) which largely target pathogens.

Unlike our genome, the microbiome can be disrupted by external factors, including antibiotics, infection, and a sub-optimal diet. Like any ecosystem, disruption of its key members can wreak havoc on its biology. In the past decade the importance of this balance has been increasingly highlighted, with the microbiome–and its disruption–having been linked to how we respond to diet (Kolodziejczyk et al., 2019) and drugs (Weersma et al., 2020), fight infection (Libertucci and Young, 2019) and cancer (Sepich-Poore et al., 2021), and even behave (Dinan et al., 2015). For example, in observational studies, individuals with major depressive disorder (MDD) have distinct gut microbiota profiles compared to healthy controls (Naseribafrouei et al., 2014; Jiang et al., 2015; Kelly et al., 2016; Zheng et al., 2016; Strandwitz et al., 2018; McGuinness et al., 2022).

The field is unraveling mechanistically how our microbes could be driving these observations, but there appears to be direct crosstalk between our microbes and our immune (Danping et al., 2020), endocrine (Neuman et al., 2015), and nervous (Fung et al., 2017) systems. This is mediated largely by secreted metabolites [such as neurotransmitters (Strandwitz, 2018)], protein-ligand interactions, and/or diet (Kolodziejczyk et al., 2019) or even drug interactions (Weersma et al., 2020). Beyond combating disease and making people live better lives here on Earth, unlocking the power of the microbiome could help humanity become multi-planetary. Manipulating the microbiome has the potential to combat spaceflight hazards, such as protecting against radiation damage (Guo et al., 2020), increasing resilience to stress (Berding et al., 2022), optimizing nutrition (Zeevi et al., 2015), and responding appropriately to medications (Gopalakrishnan et al., 2018). As such, there is a high potential in using our second genome as a "backup crew," but to do so we need proper tools.

Probiotics

At its core, the microbiome is microbes, and one way to change it is through the consumption of probiotics. Probiotics are defined as "live microorganisms that are intended to have health benefits when consumed or applied to the body" (Hill et al., 2014). As such, ideal processes to find probiotics include microbiome research, leveraging a combination of human cohorts and preclinical models, and identifying specific bacterial strains or combinations thereof which have a potential impact on a desired aspect of host biology. These strains are then put through manufacturing processes to ensure viability and stability, tested in placebo-controlled trials to generate confidence they are safe and do what we think they can, and then distributed either as a consumer product or drug with appropriate health claims, backed by strong data packages.

Unfortunately, while there are exceptions, many bacteria sold today have little or no data to support being a "probiotic." Instead, the probiotic industry is dominated by products containing bacteria that are either absent from or are a very minor constituent of the adult gut microbiome, such as bacteria derived from the soil (e.g., *Bacillus*), the food/dairy industries (e.g., *Lactobacillus*, *Lactococcus*), and infants (*Bifidobacterium*). While these bacteria are largely safe, they represent a tiny fraction of the diversity and functional potential of the adult microbiome. To provide metrics, there are a few dozen species of bacteria sold as consumer probiotics, and very few are used as drugs or medical foods. In contrast, in each human, there are estimated to be several *hundred* unique bacterial species, and nearly 5,000 species in the collective human gut microbiome, most of which have no cultured representatives (Nayfach et al., 2019) (while each person has a few hundred species, not everyone has the same species).

The status is simple—today we do not have probiotics containing 99% of the diversity of what exists within us. This means we do not have a way to introduce these back into people who could benefit from their functions, except for fecal microbiome transplants. However, through advances in cultivation methods, the creation of comprehensive strain collections, and throughput mapping of host-microbiome interactions, the "next generation" of probiotics is coming.

Prebiotics

A secondary means to modulate the microbiome is with prebiotics—often defined as "a fermented ingredient that results in specific changes in the composition and/or activity of the gastrointestinal microbiota, thus conferring benefit (s) upon host health" (Davani-Davari et al., 2019). In other words, something you eat impacts your microbes in a way beneficial to the system. Like probiotics, the field of prebiotics is still largely uncharted. Our food contains many components that our microbes use for their own metabolism—such as glycans, oligosaccharides, flavonoids, and peptides. Some have been purified and are commonly added to food or sold as supplements, like wheat dextrin, inulin, psyllium, and methylcellulose.

However, recent work has highlighted there is not a one size fits all approach. Different fibers (cellulose, inulin, pectin, and mixed fiber) elicited differential microbiome and metabolic signatures in mice with normalized microbiomes (Murga-Garrido et al., 2021). Similarly, in mice colonized with the microbiome from nine different human donors, significant variation of three different fiber sources (pea, orange, and barley bran) was seen amongst the different microbiome backgrounds (Delannoy-Bruno et al., 2021). This is further supported by a series of human studies monitoring the glycemic responses of individuals challenged with normalized diets—responses can vary widely. Some people had spikes with chocolate, some with bananas, and some with bread, an effect that appears to be driven by the composition of their microbiome (Zeevi et al., 2015; Korem et al., 2017). This highlights that we need a better understanding of the interactions between our microbes, their functions, and our food.

Historically, major challenges to advancing the next generation of prebiotics revolve around not knowing the chemical composition of our food, difficulties in producing more complex ingredients, and the absence of datasets directly interrogating how food and food ingredients impact the microbiome. It's also important to reiterate that not all people have the same microbes, and in some cases, people simply will not have the microbes that certain prebiotics or diets are designed to support. This is a solvable problem if we can also deliver the right microbes in combination with the food. Reduced costs for microbiome sequencing, efforts to broadly annotate food chemistry, and better methods to track diet data leveraging digital health tools—coupled with screening efforts of food ingredients and human gut microbes—will pave the way for the future of precision prebiotics and nutrition.

The future

A long-duration deep space mission where a combination of the major environmental hazards will challenge the physical and mental resilience of the crew will require a holistic approach to countermeasures. The food system can play a major role in safeguarding health and performance beyond just providing the minimum: nutrients and calories. It can be optimized using a variety of new food sources. Lab-grown animal products such as cultured meats and dairy could provide fresh supplies of sufficiently dense protein sources (Handral et al., 2022; Waltz, 2022). Algae and engineered plants that are optimized for growth in space can provide nutrients and bioactive compounds necessary for brain and physical health (Holly, 2019; Stewart et al., 2021).

In addition to novel methods to provide the daily requirements of macronutrients such as protein, fats, and carbohydrates, a deep space food system could be enhanced with an armamentarium of probiotics, representative of the diversity and functions we have evolved with, coupled with prebiotics to selectively support them. Such microbiome-modifying tools could be used to augment an astronaut's biology and come with several advantages. Probiotics are user-friendly, self-replicating, and could be swallowed before launch and be designed to remain within the traveler's gastrointestinal tract. By using appropriate prebiotics or dietary inputs (Abramson et al., 2019; Jimenez et al., 2019), these microbes can then become internalized bio-factories, producing essential nutrients otherwise difficult to attain with space diets, such as B and K vitamins (Hill, 1997), or other factors that modulate host systems relevant for a given stress. Leveraging synthetic biology, probiotics can also be engineered to produce and deliver drugs and other payloads (Canale et al., 2021; Russell et al., 2022), serve as biosensors for health risks (Chang et al., 2021), and even be improved to withstand various space-relevant stressors, like ionizing radiation (Jimenez et al., 2019). This provides a powerful technological tool—built on the brilliance of our own biology—that requires no change in the routine of the astronaut, and one that can be personalized ahead of the journey to space (Holmes et al., 2022).

The hazards of deep space missions demand nothing short of radical approaches to safeguarding the health of the crews that dare. The damage to the brain from ionizing radiation and the stressors of microgravity, isolation, and physical confinement can be at least partially mitigated by a robust and holistic food system, developed with state-of-the-art methods providing fresh proteins and vegetable products, and supplemented with bioactive compounds and personalized prebiotics and probiotics. As we build a novel deep-space food system, we also invest in sustainably feeding future generations on *terra firma*.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

DD organized the topic and recruited the authors. NP organized the manuscript and assisted with writing the manuscript. All authors wrote the portions of the manuscript.

Funding

DD, JF, and GS are currently and PS was previously supported by the Translational Research Institute for Space Health (TRISH) through NASA NNX16AO69A.

Conflict of interest

PS was a founder, employed by, and holds equity in Holobiome, Inc.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Neural Circuits

TYPE Original Research
PUBLISHED 22 September 2023
DOI 10.3389/fncir.2023.1163346

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RECEIVED 10 February 2023
ACCEPTED 29 August 2023
PUBLISHED 22 September 2023

CITATION
Nosikova I, Riabova A, Kitov V and Tomilovskaya E (2023) Corticospinal excitability after 5-day Dry Immersion in women.
Front. Neural Circuits 17:1163346.
doi: 10.3389/fncir.2023.1163346

Corticospinal excitability after 5-day Dry Immersion in women

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In light of the development of manned astronautics and the increasing participation of women in space flights, the question of female body adaptation to microgravity conditions becomes relevant. Currently, one of the important directions in this issue is to study the effects of support withdrawal as a factor of weightlessness on the human sensorimotor system. Dry Immersion is one of the well-known ground-based models, which adequately reproduces the main physiological effects of space flight. The aim of this study was to evaluate the changes in motor evoked potentials of the lower leg gravity-dependent muscles in women after a 5-day Dry Immersion. We analyzed evoked responses to transcranial and trans-spinal magnetic stimulation. In this method, areas of interest (the motor cortex and lumbosacral thickening of the spinal cord) are stimulated with an electromagnetic stimulus. The experiment was conducted with the participation of 16 healthy female volunteers with a natural menstrual cycle. The thresholds, amplitudes, and latencies of motor potentials evoked by magnetic stimulation were assessed. We showed that 5-day exposure to support withdrawal leads to a decrease in motor-evoked potential thresholds and central motor conduction time, although changes in motor response amplitudes were ambiguous. The data obtained correspond to the results of previous research on Dry Immersion effects on the sensorimotor system in men.

KEYWORDS

dry immersion, microgravity, transcranial magnetic stimulation, trans-spinal magnetic stimulation, support unloading, motor evoked potentials, hypogravitational hyperreflexia

1. Introduction

The key problem of long-term space flights (SF) is extreme conditions for the human body. The space crew needs to live and work in this environment for a long time. Additionally, constant dangers and a high probability of unforeseen emergencies may require an instant shift of attention. Therefore, for successful work in these conditions, it is necessary to correctly assess the capabilities of the body as a whole (Grigoriev and Ushakov, 2013). Under the conditions of constant and continuous stressors, a favorable psychological climate on the spacecraft is crucial, and the presence of women will contribute to its formation and maintenance. Even though, at this date, ~600 people have participated in space missions, only 65 of them were women.

In their review article, Mark et al. (2014) noted that the physiological adaptation to weightlessness in women and men is different. For example, the specifics of vascular resistance dynamics, circulating blood volume regulation, and a more pronounced course of space motion sickness are noted in women; however, clinically significant visual and hearing impairments caused by SF are observed only in male astronauts. This study draws attention to the problem that there is a lack of data to narrow down the features of female body adaptation to the conditions of SF (Mark et al., 2014). In another study, the same authors pointed out the sex differences in the musculoskeletal system, which entails the need to consider astronauts' sex when developing countermeasures for long-term and extra-long-term SF (Mark, 2007; Holt et al., 2016).

Previously, for the first time, a comprehensive experiment to study the effects of 3-day support unloading on the sensorimotor system in women of reproductive age was carried out. It showed the possibility and safety of such exposure, as well as the comparability of the results with data obtained in similar experiments with the participation of male volunteers (Amirova et al., 2021; Tomilovskaya et al., 2021; Nosikova et al., 2021a).

The changes in motor function caused by microgravity exposure may affect astronauts' performance, and although there are many studies of the sensorimotor system in SF and model experiments, the mechanisms of the occurring changes are still not fully understood. Thus, research in this field continues to be of high importance. It is known that exposure to real or simulated microgravity leads to the development of hypogravitational motor syndrome (Kozlovskaya et al., 1988), which is defined by both structural and functional alterations in the neuromuscular system. Changes in brain volume, microstructure, and connectivity were observed after SF (Koppelmans et al., 2016; Jillings et al., 2020) and head-down tilt bed rest (Koppelmans et al., 2017; Lee et al., 2021), and the increase in excitability of motor responses was noted during support withdrawal (Zakirova et al., 2015) and parabolic flight (Davey et al., 2004; Badran et al., 2020). At the molecular level, changes in neuromuscular junctions, such as a decline in the postsynaptic excitatory potential amplitudes, a change in the enzyme activity, and a shift in the level of the ion equilibrium potentials, were reported in both animal (Tyapkina et al., 2006; Chibalin et al., 2018; Vilchinskaya et al., 2018) and human studies (Shenkman et al., 2017; Shenkman, 2020).

As it is not possible to use invasive techniques to study the human brain and the spinal cord during SF or under the conditions of support withdrawal, a different method is required. In the past couple of decades, the transcranial magnetic stimulation (TMS) technique has received widespread use in the fields of space medicine and physiology (Davey et al., 2004; Roberts et al., 2010; Badran et al., 2020; Romanella et al., 2020). Besides its contribution to studying cognition, behavior, and neuropathology, TMS of the motor cortex has a well-established role in clinical neurophysiology. In this method, a target area is stimulated with electromagnetic stimuli, which generates suprathreshold current in the brain. Standard TMS parameters that are analyzed in clinical and research studies include motor thresholds, motor evoked potential (MEP) amplitudes, MEP latencies, etc. Each of these variables has physiological correlates; for instance, MEP thresholds reflect the excitability of cortical or spinal neurons, but at the same time, they depend on the individual arousal level and environmental noise. Amplitudes of the evoked responses are often used to study corticospinal excitability, and the difference between MEP latencies to stimulation of the motor cortex and spinal roots, called central motor conduction time (CMCT), is calculated to estimate corticospinal conductibility (Rossini et al., 2015). Moreover, MEPs to TMS depend on physical individual features such as age, body constitution, and height. Regarding sex-specific differences, there is evidence that women show smaller latencies of responses in upper limb muscles to both cortical and spinal stimulation when compared to men (Cantone et al., 2019). Previously, TMS studies in the field of space physiology were conducted in parabolic flight (Davey et al., 2004; Badran et al., 2020) and long-term bedrest (Roberts et al., 2010), but their results are contradictory and the samples are very small. Moreover, there is almost no data on female subjects and how they compare to men.

Given the above, our work was dedicated to the study of changes in the sensorimotor system in women after exposure to simulated microgravity. We chose Dry Immersion (DI) as one of the most widely used ground-based microgravity models, which adequately reproduces the main physiological effects of weightlessness (Tomilovskaya et al., 2019) and conducted a comprehensive experiment to assess the characteristics of motor responses evoked by transcranial and trans-spinal magnetic stimulation in women before and after exposure to 5-day DI.

2. Materials and methods

2.1. Participants

A total of 16 healthy female volunteers (mean age 28.06 ± 4.85 years) of reproductive age participated in this study. The participants' height did not exceed 180 cm, and their body weight was not more than 75 kg. All subjects had a natural menstrual cycle (MC) and no history of motor impairments or neurological diseases. Each participant signed an informed consent after the experimental procedures, and possible consequential effects and risks were explained to them.

This study was approved by the Bioethical Commission of the Institute of Biomedical Problems of the Russian Academy of Sciences (Protocol No. 615 of 6 June 2022) and fully complied with the principles of the Declaration of Helsinki.

2.2. Experimental design

The study was carried out at the Dry Immersion (DI) facility (Tomilovskaya et al., 2019), which is a part of the unique scientific installation "Medical and technical complex for testing innovative technologies of space biomedicine in the interests of supporting orbital and interplanetary missions and for the development of practical healthcare" of the Institute of Biomedical Problems, Russian Academy of Sciences, and at the unique scientific installation "Transgenbank." Participants spent 5 days in the immersion bath (Figure 1), with the restriction of motor activity; among other factors, lower limb movements were limited. The water temperature in the bath was kept at the level of 33 ± 1°C. During hygiene procedures scheduled in the evening, the subjects were lifted out of the bath for no longer than 15 min, and most of that time they remained in the supine position. The subjects were also raised from the bath during the day for certain short-term experimental examinations that were also carried out in the supine position. The crew, which included a medical doctor, an assistant, and a technician, provided 24-h monitoring of the participants' health and the condition of the technical equipment. In their free

FIGURE 1
View of a dry immersion bath with the subject and the crew. Image credit: IBMP/Oleg Voloshin.

time, subjects were allowed to read, work on a laptop, watch TV, talk on the phone, etc.

Half of the experimental group (nine participants) additionally got the food supplement “Goldoferrin C” starting from the 1st day of DI until the 29th day of the recovery period. “Goldoferrin C” contains human lactoferrin, which is a globular glycoprotein of the transferrin family and is widely present in various secretory liquids such as milk, saliva, tears, and nasal gland secretion. This protein is considered a multifunctional factor in constitutive immunity, tissue differentiation, and cell activation. It also serves as an anabolic factor, promoting bone mass growth. The food supplement “Goldoferrin C” was taken daily: twice a day (in the morning and the evening) during DI and on the day of its completion, then only once a day in the morning. The supplement intake was carried out at least 30 min before the meal. Placebo was used in the control group.

2.3. Magnetic stimulation procedure

Experimental sessions were conducted according to the schedule (Figure 2). There were seven sessions in total: 4 before DI (14, 7, 6, and 3 days before the start of DI, baseline studies), one on the day of DI completion, referred to as R+0, and 2 during the recovery period (on the 3rd day and the 6th day after DI accomplishment, referred to as R+3 and R+6). Every experimental stage started on a specific day of the MC.

Participants were instructed to abstain from alcoholic and tonic drinks the day before each session. During the procedure, the subjects lay prone, relaxed, and with their eyes open. A special rigid cushion was placed under the ankles for better relaxation. Transcranial and trans-spinal magnetic stimulation (MS) was used to obtain MEPs from the soleus and gastrocnemius (lateral head) muscles of the right leg.

Transcranial MS was delivered with the eight-shaped coil (DB-80 Butterfly) of the MagPro X100 magnetic stimulator (Medtronic, Denmark). Stimuli were directed to the area of cortical motor projections of the right lower leg muscles (Figure 3A). First, the intersection point of the vertex and the line connecting the pre-auricular points was determined, and then the coil was placed 1–2 cm to the left from that point and was gradually moved to the position at which stimulation was followed by the MEPs with the greatest amplitude and a constant shape. Trans-spinal MS was delivered using a flat round coil with an outer diameter of 114 mm. As in the case of transcranial MS, the coil was first placed at the level of L5–S1 segments of the lumbar spine, and then its position was adjusted to achieve the largest MEPs (Figure 3B). The stimulation area was picked in such a way that MEP amplitudes were generally stable, which means MEPs had a constant shape and their amplitudes were similar. Motor responses of soleus and gastrocnemius muscles were recorded with bipolar surface silver-chloride electrodes that were placed in the center of the muscle belly projections with a 20-mm interelectrode distance (Figure 3C). Electromyographic signals (Figure 3D) were recorded using a Viking Quest 4-channel myograph (Viasys, USA) with a 2-Hz to 10-kHz passband. The sensitivity band was 0.1 μV to 10 mV, and the input noise did not exceed 40 μV.

After obtaining proper coil positioning, we first retrieved the resting MEP thresholds. For this, we decreased or increased the stimulation magnitude in steps of 2–5% of maximal output until reaching the minimal stimulus magnitude to evoke motor responses of 20–50 μV amplitude with 50% or more probability. That magnitude was taken as a threshold (Nikitin and Kurenkov, 2003). The muscle relaxation during threshold evaluation was monitored *via* a real-time electromyogram (EMG). We then increased stimulation magnitude to 80% of maximal output during transcranial MS and to 70% during trans-spinal MS and recorded at least eight evoked responses. MEPs for transcranial and trans-spinal MS are referred to as “cortical MEPs” and “spinal MEPs,” respectively.

2.4. Data processing and statistical analysis

MEP data were extracted from muscle curves using the Viking Quest 11.1 software, and the muscle response’s raw latency and amplitude values for each stimulus were obtained. For each subject, we evaluated MEP thresholds, mean peak-to-peak amplitudes at chosen stimulation magnitudes, and mean latencies (the time interval between the MS artifact and the first deflection of the muscular response from the EMG baseline) at four registration points, namely, baseline (average of four baseline points; outliers were excluded), R+0, R+3, and R+6. We also evaluated CMCT, which was calculated with the following formula: CMCT = cortical MEPs latency—spinal MEPs latency.

For demonstration purposes, threshold, amplitude, and latency values were presented as mean ± SEM of percent changes from baseline, which was taken as zero. Statistical analysis was performed with the GraphPad Prism 8 software. Data normality was assessed using the Kolmogorov-Smirnov test. For normally distributed datasets, mean values were compared using a repeated measures one-way ANOVA with a *post-hoc* Tukey’s multiple comparisons test. In cases where data was not normally distributed, we used the Friedman test with a *post-hoc* Dunn’s multiple comparisons test. The data were assumed to be statistically significant at $p<0.05$.

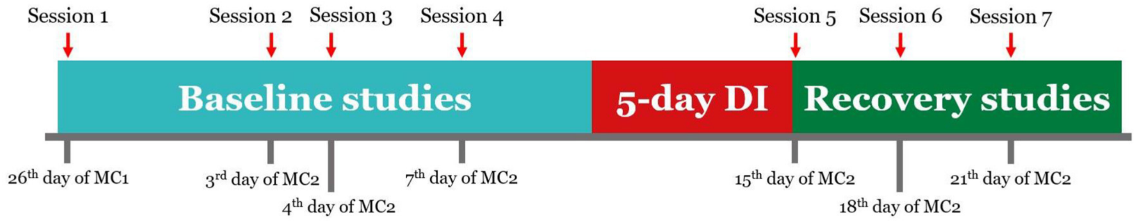

FIGURE 2
Schedule of the experiment. Sessions 1-4 were conducted 14, 7, 6, and 3 days before the start of DI. Session 5 was conducted on the day of DI completion. Sessions 6 and 7 were conducted 3 and 6 days after DI. MC1, MC2—two consecutive menstrual cycles.

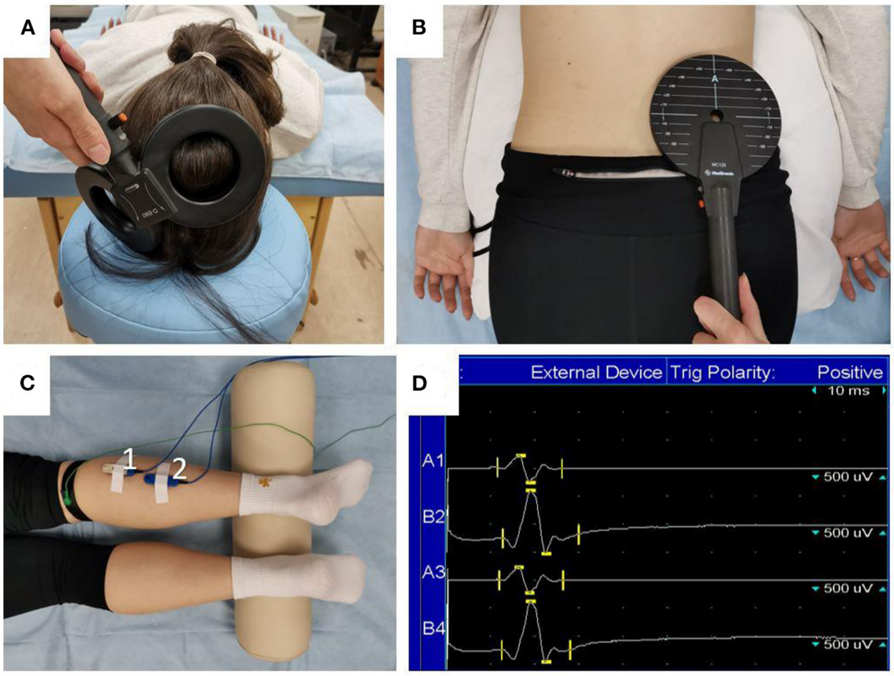

FIGURE 3
Magnetic stimulation procedure. The position of the stimulator's coil during transcranial **(A)** and trans-spinal **(B)** MS, and the placement of the surface electrodes **(C)** to record MEPs: 1—gastrocnemius muscle (lateral head); 2—soleus muscle. Raw EMG tracings **(D)** are presented for two recordings of MEPs in the gastrocnemius (lines A1 and A3) and soleus (lines B2 and B4) muscles.

3. Results

3.1. Goldoferrin C vs. control

The group of participants who got the food supplement "Goldoferrin C" during the experiment did not statistically differ from the control group in terms of MEP thresholds, amplitudes, and latencies. Thus, two groups were combined. The following are the overall results for 16 volunteers.

3.2. MEP thresholds

On the day of DI completion, spinal MEP thresholds decreased compared with baseline in both studied muscles (Figure 4): by 9.2 ± 2.7% in m. gastrocnemius ($p = 0.042$) and by 9.5 ± 2.4% in m. soleus ($p = 0.017$). During the recovery period, threshold values returned to baseline. Cortical MEP thresholds slightly decreased after DI completion: by 2.4 ± 2.2% in m. gastrocnemius and by 2.1 ± 2.5% in m. soleus. Interestingly, the biggest decrease was observed in the soleus muscle on the 3rd day after DI completion and reached 5.8 ± 2.9%.

3.3. MEP amplitudes

The dynamics of spinal MEP amplitude changes during the experiment differed between the subjects. More specifically, seven subjects showed an increase in spinal MEP amplitudes after DI completion in both studied muscles. The other seven subjects had an amplitude increase in one muscle but a decrease in another one. Two subjects showed a decrease in amplitudes in both muscles.

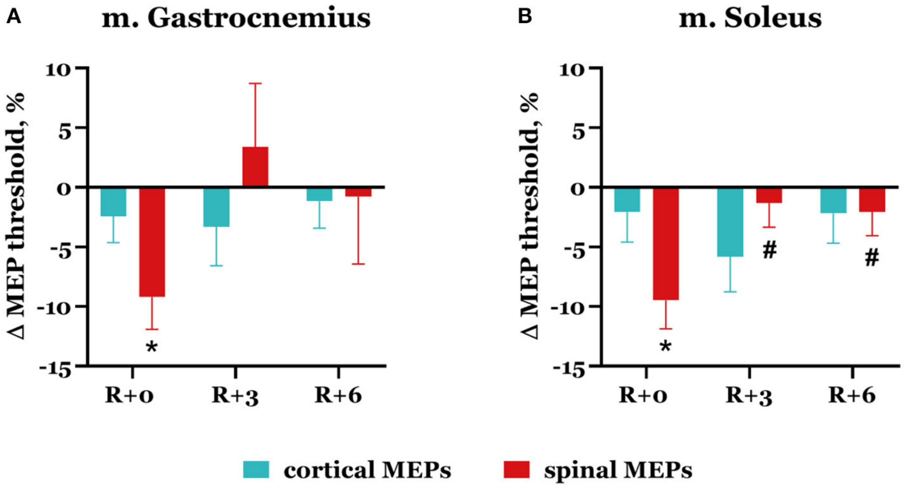

FIGURE 4
Percent changes from baseline of cortical (blue bars) and spinal (red bars) MEP thresholds in gastrocnemius **(A)** and soleus **(B)** muscles. Data are presented as mean ± SEM; baseline values are taken as zero. R+0—the day of DI completion; R+3, R+6—3rd and 6th days after DI. **p* < 0.05 vs. baseline; #*p* < 0.05 vs. R+0.

After DI, spinal MEP amplitudes increased in the gastrocnemius muscle in 10 subjects overall by 46.1 ± 9.3% (Figure 5A) and the soleus muscle in 11 subjects by 98.0 ± 46.5% (Figure 5B). For six participants, amplitudes decreased by 25.9 ± 4.3% in the gastrocnemius muscle (Figure 5C), and for five participants, by 37.8 ± 4.5% in the soleus muscle (Figure 5D). These effects were more prominent in the soleus muscle. Generally, a degree of increase in amplitude was greater than a decrease. The described changes persisted in the recovery period, although by the 3rd day after DI, amplitude values had partially returned to baseline (Table 1). None of these changes were statistically significant.

In the group of nine subjects that showed a decrease in spinal MEP amplitudes in one or both muscles, only one participant had an increase in spinal MEP threshold after DI completion, and only in the soleus muscle. It is worth noting that the spinal MEP amplitudes of this participant varied greatly even in the baseline studies. Such variability was also observed in another participant, but only about spinal MEP amplitudes in the soleus muscle. For the rest of this group (seven subjects), spinal MEP amplitudes in baseline sessions were mainly stable, and a common decrease in spinal MEP thresholds was observed (Figure 4).

In the majority of cases, the decrease in spinal MEP amplitude was accompanied by a decline in cortical MEP amplitude after DI completion. Although there were exceptions, specifically, one of the two participants that showed a decrease in spinal MEP amplitudes in both muscles had an increase in cortical MEP amplitudes in both muscles compared with baseline. Moreover, for some of the subjects, an increase in spinal MEP amplitude was coupled with a decrease in cortical MEP amplitude. In total, cortical MEP amplitudes increase after DI was observed in 10 subjects, of whom 6 exhibited a decrease in spinal MEP amplitudes. In the gastrocnemius muscle, cortical MEP amplitudes increased by 81.5 ± 24.7% in 8 participants (Figure 6A), and in the soleus muscle, by 31.7 ± 10.3% in 7 participants (Figure 6B). The decrease in cortical MEP amplitudes in gastrocnemius muscle was observed in 8 participants and reached 19.8 ± 5.3% (Figure 6C); in the soleus muscle, it was observed in 9 participants, reaching 39.9 ± 7.7% (Figure 6D). Cortical MEP amplitudes decreased in both muscles in 7 subjects. Interestingly, as in the case of spinal MEPs, the 6th day of the recovery period was marked by a repeated increase or decrease of cortical MEP amplitudes, even if on the 3rd day after DI amplitudes partially returned to baseline (Figures 6A, C, D, Table 1). All the described changes were not statistically significant.

It should be noted that cortical MEP characteristics varied more in baseline studies compared with spinal MEP characteristics. For instance, instability of the cortical MEP threshold or amplitude values was observed in 10 subjects. The cases of cortical MEP amplitudes increasing on the day of DI completion compared with baseline were more often accompanied by a decrease in cortical MEP thresholds, whereas when amplitudes decreased, thresholds predominantly did not differ from baseline.

3.4. MEP latencies and CMCT

Spinal MEP latencies increased after DI in both studied muscles: by 4.39 ± 2.2% in m. gastrocnemius and by 3.22 ± 1.65% in m. soleus (Figure 7), but these changes were not significant. Cortical MEP latencies, on the contrary, slightly decreased in the same experimental session, reaching 0.75 ± 1.06% and 1.72 ± 0.79% in the gastrocnemius and soleus muscles, respectively. By the third day of the recovery period, spinal MEP latencies returned to baseline; they averaged out at 0.66 ± 1.31% in the gastrocnemius muscle and at 0.62 ± 1.55% in the soleus muscle. At the same time, cortical MEP latencies continued to decrease: their mean values were −2.29 ± 0.97% and −3.78 ± 0.88% lower than baseline ($p = 0.0044$) in the gastrocnemius and soleus muscles, respectively.

Naturally, mean CMCT decreased on the day of DI completion compared with baseline (Figure 8). In baseline studies, the mean CMCT in the group was 17.83 ± 0.40 ms in the gastrocnemius

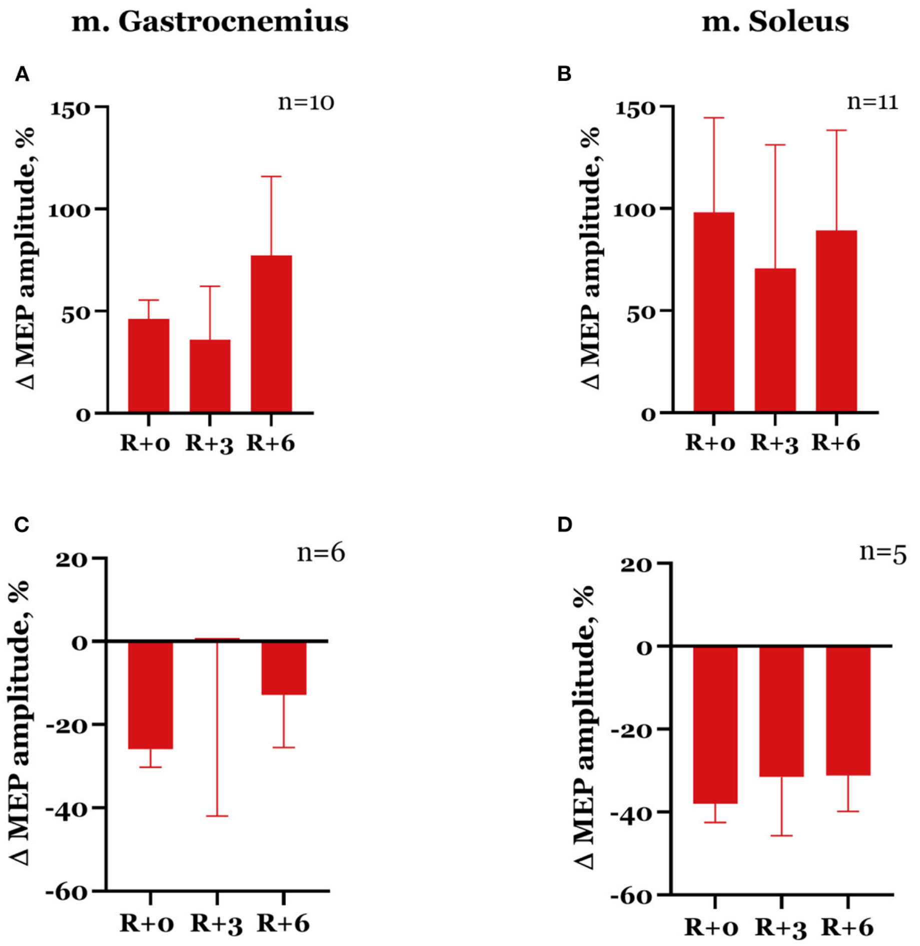

FIGURE 5
Percent changes from baseline of spinal MEP amplitudes in gastrocnemius **(A, C)** and soleus **(B, D)** muscles. Data are presented as mean ± SEM; baseline values are taken as zero. R+0—the day of DI completion; R+3, R+6—3rd and 6th days after DI.

muscle and 18.18 ± 0.38 ms in the soleus muscle. On the day of DI completion, CMCT was 17.06 ± 0.37 ms and 17.22 ± 0.38 ms in the gastrocnemius and soleus muscles, respectively, although this decrease was not statistically significant. A further decrease observed in the soleus muscle on the 3rd day of the recovery period showed statistical significance compared with baseline: CMCT was 16.92 ± 0.46 ms ($p = 0.019$).

4. Discussion

4.1. General effects

After 5-day DI, we observed a decrease in MEP thresholds in gastrocnemius and soleus muscles (Figure 4), which was significant for trans-spinal MS, and a decrease in CMCT (Figure 8) in women. However, the changes in spinal and cortical MEP amplitudes in both studied muscles were ambiguous after DI completion (Figures 5, 6).

The decrease in MEP thresholds for both trans-spinal and transcranial MS and the increase in spinal MEP amplitudes in the majority of the group reflect the phenomenon of hypogravitational hyperreflexia (Kozlovskaya et al., 1988), which develops in the microgravity environment. Previously, hypogravitational hyperreflexia development on the spinal level was shown in similar immersion experiments: 5-day DI with the participation of male volunteers (Nosikova et al., 2021b) and 3-day DI with the participation of female volunteers (Nosikova et al., 2021a). There is also evidence of an increase in spinal excitability in the model of unilateral lower limb suspension (Clark et al., 2006, 2007). The majority of researchers who studied spinal reflexes in humans and animals (rats) under the conditions of SF or model experiments noted a decrease in reflex thresholds and an increase in their amplitudes (Egawa et al., 2000; Kornilova and Kozlovskaya, 2003; Zakirova et al., 2015; Tomilovskaya et al., 2019). However, the observed tendency toward a decrease in cortical MEP thresholds may suggest that hyperreflexia develops not only on the spinal level but also on the cortical level. The decrease in CMCT while spinal MEP latencies increased (Figure 7) suggests that corticospinal conductibility also increases after DI.

It is worth noting that in TMS studies conducted in other ground-based models of microgravity, there are inconsistencies in MEP characteristics' dynamics. For instance, in the parabolic flight model, an increase in cortical MEP amplitudes (Davey et al.,

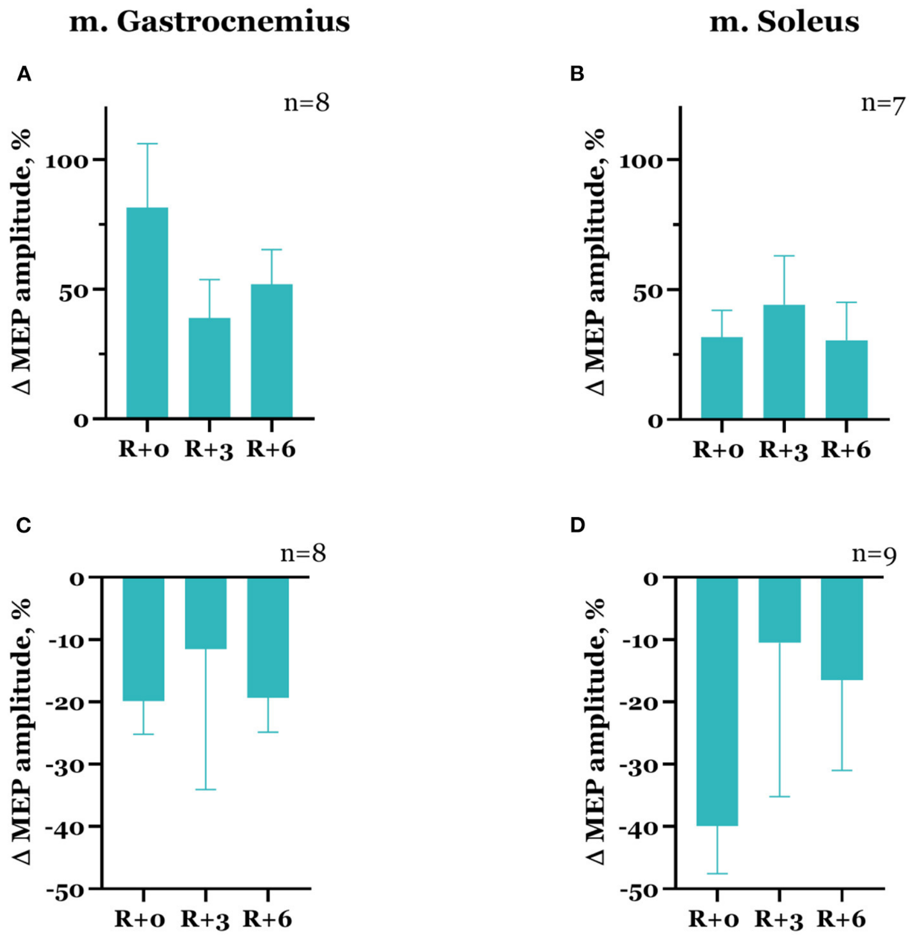

FIGURE 6
Percent changes from baseline of cortical MEP amplitudes in gastrocnemius **(A, C)** and soleus **(B, D)** muscles. Data are presented as mean ± SEM; baseline values are taken as zero. R+0—the day of DI completion; R+3, R+6—3rd and 6th days after DI.

TABLE 1 **MEP amplitudes mean ± SEM percent changes from baseline.**

	Gastrocnemius muscle		Soleus muscle	
	Spinal MEPs	Cortical MEPs	Spinal MEPs	Cortical MEPs
R+0	46.1 ± 9.3 ($n = 10$)	81.5 ± 24.7 ($n = 8$)	98.0 ± 46.5 ($n = 11$)	31.7 ± 10.3 ($n = 7$)
	−25.9 ± 4.3 ($n = 6$)	−19.8 ± 5.3 ($n = 8$)	−37.9 ± 4.5 ($n = 5$)	−39.9 ± 7.7 ($n = 9$)
R+3	36.0 ± 26.2 ($n = 10$)	38.9 ± 14.8 ($n = 8$)	70.7 ± 60.5 ($n = 11$)	44.2 ± 18.8 ($n = 7$)
	−0.4 ± 41.6 ($n = 6$)	−11.5 ± 22.6 ($n = 8$)	−31.6 ± 14.1 ($n = 5$)	−10.5 ± 24.6 ($n = 7$)
R+6	77.2 ± 38.7 ($n = 10$)	51.9 ± 13.4 ($n = 8$)	89.2 ± 49.1 ($n = 11$)	30.5 ± 14.6 ($n = 7$)
	−12.8 ± 12.6 ($n = 6$)	−19.3 ± 5.5 ($n = 8$)	−31.2 ± 8.7 ($n = 5$)	−16.5 ± 14.5 ($n = 7$)

2004) and a decrease in thresholds (Badran et al., 2020) were revealed, which the authors, among other things, associated with an increase in corticospinal excitability. An increase in excitability was also observed after 10 days of lower limb immobilization (Roberts et al., 2007), although there were no significant changes in the evoked response thresholds. In contrast, the study in the 90-day bedrest model showed a decrease in corticospinal excitability immediately after the bedrest period ended (Roberts et al., 2010). Less research in this field and predominantly small sample sizes do not allow us to draw a firm conclusion about what may cause the described differences.

The high variability of cortical MEP characteristics in our study is possibly caused by the functional state of the subjects during experimental sessions. It is known that during the transition from wakefulness to deep sleep, corticospinal excitability decreases, which manifests in a decrease in MEP amplitudes and an increase in MEP thresholds and latencies (Grosse et al., 2002; Avesani et al., 2008). When experiencing the procedure

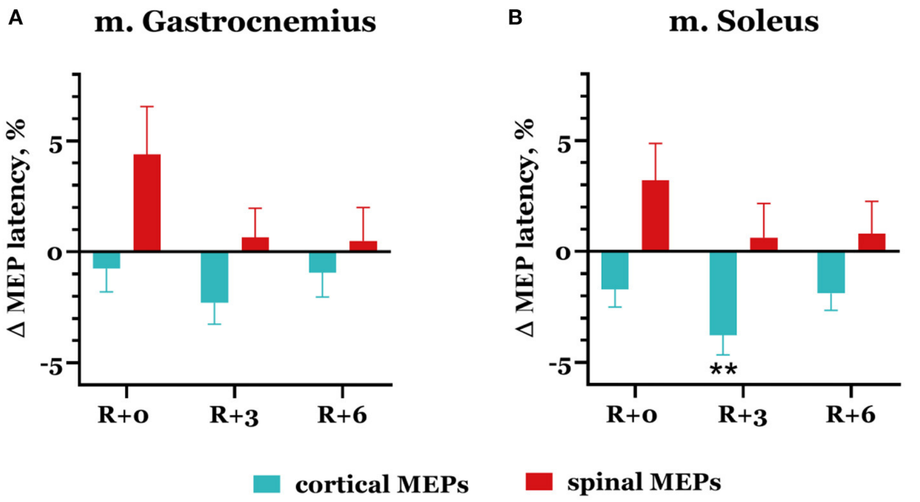

FIGURE 7
Percent changes from baseline of cortical (blue bars) and spinal (red bars) MEP latencies in gastrocnemius **(A)** and soleus **(B)** muscles. Data are presented as mean ± SEM; baseline values are taken as zero. R+0—the day of DI completion; R+3, R+6—3rd and 6th days after DI. $^{**}p < 0.01$ vs. baseline.

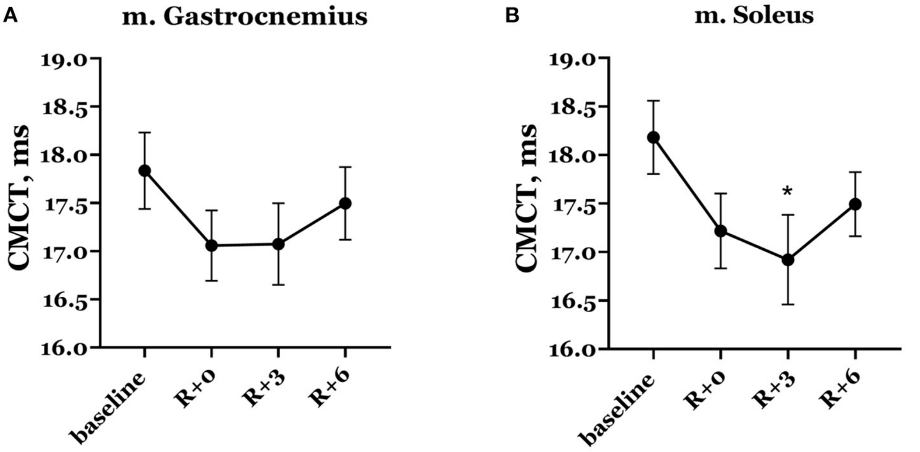

FIGURE 8
Central motor conduction time in gastrocnemius **(A)** and soleus **(B)** muscles. Data are presented as mean ± SEM. R+0—the day of DI completion; R+3, R+6—3rd and 6th days after DI. $^{*}p < 0.05$ vs. baseline.

for the first time, many participants were alert and even excited, which often resulted in higher MEP amplitudes and lower thresholds in the first session compared to subsequent sessions. On the next visits, the subjects already familiar with the procedure were calmer and more relaxed; moreover, in the sessions conducted after DI completion, several participants reported being sleepier than before DI, which could affect the obtained results.

4.2. Comparison of male and female groups

Previously, we conducted a similar experiment with female volunteers participating in 3-day DI (Nosikova et al., 2021a). In that work, a significant decrease in spinal MEP thresholds and a small decrease in CMCT were also observed after DI. Thresholds' decrease in the gastrocnemius muscle was twice as large as in this study; in the soleus muscle, the decrease was slightly less. It is also important to note that threshold values' variability (SEM) was substantially larger in the 3-day DI study (almost four times as large), although it was probably caused by the small sample size: only six female volunteers participated in the 2021 study. The decrease in CMCT was similar in both 3-day and 5-day DI studies, but during the recovery period after 3-day DI, CMCT increased greatly as opposed to the current results. This may suggest that longer DI exposure leaves a more persistent effect on corticospinal conductibility. After 3-day DI, mean spinal MEP amplitudes increased, though the increase was not statistically significant; moreover, the amplitudes were marked by high variability. In this study, there was an increase in spinal MEP amplitudes in the majority of the subjects; besides, the increase in amplitudes was more pronounced in the group than the decrease. As in the case of spinal MEP thresholds, spinal MEP amplitudes' increase in the gastrocnemius muscle was more than twice as large after 3-day DI compared to 5-day DI. In the soleus muscle, on the contrary, the increase in amplitudes was ~20% less in the previous study. Cortical MEP characteristics in the present work and the 2021 study were different. After 3-day DI, cortical MEP amplitudes decreased while thresholds increased. In the present study, the changes in cortical MEP amplitudes after DI completion were ambiguous, and the thresholds tended to decrease. These differences may derive from both the small sample size and the different durations of DI exposure. What is more, in the previous study, we analyzed maximal MEP amplitudes, while in the present study, we analyzed amplitudes at the fixed magnetic stimuli magnitudes, which could also cause the difference in the results. The MS protocol was adapted to minimize subjects' discomfort and to increase the quality of raw data without prolonging the procedure.

The results of our study correspond with the data obtained in the 5-day DI experiment with the participation of male volunteers (Nosikova et al., 2021b). In the male group, a significant decrease in spinal MEP thresholds and a tendency to decrease in cortical MEP thresholds were also observed. In addition, maximal spinal MEP amplitudes in men were significantly increased after DI in both muscles (the increase exceeded 100%), and maximal cortical MEP amplitudes also increased, reaching the level of significance compared with baseline in the m. soleus (increased by 60%). The increase in MEP amplitudes in the female group generally was less pronounced, which may be caused not only by a different approach to amplitude analysis (we did not assess maximal amplitudes in the female group) but also by hormonal impact on the studied characteristics in women.

There are almost no TMS studies on women in ground-based conditions modeling some or other of the SF factors. The above-mentioned experiments by Roberts et al. (2007, 2010) were conducted with the participation of mixed groups, but the data of male and female volunteers were not compared. After that, the results of those experiments were conflicting. Regarding other works dedicated to studying the neuromuscular system in SF or ground-based models, in the research of the contractile properties of the leg triceps muscle before and after 120-day HDBR, a greater depth of changes in strength characteristics was shown in men than in women (Koryak, 2009). The author links it to both the changes at the muscle fiber level and the alterations in the central mechanism of voluntary movement control.

Since the women with a natural MC participated in our study, hormonal fluctuations during MC could affect the obtained results. According to the literature, evidence of the effects of sex hormones on the neuromuscular system is contradictory. Estradiol increases cortex excitability, while progesterone modulates inhibition, and the balance of these hormones affects intracortical facilitation (ICF) and inhibition (ICI): the greatest ICF is observed at the late follicular phase, when estradiol levels are high and progesterone is low, and ICI is the greatest at the luteal phase, when progesterone levels rise (Smith et al., 2002). A better performance in the manual dexterity task was shown at the mid-luteal phase of MC compared to the ovulation phase (Zoghi et al., 2015), and grip strength decreased during the early follicular phase (Weidauer et al., 2020), although the authors did not find any correlation between these measures and the changes in estradiol and progesterone levels during MC. Several other studies did not show significant differences in strength and biomechanical characteristics of leg muscles during MC (Abt et al., 2007; Ansdell et al., 2019), and there were no changes in spinal (Casey et al., 2016) or corticospinal excitability (Ansdell et al., 2019). However, there is evidence of an increase in TMS-evoked motor responses during muscle contraction on the 14th day of MC (late follicular phase) and a decrease in neuromuscular fatigability on the 21st day of MC (Ansdell et al., 2019). In our study, baseline TMS sessions were conducted at the early follicular phase; the session on the day of DI completion coincided with the ovulation phase; and the sessions in the recovery period fell within the luteal phase (Figure 2). Since the dynamics of MEP characteristics in our study largely correlated with the data obtained in the experiment with the participation of men (Nosikova et al., 2021b), hormonal fluctuations during MC probably did not significantly affect the recorded values compared with the effects of immersion. Nevertheless, high MEP amplitudes' variability and a tendency of amplitude values on the 6th day of the recovery period to return to the state of the day of DI completion (Figures 5, 6) in women may be associated with both the hormonal level fluctuations and individual aspects of the nervous system's adaptation to the experimental conditions.

4.3. Effects of exposure duration

The described differences in the results of two immersion experiments with the participation of women may derive from DI duration. It is possible that after a longer exposure to support withdrawal, CNS reactions and corticospinal excitability change, which is reflected in the characteristics of cortical MEPs: cortical MEP thresholds increased after 3-day DI and amplitudes decreased (Nosikova et al., 2021a), while in the present study, cortical MEP thresholds tended to decrease and amplitudes in roughly half the instances increased after DI completion. The duration of immersion exposure could also affect the peripheral nervous system because spinal MEP latencies slightly decreased after 3-day DI and, on the contrary, increased after 5-day DI. CMCT decreased insignificantly after 3 days of the immersion experiment, but the decrease was more prominent after 5 days of exposure to support withdrawal, and by the 6th day of the recovery period, CMCT did not completely return to baseline. Different systems of the body react to the immersion exposure at different speeds, for example, heart rate and blood pressure parameters, as well as muscle tone, change significantly in the first hours of DI, while the state of bone tissue remains stable for 7 days of DI (Navasiolava et al., 2011). It was shown that H- and M-responses characteristics differ on the 3rd and 7th day of DI; moreover, the relative amplitude of the H-response gradually increases throughout the experiment (Zakirova et al., 2015). Similarly, the size of muscle fibers gradually decreases over the course of the 7-day DI (Shenkman and Kozlovskaya, 2019). Thus, longer immersion exposure leads to more profound changes in the neuromuscular system, which may be reflected in MEP characteristics.

In particular, the increase in spinal MEP latencies after 5-day DI, compared with the slight decrease in latencies after 3-day DI, could have been affected by the changes in muscles and neuromuscular synapse activity. It is known that support afferentation withdrawal leads to fast and prominent changes in both postural and mixed postural-locomotor muscles, primarily to muscle atony and atrophy, which mostly affect slow muscle fibers. Due to the changes in the cytoskeleton, muscle fibers become less sensitive to calcium, and their contractility decreases (Shenkman and Kozlovskaya, 2019). In animal experiments, it was shown that support withdrawal results in a decrease in the postsynaptic membrane surface area covered with acetylcholine receptors, as well as a decrease in the number of receptors on the "fast" muscles' nerve endings (Tyapkina et al., 2006). Although the increase in spinal MEP latencies was not significant, and we do not know how pronounced the described molecular changes are after 5 days of DI, it is worth considering the possibility of these mechanisms affecting the evoked muscle responses. It may be noted that despite the increase in spinal MEP latencies, cortical MEP latencies and CMCT decreased after DI, which potentially indicates some compensatory and adaptive processes in the CNS. Further research is needed for a more detailed analysis of the discovered phenomena and the revealing of the mechanisms behind them.

5. Conclusion

The results of our study show that exposure to 5-day DI in women led to the development of hyperreflexia. This phenomenon was manifested in the decrease in MEP thresholds, the predominant increase in spinal MEP amplitudes, and the decrease in CMCT. These effects correspond with the results obtained in similar experiments with the participation of men. The decrease in MEP thresholds and the increase in MEP amplitudes indicate an increase in both spinal and corticospinal excitability due to the DI exposure, while the decrease in CMCT may suggest an increase in corticospinal conductibility. The observed variability of MEP amplitudes could be caused by several factors, and more research is needed to identify its origin. The described changes in MEP characteristics during the experiment are within the limits of the physiological norm, though they still might affect astronauts' performance and should be considered for further studies.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Bioethical Commission of the Institute of Biomedical Problems of the Russian Academy of Sciences. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

IN and AR collected data, performed data analysis, and wrote the draft of the manuscript. VK contributed to the technical support. ET revised the manuscript and was a supervisor of the study.

Funding

The study was supported by a grant from the Russian Science Foundation No. 19-15-00435, https://rscf.ru/en/project/19-15-00435/.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Frontiers in Human Neuroscience

TYPE Clinical Trial
PUBLISHED 26 September 2023
DOI 10.3389/fnhum.2023.1208273

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RECEIVED 21 April 2023
ACCEPTED 29 August 2023
PUBLISHED 26 September 2023

CITATION
Blaber AP, Sadeghian F, Naz Divsalar D and Scarisbrick IA (2023) Elevated biomarkers of neural injury in older adults following head-down bed rest: links to cardio-postural deconditioning with spaceflight and aging. *Front. Hum. Neurosci.* 17:1208273. doi: 10.3389/fnhum.2023.1208273

Elevated biomarkers of neural injury in older adults following head-down bed rest: links to cardio-postural deconditioning with spaceflight and aging

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Introduction: Prolonged physical inactivity with bed rest or spaceflight is associated with cardiovascular and neuromuscular deconditioning; however, its impact on neural integrity of cardio-postural reflexes and possible mitigation with exercise has not been examined. We assessed the association between the physiological deconditioning of bed rest immobilization with neural injury markers and the effects of 60–75 min of daily exercise.

Methods: Data were collected as part of a randomized clinical trial (clinicaltrials.gov identifier: NCT04964999) at the McGill University Medical Centre. Twenty-two 55- to 65-year-old healthy volunteers gave informed consent and took part. Within sex, participants were randomly assigned to exercise (60- to 75-min daily) or control (inactive) groups and spent 14 days in continuous 6° head-down tilt. Neural injury [neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), total tau (t-Tau), myelin basic protein (MBP), brain-derived neurotrophic factor (BDNF), ubiquitin carboxy-terminal hydrolase L1 (UCH-L1)], as well as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and insulin-like growth factor 1 (IGF-1) biomarkers were measured before, during, and after bed rest. The false discovery rate with Huber M-estimation was used to correlate changes in biomarkers with cardiovascular and muscular function changes over bed rest.

Results: Bed rest elevated NfL, GFAP, TNF-α, and IL-6 in all participants and reduced IGF-1 in females only. With standing, changes in heart rate, blood pressure, and lower limb muscle motoneuron activity correlated with changes in TNF-α and BDNF. Baroreflex control, leg muscle maximal voluntary contraction, and postural sway are correlated with GFAP and NfL. Exercise participants had fewer interactions than control participants, but significant correlations still existed, with both groups exhibiting similar reductions in orthostatic tolerance.

Discussion: An hour of daily exercise in older persons otherwise immobilized for 2 weeks did not abate bed rest-induced increases in serum signatures of neural injury or pro-inflammatory markers. Exercise reduced the number of physiological interactions of biomarkers, but significant cardio-postural correlations remained with no protection against post-bed rest orthostatic intolerance. The identification of associations of inflammatory and neural injury biomarkers with changes in cardio-postural physiology and exercise points to biotherapeutic opportunities and improved exercise interventions for astronauts and individuals in bed rest.

Clinical trial registration: https://www.clinicaltrials.gov/search?cond=NCT04964999, identifier: NCT04964999.

KEYWORDS

neural injury markers, bed rest immobilization, spaceflight analog, baroreflex, electromyogram (EMG), orthostatic intolerance (OI), cardio-postural control

Introduction

Spaceflight produces observable physiological changes in humans (Vernikos and Schneider, 2010), leading to time-dependent adaptation processes. Weightlessness instantaneously removes physical processes that depend on weight for their effect and is experienced by bodily systems in different ways. Eventually, weightlessness affects every part of the body, either directly or indirectly.

Neural activity driven by motor and sensory experience plays essential roles in neural development, plasticity, and aging (Stimpson et al., 2018). Data from 60 days of head-down tilt bed rest, an analog for spaceflight, revealed neurological deficits in the baroreflex. On the first day of recovery, the formerly healthy younger individuals had a 61% reduction in total muscle-pump baroreflex (reflex changes in skeletal muscle activation to changes in blood pressure) gain and only a partial return 8 days later (Xu et al., 2020). The cardiac baroreflex (reflex changes in heart rate to changes in blood pressure) was also reduced in these same participants immediately after bed rest, but it recovered 8 days later (Blaber et al., 2022).

Causal analysis of the cardiac and muscle-pump baroreflex feedback loops following bed rest revealed a significant reduction in the coupling along the neural reflex segment of the bi-directional baroreflex interaction (Xu et al., 2020; Blaber et al., 2022) (blood pressure driving heart rate and muscle pump) but not for the mechanical coupling of heart rate and muscle pump on blood pressure. These data suggested an impairment or degradation of the neural regulation of blood pressure independent of cardiac or skeletal muscle mechanics. However, it could not be determined from these data where, in the reflex signal integration or efferent pathway, the deficit occurred.

From these results, we hypothesized that inactivity induced by bed rest immobilization and the fluid shift accompanying 6° head-down tilt affects the central nervous system (CNS) and activates neurodegenerative processes. Since exercise training has been shown to improve myelin outcomes, including related elevations in spinal cord IGF-1 (insulin-like growth factor 1) in adult mice (Yoon et al., 2016), we hypothesized that an exercise program involving the major upper and lower body muscles would reduce signs of neural insult occurring with bed rest.

Such an exercise program was proposed and supported by the Canadian Space Agency (CSA), the Canadian Institutes of Health Research (CIHR), and the Canadian Frailty Network (CFN) as part of the Canadian Aging and Inactivity Study (CAIS) involving older adults placed in 14 days of 6° head-down tilt bed rest (HDBR). HDBR is often used as an analog of spaceflight because it induces inactivity, unloads the musculoskeletal system in the head-to-feet axis (z-axis), and simulates the fluid shift seen in spaceflight. Our team was one of eight chosen to participate in this first-of-its-kind project that combined older adults in a space analog with a space-based exercise intervention (Hedge et al., 2022).

Although our foundational research was based on young to middle-aged volunteers (Xu et al., 2020), given the increased age of the CAIS participants, we expected and observed similar declines in cardiac and muscle-pump baroreflex over 14 days (Sadeghian et al., 2022). Moreover, we found the exercise program was not effective in preventing reductions in cardiac baroreflex and only partially blunted the decline in muscle-pump baroreflex. Based on these results, we concluded that the exercises did not preserve orthostatic reflexes. This was reflected in reduced orthostatic tolerance in our 5-min stand test after bed rest, where 7 of 20 participants, equally distributed between control and exercise, could not complete the test after bed rest when all were successful during baseline (Sadeghian et al., 2022). None were able to complete a standard 15-min 80° head-up tilt test immediately after bed rest (Hajj-Boutros et al., 2023).

Mobility, especially ambulatory mobility, is essential for quality of life and independence. With aging, ambulatory ability tends to deteriorate due to sarcopenia (aging-associated degenerative loss of skeletal muscle quality, mass, and strength; Phillips, 2015) and dynapenia (aging-associated loss of muscle strength not arising due to muscular and/or neurological diseases; Clarke and Manini, 2008). Avoiding the cycle of bed rest-induced muscle wasting and further reduced ambulation requires immediate intervention after hospital admission to remobilize the patient as early as possible (Singh et al., 2008; Goswami, 2017). There is evidence to show that strength training can evoke muscle hypertrophy and positive changes in neuromuscular function, even at >80 years of age (Aagaard et al., 2010).

The goal of this research was to use the unique opportunity of 6° head-down tilt bed rest to further our understanding of cardiac and muscle-pump baroreflexes in relation to the development of orthostatic intolerance in older adults. In this pilot study, we examined inflammatory and neurodegenerative markers to further assess their relationship with neural deficits in cardiac and muscle-pump baroreflexes and with physical and physiological declines commonly associated with bed rest. We also explored the impact of 60–75 min of daily exercise to counter the bed rest-induced cardiovascular and skeletal muscle deconditioning.

Materials and methods

Study design and testing protocols

Our research was conducted as part of a clinical trial implemented through collaboration with the Canadian Institutes of Health Research (CIHR), the Canadian Frailty Network (CFN), and the Canadian Space Agency (CSA). The overall aim was to investigate the effects of bed rest inactivity/immobilization on older persons (55–65 years old), with specific emphasis on exercise interventions and applications to spaceflight. The Center for Innovative Medicine (CIM) of the McGill University Health Centre Research Institute (RI-MUHC) conducted the trial, which comprised four 26-day bed rest campaigns during which 5–6 participants per campaign were placed in HDBR as a ground-based analog to spaceflight.

Recruitment provided a balance between biological sex across test groups, with half of the participants receiving bed rest-specific exercise counter measures (CMs) (Hedge et al., 2022), while the other half served as controls, receiving stretch and joint movement physiotherapy. The exercises consisted of three sessions each day of high-intensity interval training (HIIT), low-intensity aerobic activity, and lower body strength exercises, resulting in an average of 1 h of daily physical activity (Hedge et al., 2022). Workouts were performed in the head-down tilt position using specially modified equipment. The intensity of the exercise CMs was adjusted to the individual participants' maximal performance and tolerance prior to bed rest. All other standards of care were consistent between the control and exercise groups (Hedge et al., 2022; Sadeghian et al., 2022).

Ethical approval for the research was obtained from the research ethics board of the MHUC. Research and data collection associated with our study were approved by the Office of Research Ethics at Simon Fraser University. The research was conducted in compliance with the guidelines and regulations of the above agencies. The inclusion and exclusion criteria were previously reported (Hedge et al., 2022; Sadeghian et al., 2022). In brief, older persons (55–65 years old) and healthy male and female individuals, with women being menopausal, were included. Volunteers were included if they spent at least 2.5 h of moderate- to vigorous-intensity aerobic activity per week. Sedentary people and people who were addicted to exercise were excluded. Out of 219 healthy volunteers, 22 entered the study after passing screening and giving informed consent. The participants signed written informed consent and agreed to be available at MHUC for the entire 26-day study period.

Data collection

Blood sampling and analysis

We quantified well-studied serum biomarkers of neural injury across the neuronal and glial substrates of the central nervous system (CNS). Specifically, we quantified changes in the well-studied marker of astrocyte reactivity, glial fibrillary acidic protein (GFAP) (Stukas et al., 2023). In addition, we quantified both tau and neurofilament light chain (NfL), which have emerged as sensitive serum markers of CNS neurodegeneration (Kuhle et al., 2015; Dage et al., 2016; Mattsson et al., 2017; Thompson et al., 2018). We also quantified serum levels of markers that could arise from the CNS or peripheral organs, including brain-derived neurotrophic factor (BDNF) and ubiquitin C-terminal hydrolase L1 (UCH-L1). BDNF and UCH-L1 are associated with neuron and glial development and survival and have been linked to neurodegenerative conditions and aging in prior studies (Ziegenhorn et al., 2007; Reinicke et al., 2019). Insulin-like growth factor 1 (IGF-1) and two inflammatory cytokines, tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6), all of which have the potential to impact CNS integrity, were also quantified.

Standard venipuncture from the antecubital vein of the arm was performed during baseline data collection 2 days before bed rest (BDC-2), the ninth day of bed rest (HDBR9), and the day they came out of bed rest (R+0) (Figure 1). One allotment was transported to the MUHC laboratory for hemoglobin analysis. Another was centrifuged, and sera were frozen in liquid nitrogen and stored at −80°C before being shipped overnight on dry ice to the Wellington Laboratory at the Djavad Mowafaghian Center for Brain Health at the University of British Columbia. Single Molecular Array (Simoa®, Quanterix Corp., USA) HD-kit analysis was performed for NfL, GFAP, UCH-L1, IL-6, TNF-α, and t-Tau. IGF-1, myelin basic protein (MBP), and BDNF were analyzed from aliquots of the same serum samples with multiplex Luminex ELISA (Thermo Fisher Scientific) in the Brockman and Brumme Laboratory at Simon Fraser University.

Variables from supine-to-stand test

The cardio-postural control system was activated and evaluated using a supine-to-stand (StS) test (Blaber et al., 2009; Garg et al., 2013, 2014; Rodriguez et al., 2017; Verma et al., 2017; Xu et al., 2017) prior to bed rest (BDC-1, Figure 1) and twice after recovery (Sadeghian et al., 2022). For comparison with serum analysis, we used the StS results on BDC-1 and R+0 that were closest to the blood draws (BDC-2, R+0; Figure 1). The StS test, previously described (Sadeghian et al., 2022), was conducted in the morning, 1 h after the Canadian Space Agency (CSA) standard 15-min tilt test. Participants were instrumented in the supine position for electrocardiogram (IX-BIO4, iWorx, USA), non-invasive beat-to-beat blood pressure (Portapres, FMS Technologies, the Netherlands), and bi-lateral electromyography (EMG) (8-channel Bagnoli, Delsys Inc., Natick, MA, USA) of the soleus (S), medial gastrocnemius (MG), lateral gastrocnemius (LG), and tibialis anterior (TA). To determine the placement locations for the EMG sensors, the recommendations of the SENIAM project (Hermens et al., 1999) were followed. Data were collected at a rate of 1,000 Hz with National Instruments USB-6218 16-bit data capture equipment and LabVIEW 2013 software from National Instruments Inc. (Austin, TX, USA).

Once the participant was instrumented, the lights were turned off, and they closed their eyes for the 5-min baseline data collection. Afterward, the participant was assisted into a standing position. One researcher swept their legs off the bed, and another assisted with raising their torso. Each participant stood with their feet

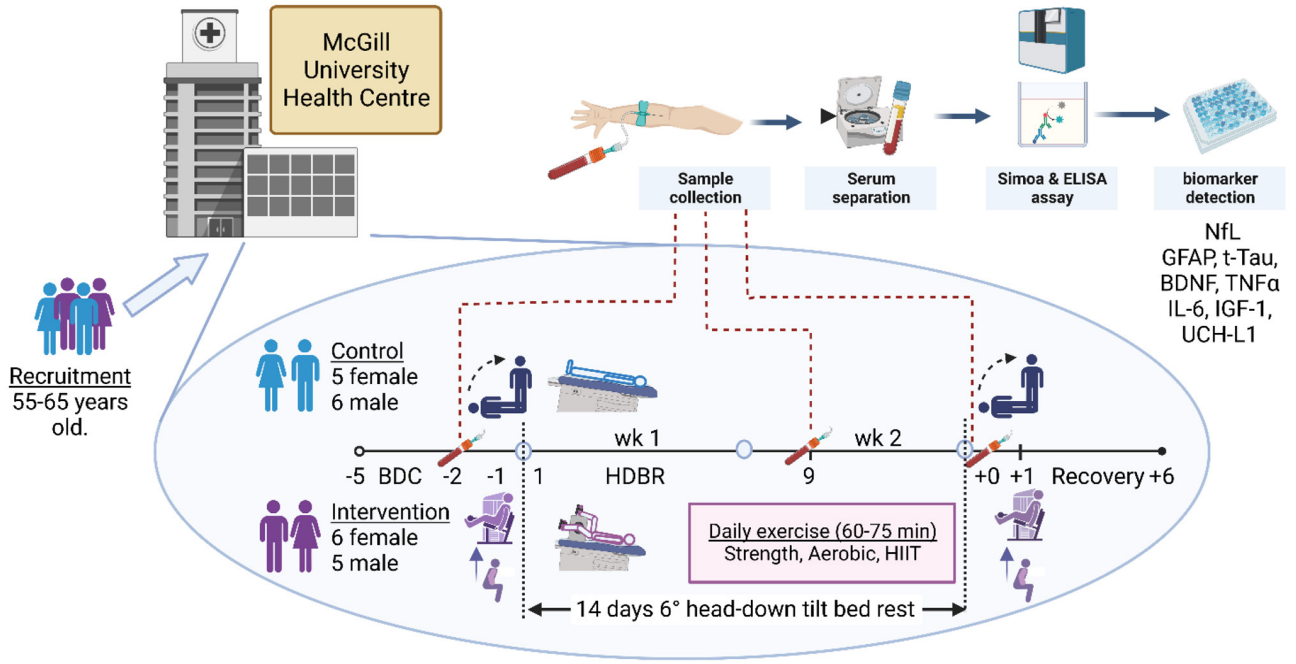

FIGURE 1
Staff screened volunteers between the ages of 55 and 65 years old from the Montreal region at the Centre for Innovative Medicine at the McGill University Health Centre. Following recruitment and screening, 22 participants, equally represented by males and females, consented to take part and provided blood samples on all days of collection. Within each sex, participants were randomly assigned to either the control or the exercise intervention. The daily exercise routine comprised upper and lower body strength regimens and aerobic and high-intensity interval training dispersed through three sessions a day. Daily exercise time ranged from 60 to 75 min. In the first 5 days, the participants were ambulatory for baseline data collection (BDC-5 to BDC-1), following which they entered the 14-day head-down bed rest (HDBR) phase of the study (HDBR1 to HDBR14). Immediately after HDBR, the participants returned to ambulation recovery (R+0 to R+6) within the facility, exiting on R+7. Blood draws were taken in the mornings of BDC-2, HDBR9, and R+0 after overnight fasting and prior to eating. Thereafter, blood was centrifuged, and blood sera and plasma were frozen in liquid nitrogen and stored at −80°C. Hemoglobin was analyzed at MUHC, while NfL (neurofilament light chain), GFAP (glial fibrillary acidic protein), TNF-α (tumor necrosis factor alpha), IL-6 (interleukin-6), t-Tau (total tau protein), IGF-1 (insulin-like growth factor 1), BDNF (brain-derived neurotrophic factor), and UCH-L1 (ubiquitin carboxy-terminal hydrolase L1) were analyzed by independent laboratories at the University of British Columbia and Simon Fraser University. The supine-to-stand baroreflex and postural sway test were performed on the mornings of BDC-1, the last day before HDBR, and R+0. The physical jump, muscle activity, and strength tests were conducted on BDC-1 and R+1. Created with Biorender.com.

parallel and 5 cm apart, without moving their feet, and with their arms relaxed at their sides. Their eyes remained closed with an imaginary gaze at eye level for the subsequent 6 min of quiet stance.

Jump test

A countermovement jump was used to measure whole-body power. The jump maneuver started with an upright stance with hands on the waist. Participants quickly squatted down and pressed firmly on a force plate to jump as high as possible with hands on hips to prevent arm movement. Participants performed mild aerobics and three sets of warm-up squats before the test. Each participant recorded three maximum jump efforts with their heads held as high as possible throughout the test. A rest period of 60–90 s between each jump was allowed for recovery. The vertical ground reaction force was used to determine the subject's acceleration, velocity, power profile, flight altitude, and total time in the air. Body mass was assessed by having the subjects stand motionless for 30 s on a force plate. All participants were at least 1.5 h post-prandial and had not performed any vigorous exercise in the previous 18 h.

Muscle characteristics

To measure the strength of various leg muscles, a multi-joint muscle dynamometer (Biodex Systems, USA) was used. The device was used to examine both isometric and isotonic maximum voluntary contractions (MVC). Isometric contractions involve holding a muscle contraction without joint movement, while isotonic contractions involve moving a joint through a specific range of motion while maintaining a constant force output. Simultaneous EMGs from the S, MG, and LG were collected using the same procedure described for supine-to-stand. During the isometric test, the participants sat and pushed against the device using their ankle muscles (S, LG, and MG), aiming to produce the strongest possible isometric contractions. The dynamometer was attached to the feet to measure the strength and power of the ankle plantar flexor muscles. During the isotonic assessments, each participant moved their ankle joint back and forth while applying force against the device, which generated a resistance load. The test consisted of three repetitions of either isometric or isotonic movements, and the MVC for each muscle was determined based on the highest muscle contraction recorded across all three tests. Throughout the examination, participants received both verbal and visual feedback. Prior to the test, the subjects received instruction on appropriate exercise techniques and equipment orientation.

The soleus, medial gastrocnemius, and lateral gastrocnemius muscles make up most of the plantar flexor muscles of the ankle joint (Sadeghian et al., 2018, 2019). During isometric contractions, the magnitude of the force produced by these muscles was recorded with the Biodex. The non-linear and dynamic aspects of the ankle joint can be disregarded since isometric contractions minimize the effects of parameters related to joint angle (Leardini et al., 2000; Sadeghian et al., 2019). Therefore, the S, MG, and LG muscles were responsible for producing the measured force, and therefore the maximum force produced by each muscle may be calculated as a ratio of its peak EMG signals (Troiano et al., 2008).

Statistical analyses

Statistical analyses were performed using JMP 16 (SAS Institute).

Serum biomarkers

Data are presented as mean (95% lower and upper confidence limits). Data within groups (sex, intervention) were tested for normality using the Shapiro–Wilk goodness-of-fit test. If the variables were normally distributed, a repeated measures ANOVA was used to assess time-dependent changes of the biomarkers as a function of sex (female, male) and intervention (control, exercise). If the RM-ANOVA revealed significant differences, *post-hoc* tests were performed using Tukey's HSD. If the data were determined to be not normally distributed, a Friedman test was used.

Correlations between serum biomarkers and physiological measures

To investigate the possible relationship between changes in participant physiological characteristics and the serum biomarkers, data were converted from absolute pre- and post-values to the change (Δ) from pre- to post-HDBR. Negative values represented a decrease in biomarker or physiological value, and positive values represented an increase after bed rest.

Given the small number of participants in the subject groups and the possible non-linear relationship between biomarkers and physiological measurements, Spearman's rank correlation was used to assess the strength of correlations between changes in biomarker concentration and changes in physical assessments made by the participants before and after bed rest. Data are presented using the correlation coefficient (ρ).

With multiple comparisons, the false discovery rate (FDR) (Benjamini and Hochberg, 1995) was used to estimate the significance of the correlations. The response screening function with the robust Huber M-estimation method was used (Huber and Ronchetti, 2009). The threshold was set to positive false discovery rate (pFDR) < 0.05 (Korthauer et al., 2019). Data are quoted as variable (pFDR).

To assess the interaction of biomarkers and physical measurements with changes observed in the cardiac and muscle-pump baroreflexes, we performed a stepwise multiple regression analysis. Variables entered or exited the model to provide a minimum Bayesian information criterion (BIC). We also performed discriminant analysis on our data to investigate whether biomarkers and physiological variables could be used to differentiate between the categorical groups of sex (male, female) and intervention (control, exercise), as well as the four subgroups (male control, male exercise, female control, female exercise). A stepwise procedure was used to enter and exit variables until there was no overlap between the groups.

Results

One participant dropped out of the study on day 3 of HDBR, leaving 22 participants equally divided between exercise [five males 58.0 (0.8) years, six females 60.6 (0.1)] and control [six males 60.8 (1.5), five females 56.6 (0.5); mean (SEM)]. Control and exercise participants were not significantly different in aerobic fitness as measured by $\dot{V}O_2$peak (mean ± SD; control: 30.2 ± 5.8; exercise: 32.0 ± 6.6 $mL{\cdot}min^{-1}{\cdot}kg^{-1}$). Two participants withdrew from the study on R+2 for medical reasons following the completion of the post-bed rest physical measurements; however, three participants (two males and one female) were missing muscle and/or baroreflex data because of poor signal quality. Therefore, correlational analysis of the biomarkers with physical measurements contains the results from 19 participants.

Blood analysis

Aliquots for serum analysis were taken from the same sample used for the blood biomarkers. Hemoglobin was used as a systemic control protein for all analyses using an identical statistical approach. No significant change in hemoglobin was found over the time course of BDC-2 through R+0 ($p = 0.854$) with an overall value of 135 (132, 139) g/L. Male participants had consistently higher hemoglobin values than female participants [146 (141, 150) g/L, 126 (121, 130) g/L, respectively].

Serum assays

We analyzed sera to investigate whether bed rest, intervention, or sex significantly altered the concentrations of our selected biomarkers. All ($p \geq 0.05$) but UCH-L1 ($p = 0.027$) were found to be normally distributed (Shapiro–Wilk) within sex and intervention. NfL increased from the beginning to the end of bed rest ($p < 0.0001$), mostly by day 9 (Figure 2A; Table 1), with no sex ($p = 0.34$) or intervention ($p = 0.80$) effects. GFAP increased from the beginning to the end of bed rest ($p < 0.0001$) (Figure 2B; Table 1) with no sex ($p = 0.53$) or intervention ($p = 0.56$) effects. Bed rest elevated TNF-α ($p = 0.006$) (Figure 2C; Table 1), increasing HDBR9 and R+0 with consistently higher values in males [2.61 (0.12) pg/mL] than females [2.01 (0.12) pg/mL] ($p = 0.006$). IL-6 increased significantly from the start of bed rest to HDBR9, when it plateaued (Figure 2D, $p = 0.0006$) (Table 1) with no effect of sex ($p = 0.97$) or intervention ($p = 0.90$). No group effects were observed for t-Tau [1.06 (0.35) pg/mL, $p = 0.41$] (Figure 2E; Table 1). IGF-1 decreased significantly in females from pre- to post-bed rest but not in males (regardless

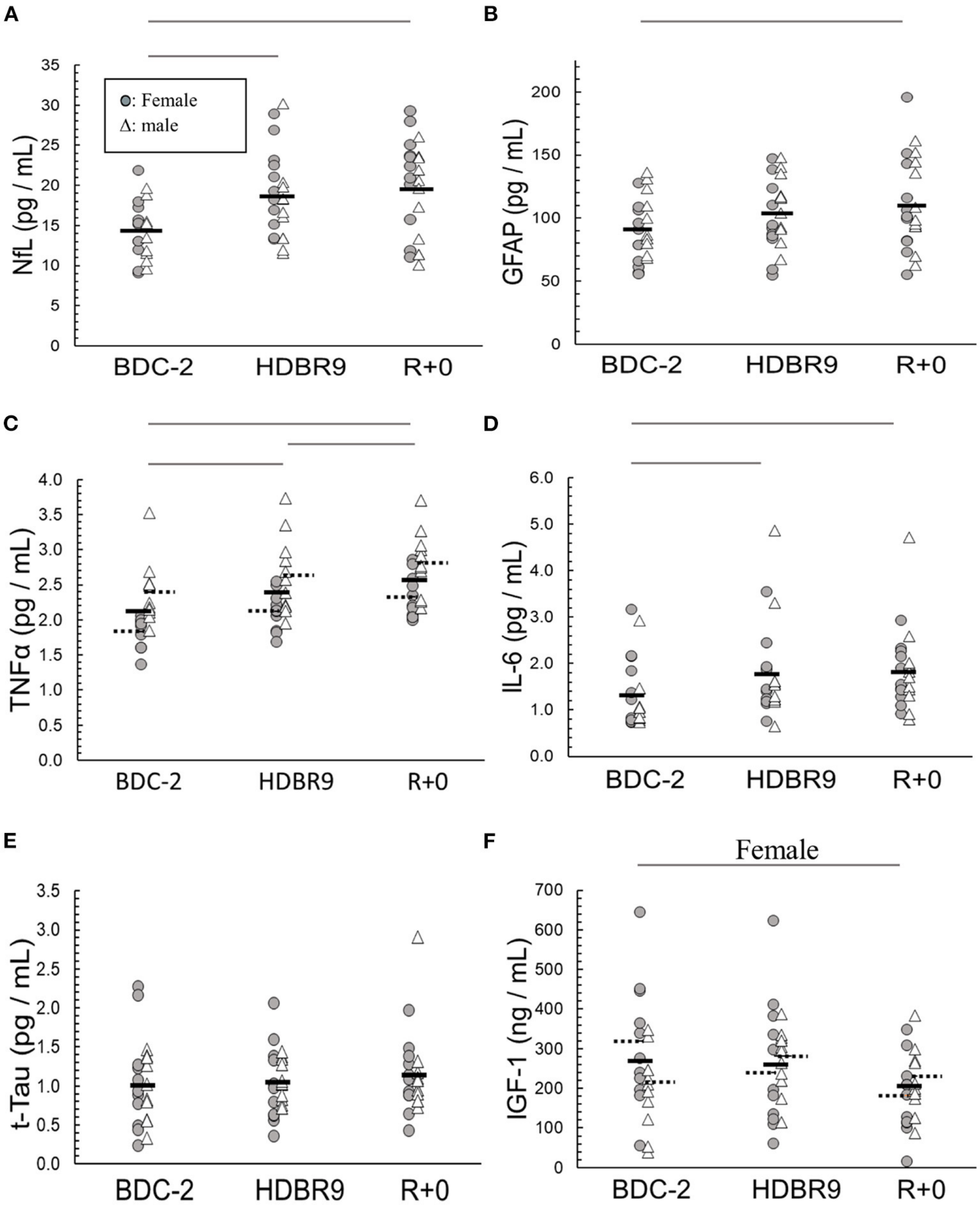

FIGURE 2
Main effect changes over time in **(A)** NfL (neurofilament light chain), **(B)** GFAP (glial fibrillary acidic protein), **(C)** TNF-α (tumor necrosis factor alpha), **(D)** IL-6 (interleukin-6), **(E)** t-Tau (total tau), and **(F)** IGF-1 (insulin-like growth factor 1) from baseline data collection 2 days before (BDC-2) head-down tilt bed rest (HDBR) through 9 days of HDBR (HDBR9) to the first day of recovery (R+0). Females: circles (O); males: triangles (Δ). Within the data, a dashed horizontal line represents the mean of male and female data: left solid line (female mean); right solid line (male mean). The horizontal lines above the figures represent significant differences ($p < 0.05$) between days on each end of the line. For I, significance was with female participants only.

of intervention group, $p = 0.018$) (Figure 2F). No consistent group changes in BDNF or UCH-L1 were observed from the beginning to the end of bed rest ($p = 0.87$, $p = 0.42$, respectively) with intervention ($p = 0.18$, $p = 0.78$, respectively) or by sex ($p = 0.11$, $p = 0.26$, respectively). MBP was not detected with the assay used (below the detection limit in sera; assay range: 0.2–15 ng/mL).

Changes in physical/physiological measurements with bed rest

All participants

When all participants were grouped together, several measured variables were found to be significantly altered from baseline to the end of bed rest (Figure 3). Similar to what we previously

TABLE 1 Data from serum samples taken during baseline 2 days before head-down tilt bed rest (BDC-2), on the ninth day of bed rest (HDBR9), and on the day of remobilization (R+0).

		Pre-bed rest (BDC-2)		6° head-down tilt bed rest (HDBR 9)		Post-bed rest (R+0)	
Protein	Sex	Control	Exercise	Control	Exercise	Control	Exercise
NfL (pg/mL)	Male	15.3 (10.9, 19.6)	12.9 (8.2, 17.6)	18.2 (13.9, 22.6)	16.2 (11.4, 20.9)	18.2 (13.9, 22.5)	17.9 (13.1, 22.6)
	Female	15.0 (10.2, 19.7)	14.1 (9.8, 18.4)	18.4 (13.7, 23.2)	21.1 (16.7, 25.4)	21.1 (16.7, 25.8)	20.9 (16.6, 25.2)
GFAP (pg/mL)	Male	105 (78, 131)	89 (60, 118)	116 (89, 142)	103 (74, 132)	116 (90, 143)	103 (74, 132)
	Female	87 (58, 116)	81 (55, 108)	95 (66, 124)	100 (74, 127)	111 (82, 140)	108 (81, 134)
TNF-α (pg/mL)	Male	2.47 (2.12, 2.81)	2.30 (1.92, 2.68)	2.68 (2.33, 3.02)	2.59 (2.21, 2.97)	2.81 (2.46, 3.15)	2.80 (2.42, 3.18)
	Female	1.92 (1.54, 2.30)	1.76 (1.41, 2.11)	2.22 (1.84, 2.59)	2.04 (1.70, 2.39)	2.42 (2.04, 2.79)	2.24 (1.90, 2.59)
IL-6 (pg/mL)	Male	1.32 (0.61, 2.04)	1.02 (0.23, 1.81)	2.25 (1.53, 3.00)	1.32 (0.53, 2.11)	2.02 (1.30, 2.74)	1.73 (0.94, 2.52)
	Female	1.23 (0.44, 2.02)	1.58 (0.86, 2.30)	1.28 (0.49, 2.06)	2.06 (1.35, 2.78)	1.40 (0.62, 2.19)	2.04 (1.32, 2.76)
t-Tau (pg/mL)	Male	1.07 (0.65,1.49)	0.79 (0.34, 1.25)	0.97 (0.55, 1.38)	1.19 (0.73, 1.65)	1.00 (0.58, 1.42)	1.34 (0.88, 1.80)
	Female	0.96 (0.50, 1.41)	1.56 (0.74, 1.58)	1.02, (0.56, 1.48)	1.03 (0.61, 1.45)	1.13 (0.56, 1.48)	1.06 (0.64, 1.48)
IGF-1 (ng/mL)	Male	218 (119, 318)	173 (65, 282)	251 (151, 350)	294 (185, 403)	239 (139, 337)	193 (85, 302)
	Female	293 (184, 402)	324 (225, 424)	171 (63, 280)	332 (232, 431)	187 (78, 296)	170 (70, 268)
BDNF (ng/mL)	Male	12.8 (9.9, 14.9)	12.6 (9.8, 15.3)	12.4 (9.9, 14.9)	12.4 (9.7, 15.2)	13.5 (11.0, 16.0)	12.4 (9.6, 15.2)
	Female	12.9 (10.2, 15.7)	9.0 (6.5, 11.5)	11.9 (9.2, 14.7)	9.2 (6.7, 11.7)	11.6 (8.8, 14.4)	9.9 (7.4, 12.5)
UCH-L1 (pg/mL)	Male	3.9 (0, 10.5)	1.2 (0, 8.7)	2.7 (0, 9.7)	3.3 (0, 10.4)	3.2 (0, 9.8)	1.8 (0, 8.8)
	Female	5.2 (0, 11.0)	6.8 (0.3, 13.2)	5.4 (0, 12.7)	9.6 (3.1, 16.1)	3.9 (0, 11.0)	7.2 (0.7, 13.6)

Mean (95% lower and upper confidence limits) for: NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; t-Tau, total tau protein; IGF-1, insulin-like growth factor 1; BDNF, brain-derived neurotrophic factor; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.

Biomarker sensitivity. *Quanterix HD-1/HDX:* NfL (LoD: 0.104 pg/mL; LoQ: 0.241 pg/mL; dynamic range: 0–2,000 pg/mL), GFAP (LoD: 0.221 pg/mL; LoQ: 0.467 pg/mL; dynamic range: 0–4,000 pg/mL), TNF-α (LoD: 0.016 pg/mL; LoQ: 0.034 pg/mL; dynamic range: 0–400 pg/mL), IL-6 (LoD: 0.0055 pg/mL; LoQ: 0.01 pg/mL; dynamic range: 0–120 pg/mL), t-Tau (LoD: 0.019 pg/mL; LoQ: 0.061 pg/mL; dynamic range: 0–360 pg/mL), UCH-L1 (LoD: 1.74 pg/mL; LoQ: 5.45 pg/mL; dynamic range: 0–40,000 pg/mL). *Luminex:* IGF-1 (assay range: 2.9–3,000 ng/mL), BDNF (assay range: 0.4–400 ng/mL).

reported from these data (Hedge et al., 2022; Sadeghian et al., 2022), heart rate (HR) was increased, cardiac and muscle-pump baroreflexes were reduced, and muscle activation during standing was lower following bed rest. In these analyses, we observed reduced cardiac FTA and gain along with reduced muscle-pump FTA and causality. This was accompanied by reductions in summed muscle EMG and EMG impulse during standing.

Here we report for the first time, in older persons, the effects of HDBR on changes in postural sway, maximal voluntary contraction of calf muscles, calf muscle EMG during maximal isometric and isotonic contraction, and the maximal jump test (Figure 3). There was a significant reduction in force production from the MG, not the LG or S. No changes were seen in EMG output during isometric or isotonic contractions. The ability to jump was reduced with lower peak velocity, height, and flight time. Postural sway during the stand test was more pronounced with increases in radius (COPr) and velocity (COPrv).

Sex and intervention

When compared across sex (Figure 4, left) or across intervention (Figure 4, right), similar results to the analysis of all participants were found, with small variances in the component variables in a category. The increase in HR with reduced cardiac baroreflex gain, along with reduced jump characteristics (peak velocity, flight height, and flight time), and increased postural sway (COPr and COPrv) were consistent in all groups (Figure 4).

When comparing across sex, there were significant declines in more muscle-pump indices for the male participants (FTA, gain, causality) compared to the females (FTA). In female participants, there was a decline in total EMG output, while in males, the decline was observed with EMGimp. Control participants had reduced muscle-pump causality, while the exercise group had reduced FTA. There was an observed decrease in both total muscle EMG and EMGimp in the control group, with the exercise group only showing a decrease in EMGimp. Finally, only the exercise group had changes in EMG output during isotonic contractions or muscle MVC. The exercise group had lower MVC in the medial gastrocnemius and lower EMG during isotonic contractions (Figure 4).

Correlations of changes in biomarker levels with physical/physiological changes in bed rest

We used Spearman's rank correlation analysis to determine possible relationships between an individual's change in a biomarker and changes in their main cardiovascular and muscular system physiological measurements (Figure 2) for all participants and across the different participant groups (Figure 3). In the overall Spearman's analysis (Figure 3), we observed a wide range

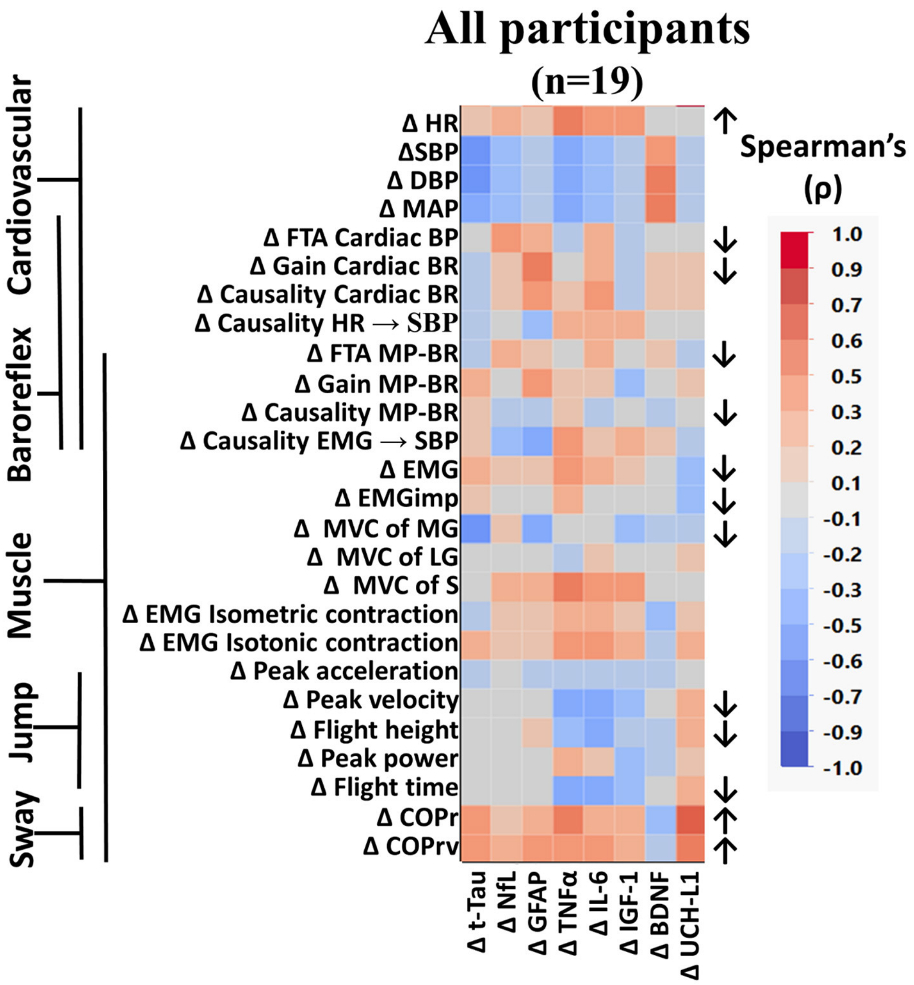

FIGURE 3
Color heat map of Spearman's rank correlation analysis for all participants. Changes in serum biomarkers (abscissa) from baseline (R−0 to BDC-2) were compared to changes in physical and physiological function (ordinate) from baseline (R−0 to BDC-1). Significant correlations are listed in Table 2. All data were found to be normally distributed using the Shapiro–Wilk test. Arrows to the right of the heat map indicate a significant increase (↑) or decrease (↓) in physical/physiological variables from BDC-2 to R+0 (mean significantly different from 0). Student's *t*-test was performed for normally distributed data. Non-normally distributed data were tested using the Wilcoxon signed rank test. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; FTA, fraction time active; MP-BR, muscle-pump baroreflex; MVC, maximum voluntary contraction; MG, medial gastrocnemius; LG, lateral gastrocnemius; S, soleus; EMG, electromyography; COPr, average center of pressure sway radius; COPrv, average COP sway velocity. Biomarkers: Tau, Tau protein; NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; BDNF, brain-derived neurotrophic factor; IGF-1, insulin-like growth factor 1; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.

of strengths in positive and negative relationships between changes in physiological measurements and the biomarkers. In the group analysis, correlations revealed distinct patterns of biomarker interactions with changes in physiological measures from bed rest for sex (Figure 4, left) and for intervention (Figure 4, right). Female and male participants showed similar numbers of darker shaded (higher correlation) compartments; whereas, compared to controls, exercise participants had a much lighter pattern, indicative of less and weaker correlations. Some of the physiological variables measured were not normally distributed (†) with double the incidence in females compared to males. There were three non-normally distributed variables in the exercise group; however, the control group had more than four times that number.

A quantitative assessment of the correlations using the false discovery rate with M-Huber estimation ($p \leq 0.05$) revealed some trends in biomarker distribution between the cardiovascular and muscular systems across all participants (Table 3).

Changes in the biomarkers BDNF and TNF-α were predominantly associated with changes in heart rate, blood pressure, and muscle contractile force, while NfL and GFAP were mostly associated with baroreflex and motoneuron (EMG and posture) control. UCH-L1 was also significantly implicated in motoneuron activation during isotonic contraction. More interactions were seen for MVC of the soleus muscle than any other measure, with positive relationships with both pro-inflammatory (TNF-α, IL-6) and neural injury (NfL, GFAP, BDNF) markers.

Although most interactions were positively correlated (Spearman's), negative relationships were observed for TNF-α with systolic blood pressure and NfL with the causality of muscle

TABLE 2 Changes in physiological measurements at the end of bed rest (R+0, R+1) compared to before bed rest (BDC-1, BDC-2) for the four different conditions.

Measure	Female		Male	
	Control (*n* = 4)	Exercise (*n* = 6)	Control (*n* = 4)	Exercise (*n*= 5)
ΔHR (bpm)	25 (5, 44)*	20 (10, 30)*	14 (3, 25)*	20 (4, 35)*
ΔSBP (mmHg)	−20 (−48, 8)	−4 (−40, 32)	27 (−29, 83)	−20 (−46, 7)
ΔDBP (mmHg)	−4 (−10, 2)	9.7 (−14, 34)	16 (−2, 33)	1 (−6, 8)
ΔMAP (mmHg)	−9 (−17, 0)*	4.7 (−23, 32)	18 (−8, 44)	−3.7 (−14, 7)
ΔFTA cardiac BR	−28 (−87, 31)	−6.8 (−24, 11)	−1.7 (−17, 13.5)	−18 (−43, 7)
ΔGain cardiac BR (ms/mmHg)	−2.6 (−4.5, −0.8)	−1.4 (−2.4, −0.4)*	−1.8 (−3.2, −0.3)*	−4 (−6.7, −1.3)*
ΔCausality cardiac BR	0.05 (−0.01, 0.1)	0.00 (−0.2, 0.2)	−0.01 (−0.09, 0.05)	−0.04 (−0.1, 0.02)
ΔCausality HR→SBP	−0.03 (−0.1, 0.04)	0.04 (−0.07, 0.1)	0.01 (−0.07, 0.08)	0.01 (−0.25, 0.09)
ΔFTA MP–BR	−10 (−24, 4)	−8.7 (−16, −1)*	−7.5 (−40, 25)	−23 (−46, 0)
ΔGain MP-BR (μV/mmHg)	0.05 (−0.6, 0.7)	−0.1 (−0.3, 0.6)	−0.26 (−0.42, −0.1)*	−0.4 (−1, 0.2)
Δcausality MP-BR	−0.07 (−0.16, 0.01)	−0.03 (−0.25, 0.19)	−0.1 (−0.2, −0.01)	−0.06 (−0.17, 0.04)
Δcausality EMG→SBP	−0.03 (−0.2, 0.15)	−0.01 (−0.08, 0.09)	0.01 (−0.02, 0.01)*	0.00 (−0.07, 0.07)
ΔEMG (μV)	−12.5 (−38.6, 13.6)	−18.7 (−58, 20.9)	−88 (−260, 84)*	−7.3 (−45, 30)
ΔEMGimp (μV·s)	−24 (−40, −9)*	−24 (−49, 1)*	−96 (−268, 76)*	−16 (−49, 17)
ΔMVC of MG (N)	0 (−40, 40)	−10 (−30, −1)*	−10 (−30, 100)	−3 (−17, 11)
ΔMVC of LG (N)	0 (−50, 50)	−25 (−55, 5)*	20 (−10, 50)	5 (−30, 40)
ΔMVC of S (N)	15 (−90, 110)	−3 (−15, 80)	−6 (−20, 6)	−2 (−30, 20)
ΔEMG isometric (μV)	6 (−90, 100)	−35 (−60, −6)*	0 (−60, 60)	0 (−75, 75)
ΔEMG isotonic (μV)	35 (−16, 23)	−145 (−244, −45)*	0 (−120, 120)	−15 (−110, 80)
Δpeak acceleration ($m\cdot s^{-2}$)	0.2 (−0.3, 7.5)	0.06 (−0.2, 0.3)	−0.3 (−1.1, 0.5)	−0.32 (−0.7, 1.3)
Δpeak velocity ($m\cdot s^{-1}$)	−0.2 (−0.26, −0.15)	−0.14 (−0.26, −0.01)*	−0.1 (−0.3, 0.15)	−0.2 (−0.5, 0.06)*
Δpeak height (m)	−3.8 (−4.6, −3.1)*	−2.3 (−4.5, −0.3)*	−2.17 (−6.4, 2)	−3.43 (−7, 0.15)*
Δpeak power (W)	0.5 (−0.5, 1.4)	−0.7 (−1.6, 0.2)*	−0.75 (−1.9, 0.4)	−0.02 (−0.57, 0.51)
Δflight time (s)	−0.04 (−0.05, −0.03)*	−0.03 (−0.05, −0.002)*	−0.02 (−0.07, 0.03)	−0.04 (−0.1, −0.01)*
ΔCOPr (mm)	6.8 (−5.4, 19)	3.8 (0.08, 7.5)*	1 (−0.8, 2.8)	4.95 (1.4, 8.4)*
ΔCOPrv ($mm\cdot s^{-1}$)	27 (−17, 71)	9.8 (3.7, 16)*	11.7 (−3.9, 27)	7.8 (−3, 18.5)

Values are the mean (95% lower and upper confidence limits).

Standing portion of the supine-to-stand test: HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; Cardiac BR, cardiac baroreflex; FTA, fraction time active; EMG, average rectified electromyogram signal; EMGimp, EMG impulse—EMG signal summed over a heartbeat; MP-BR, muscle-pump baroreflex. *Supine measurements:* MVC, maximum voluntary contraction; MG, medial gastrocnemius; LG, lateral gastrocnemius; S, soleus; EMG isometric, maximum EMG signal during maximum force against a fixed object; EMG isotonic, average EMG produced with maximum force exertion to move an object at a fixed velocity. *Jump test:* Peak acceleration, maximum acceleration during the ascending phase; peak velocity, maximum upward velocity; Peak height, maximum vertical displacement of the center of mass; Peak power, maximum mechanical power generated in the push phase; flight time, time during which an individual is airborne. *Postural sway:* COPr, average center of pressure sway radius; COPrv, average COP sway velocity.

*Indicates the mean is significantly different from zero ($p < 0.05$, Wilcoxon signed rank test), with expected increases for HR, COPr, and COPrv and decreases in all other variables.

contractions on blood pressure. Changes in the jump test results (peak velocity, flight time, and height) were negatively associated with IL-6.

Next, we investigated the quantitative relationship between sex (female, male) and intervention (control, exercise) using FDR with M-Huber estimation ($p \leq 0.05$) (Table 4).

In females, with respect to the cardiovascular system, standing heart rate was positively correlated with t-Tau, and vascular changes were positively correlated with IGF-1 and BDNF. Changes in baroreflex function were negatively related to changes in UCH-L1 and positively associated with IL-6 and GFAP. An increase in NfL was correlated with a decrease in muscle-pump coupling and changes in blood pressure. In relation to muscle contraction changes, GFAP was positively associated with MVC of the soleus and EMG generation during maximal isotonic contraction, while t-Tau, TNF-α, and IGF-1 were inversely associated with MVC of the medial gastrocnemius. Total tau was also directly correlated with sway velocity (COPrv).

In the male cardiovascular system, TNF-α was positively correlated with changes in HR, while IGF-1 was positively correlated and IL-6 was negatively correlated with blood pressure. Muscle activity was also related to biomarker changes. Total

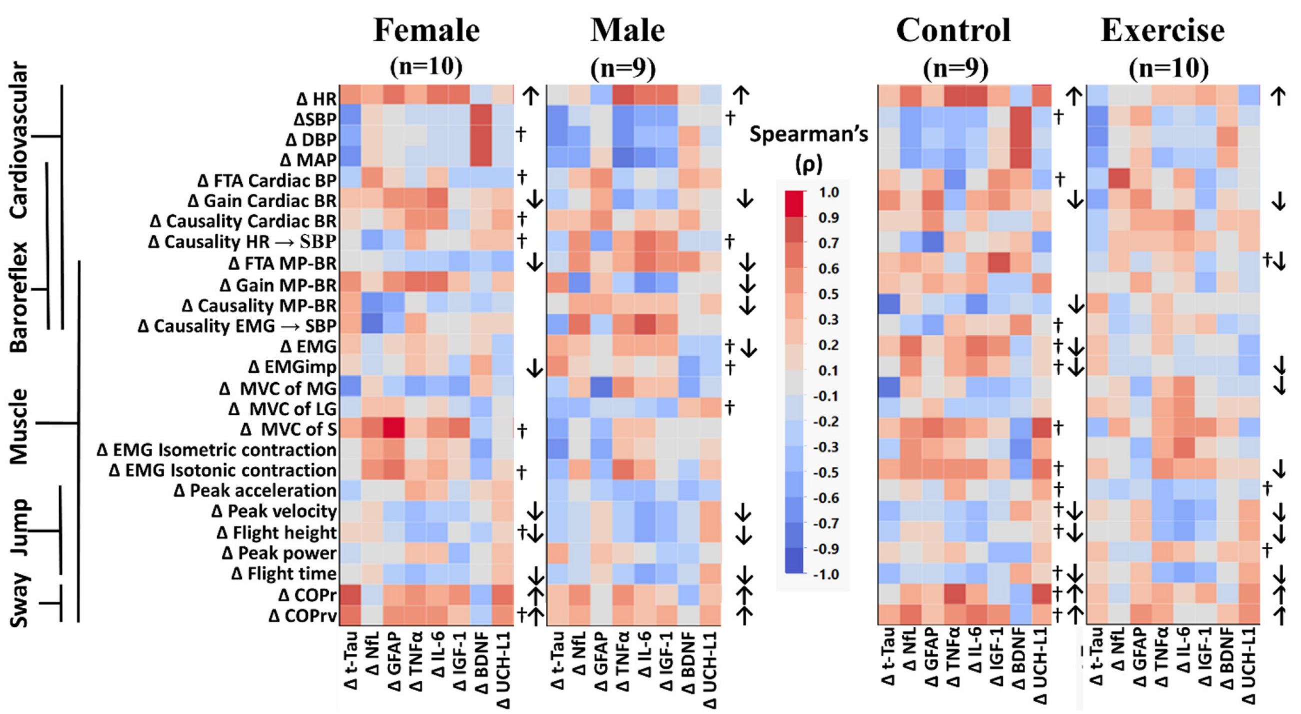

FIGURE 4
Color heat maps of Spearman's rank correlation analysis by sex (female, male) and by intervention (control, exercise). Changes in serum biomarkers (abscissa) from baseline (R−0 to BDC-2) were compared to changes in physical and physiological function (ordinate) from baseline (R−0 to BDC-1). Significant correlations using a robust false discovery rate are listed in Table 3. Physiological data were tested for normal distribution with the Shapiro–Wilk test. Data that were found to be not normally distributed are marked (†) on the right of their respective sex or intervention row. Arrows to the right of the heat map indicate a significant increase (↑) or decrease (↓) in physical/physiological variables from BDC-2 to R+0 (mean significantly different from 0). Student's *t*-test was performed for normally distributed data. Non-normally distributed data were tested using the Wilcoxon signed rank test. HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; FTA, fraction time active; MP-BR, muscle-pump baroreflex; MVC, maximum voluntary contraction; MG, medial gastrocnemius; LG, lateral gastrocnemius; S, soleus; EMG, electromyography; COPr, average center of pressure sway radius; COPrv, average COP sway velocity. Biomarkers: Tau, Tau protein; NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; BDNF, brain-derived neurotrophic factor; IGF-1, insulin-like growth factor 1; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.

tau, BDNF, and GFAP changed in the opposite direction from changes in MVC. In addition, t-Tau was negatively correlated with EMG with maximal isometric contraction, and TNF-α changed directly with changes in EMG from maximal isotonic contractions. The metrics from the jump test were predominantly associated with the pro-inflammatory proteins IFG-1 and IL-6. Decreases in peak velocity, flight time, and flight height were correlated with biomarker increases. Changes in peak power were positively associated with t-Tau. Finally, increases in sway parameters were correlated with neurodegenerative markers. COPr increased with t-Tau, and COPrv increased with UCH-L1.

In the control group, 11 physiological measures were significantly correlated with one of the seven biomarkers, whereas in the exercise group, only five physiological measures were associated with three of the biomarkers. TNF-α was positively correlated with HR and COPr and negatively correlated with cardiac baroreflex gain. Inflammatory proteins, IGF-1 and IL-6, were positively correlated with HR and muscle-pump baroreflex FTA (Table 3). Similar to females, BDNF in the controls was positively correlated and solely associated with blood pressure. All correlations with UCH-L1 were positive and correlated with HR, contraction EMG, and postural sway. Only two significant correlations were observed in the exercise group: one with t-Tau, which was negatively correlated with diastolic blood pressure, and one with NfL, which had a positive correlation with cardiac baroreflex FTA.

Discriminant analysis

Discriminant analysis for sex (Table 5), using the changes in biomarkers and physiological measures, revealed that the responses of t-Tau, COPr, muscle-pump baroreflex and gain, and MVC of the lateral gastrocnemius could identify female and male participants. With intervention (Table 6), discriminant analysis indicated that changes in three biomarkers (NfL, GFAP, and UCH-L1) and five physiological assessments (EMGimp, COPrv, muscle-pump baroreflex causality, MVC of the lateral gastrocnemius, and peak jump acceleration) could separate the control and exercise groups.

When applied to the four distinct groups (Table 7), a combination of eight variables was required: two biomarkers (t-Tau, IGF-1), three related to the muscle-pump baroreflex (gain, causality, EMGimp), two associated with muscle strength (MVC LG, peak jump power), and one with posture (COPrv).

TABLE 3 Correlation across all participants of individual changes in physical/physiological system markers from baseline (R0 to BDC-2) with the change in serum biomarkers (R1 to BDC4) using false discovery rate analysis with robust Huber M-estimation ($p < 0.05$).

System	Unit	△ Physical/physiological variable	Participants ($n = 20$) △ biomarker
Cardiovascular	Cardiac	HR	TNF-α (0.029)
	Vascular	Systolic BP	TNF-α (<0.014), BDNF (0.039)
		Diastolic BP	BDNF (0.022)
		Mean BP	BDNF (0.022)
	Cardiac BR	FTA	NfL (0.036)
		Gain	
		Causality	
	HR→SBP	Causality	
Cardiovascular and muscular	MP-BR	FTA	
		Gain	GFAP (0.011)
		Causality	
	EMG→SBP	Causality	TNF-α (<0.011), NfL (0.031)
Muscular	Muscles	Mean EMG	TNF-α (<0.001), BDNF (0.030)
		Mean EMG impulse	TNF-α (<0.001), BDNF (<0.001)
		MVC of soleus	IL-6 (<0.001), TNF-α (<0.001), NfL (0.014), GFAP (0.015), BDNF (0.048)
		MVC of lateral gastrocnemius	
		MVC of medial gastrocnemius	t-Tau (0.045)
		EMG isometric contraction	
		EMG isotonic contraction	GFAP (<0.001), NfL (<0.001), UCH-L1 (0.022)
	Jump test	Peak velocity	IL-6 (<0.001)
		Peak acceleration	
		Flight time	IL-6 (<0.001)
		Flight height	IL-6 (0.031)
		Peak power	
	Sway	COPr	TNF-α (<0.001), GFAP (0.011)
		COPrv	GFAP (0.004), NfL (0.011)

Significant correlations (robust false discovery rate [FDR] $p < 0.05$) between changes in physical/physiological variables and changes in serum biomarkers: Variable (robust FDR p-value). Data are presented for all participants. Inclusion criteria were set at FDR Huber M-estimation $p < 0.05$. Regardless of the change in physical or physiological variable, the biomarkers tracked in the opposite (red) or same direction (black) based on Spearman's coefficient (Figure 3). BP: blood pressure; FTA: fraction time active; HR→SBP: heart contractions changing systolic BP; MP-BR: muscle-pump baroreflex; EMG→SBP: leg muscle contractions changing systolic BP; MVC: maximum voluntary contraction; EMG: electromyography; COPr: average center of pressure sway radius; COPrv: average center of pressure sway velocity along the radius vector.

Interactions with baroreflex function

Based on inclusion into the multiple regression model for cardiac baroreflex, IGF-1 had a negative association, and GFAP had a positive association (Figure 5A). We also observed similar results for IGF-1 and GFAP with muscle-pump baroreflex, with an additional negative association for NfL and a positive association for TNF-α (Figure 5B).

Discussion

In this first-of-its-kind study at the intersection of spaceflight with aging and inactivity, we show that in older persons, (i) 14 days of simulated spaceflight using 6° head-down tilt bed rest promotes signs of neurodegenerative processes independent of 60- to 75-min daily rigorous exercise, and (ii) many of these biomarkers correlate with observed changes in cardiovascular and muscular function.

Elevated neural injury and inflammatory biomarkers

The global increase in neural injury markers and inflammatory cytokines in our participants is a powerful indicator of the severity of imposed inactivity in the 6° head-down position. This environment not only results in the physical deconditioning of these participants (Sadeghian et al., 2022) but is also associated with

TABLE 4 **Correlation across sex (female, male) and intervention (control, exercise) of individual changes in physical system markers from baseline (R0 to BDC-2) with the change in serum biomarkers (R1 to BDC4) using false discovery rate analysis with robust Huber M-estimation ($p < 0.05$).**

System	Unit	Δ Physical/physiological variable	Sex		Intervention	
			Females ($n = 10$) Δ biomarker	Males ($n = 9$) Δ biomarker	Control ($n = 9$) Δ biomarker	Exercise ($n = 10$) Δ biomarker
Cardiovascular	Cardiac	HR	t-Tau (0.0005) IGF-1 (0.027)	TNF-α (0.017)	TNF-α (0.006)	
	Vascular	Systolic BP	BDNF (0.045)			
		Diastolic BP		IGF-1 (0.034) IL-6 (0.015) TNF-α (0.027) t-Tau (0.034)		
		Mean BP				
	Cardiac BR	FTA	UCH-L1 (<0.0001)		IGF-1 (0.002)	NfL (0.001)
		Gain	IL-6 (0.027)		GFAP (0.039) UCH-L1 (0.045) IGF-1 (0.002)	
		Causality				
	HR→SBP	Causality				
Cardiovascular and muscular	MP-BR	FTA				
		Gain	Il-6 (0.0002) GFAP (0.032)	IL-6 (0.017) IGF-1 (0.001)		
		Causality			IL-6 (0.0001) UCH-L1 (<0.0001)	
	EMG→SBP	Causality	NfL (0.001)		GFAP (0.033)	
Muscular	Muscles	MVC of soleus	GFAP (0.023)	t-Tau (0.002)		
		MVC of lateral gastrocnemius				
		MVC of medial gastrocnemius	t-Tau (<0.0001) TNF-α (0.001) IGF-1 (0.045)	BDNF (0.016) GFAP (0.001)	t-Tau (<0.0001)	IL-6 (0.024)
		EMG isometric contraction		t-Tau (0.004)		IL-6 (0.009)
		EMG isotonic contraction	GFAP (0.045)	TNF-α (0.039)		
	Jump test	Peak velocity		IGF-1 (0.001) IL-6 (0.009)		
		Flight time				
		Flight height		IGF-1 (0.029) IL-6 (0.007)		
		Peak power		t-Tau (0.016)		
	Sway	COPr		t-Tau (<0.0001)		t-Tau (0.001)
		COPrv	t-Tau (0.028)	UCH-L1 (<0.0001)	GFAP (0.015) NfL (<0.0001)	t-Tau (0.012)

Significant correlations between changes in physical variables and changes in serum biomarkers: variable (false discovery rate, robust *p*-value). Data are presented for sex (combines the participants of a single sex from the control and exercise groups) and intervention (combines the participants of a single intervention from the female and male groups). Inclusion criteria were set at FDR Huber M-estimation $p < 0.05$. Regardless of the change in physical or physiological variable, the biomarkers tracked in the opposite (red) or same direction (black) based on Spearman's coefficient (Figure 3). BP, blood pressure; FTA, fraction time active; HR→SBP, heart contractions changing systolic BP; MP-BR, muscle-pump baroreflex; EMG→SBP, leg muscle contractions changing systolic BP; MVC, maximum voluntary contraction; EMG, electromyography; COPr, average center of pressure sway radius; COPrv, average center of pressure sway velocity along the radius vector.

neurological insult. Since these changes occurred independent of the specific space-based exercise intervention, these data suggest that the 1 h daily of applied exercise did not overcome the 23 h of inactivity. As these data were collected in the head-down and not supine position, the application to hospital bed rest is not direct, but the rapidity with which these changes occurred indicates that they are important to monitor during extended immobilization as indicators of post-intensive care syndrome (Voiriot et al., 2022).

Neural injury (NfL, GFAP)

The increase in NfL levels from the beginning to the end of the bed rest reflects similar changes reported from cosmonauts (Zu Eulenburg et al., 2021). They reported an average NfL level increase of 33% (11.4–15.2 pg/mL) in five male cosmonauts [49.2 (2.7) (SEM) years], which closely mimics the changes observed in our bed rest participants. However, the mean flight duration of the astronauts on the international space station was 169 days, 12 times

TABLE 5 Discriminant analysis of bed rest participants by sex (female, male).

	Discriminants				
	t-Tau	COPr	Gain: MP-BR	Causality: MP-BR	MVC of LG
F-ratio	25.0	10.1	7.0	2.1	18.0
Prob $> F$	0.0002	0.007	0.020	0.170	0.001
Mean					
Female ($n = 10$)	−0.12	5.00	0.10	−0.05	−0.15
Male ($n = 9$)	0.30	2.95	−0.37	−0.09	0.14
All ($n = 19$)*	0.08	4.03	−0.12	−0.07	−0.01

*Analysis used 19 participants (one male participant was missing muscle and jump data). Stepwise inclusion stopped when all were properly classified (entropy $r^2 = 0.99$; −2log-likelihood = 0.192). Control participants were on 6° head-down tilt bed rest for 14 days without daily exercise, while the exercise group had 1 h daily of a combination of high-intensity interval training, aerobic, and strength exercises. MP-BR, muscle-pump baroreflex; MVC, maximum voluntary contraction; LG, lateral gastrocnemius. Biomarkers: t-Tau, total tau protein.

All physical/physiological measurements and biomarkers were made available for discriminant analysis. Variables entered the model in a forward stepwise manner by best probability until all participants were properly classified.

TABLE 6 Discriminant analysis of bed rest participants for interventions (control, exercise).

	Discriminants							
	NfL	GFAP	UCH-L1	EMGimp	COPrv	Causality, MP-BR	MVC of LG	Jump peak acceleration
F-ratio	8.4	2.1	15.3	8.5	31.8	9.5	0.05	2.7
Prob $> F$	0.016	0.178	0.003	0.016	0.0002	0.012	0.835	0.133
Mean								
Control ($n = 9$)	4.56	18.1	−1.81	−64.0	18.6	−0.094	0.121	−0.075
Exercise ($n = 10$)	6.49	21.3	2.48	−20.5	9.10	−0.047	−0.126	0.187
All ($n = 19$)*	5.58	19.8	0.448	−41.1	13.60	−0.069	−0.009	0.063

All physical/physiological measurements and biomarkers were made available for discriminant analysis. Variables entered the model in a forward stepwise manner by best probability until all participants were properly classified.

*Analysis used 19 participants (one male control participant was missing muscle and jump data). Stepwise inclusion stopped when all were properly classified (entropy $r^2 = 0.99$; −2log-likelihood = 0.246). Control participants were on 6° head-down tilt bed rest for 14 days without daily exercise, while the exercise group had 1 h daily of a combination of high-intensity interval training, aerobic, and strength exercises. MP-BR, muscle-pump baroreflex; MVC, maximum voluntary contraction; LG, lateral gastrocnemius; EMGimp, electromyogram impulse—the area of the rectified EMG signal between heartbeat R wave peaks (RR interval); COPrv, average center of pressure sway velocity. Biomarkers: NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; UCH-L1, ubiquitin carboxy-terminal hydrolase L1.

TABLE 7 Discriminant analysis of bed rest participants for all conditions (female controls, female exercise, male controls, male exercise).

	Discriminants							
	t-Tau	IGF-1	Gain MP-BR	Causality MP-BR	EMGimp	MVC of LG	Peak jump power	COPrv
F-ratio	51.7	3.83	9.63	11.0	14.8	34.4	28.7	13.0
Prob $> F$	<0.0001	0.057	0.005	0.003	0.001	<0.0001	<0.0001	0.002
Mean								
Female control ($n = 4$)	−0.158	−116	0.054	−0.073	−24.2	0.00043	0.475	27.2
Female exercise ($n = 6$)	−0.093	−155	0.132	−0.031	−24.0	−0.244	−0.688	9.81
Male control ($n = 5$)	0.048	−28.4	−0.265	−0.111	−95.8	0.217	−0.754	11.7
Male exercise ($n = 4$)	0.615	26.0	−0.499	−0.071	−15.1	0.052	−0.049	8.05
All ($n = 19$)*	0.080	−75.2	−0.122	−0.069	−41.1	−0.009	−0.326	13.6

All physical/physiological measurements and biomarkers were made available for discriminant analysis. Variables were entered into the model in a forward stepwise manner by best probability until all participants were properly classified.

*Analysis used 19 participants (one male control participant was missing muscle and jump data). Stepwise inclusion stopped when all were properly classified (entropy $r^2 = 0.99$; −2log-likelihood = 0.192). Control participants were on 6° head-down tilt bed rest for 14 days without daily exercise, while the exercise group had 1 h daily of a combination of high-intensity interval training, aerobic, and strength exercises. MP-BR, muscle-pump baroreflex; MVC, maximum voluntary contraction; LG, lateral gastrocnemius; EMGimp, electromyogram impulse—the area of the rectified EMG signal between heartbeat R wave peaks (RR interval); COPrv, average center of pressure sway velocity. Biomarkers: t-Tau, total tau protein; IGF-1, insulin-like growth factor 1.

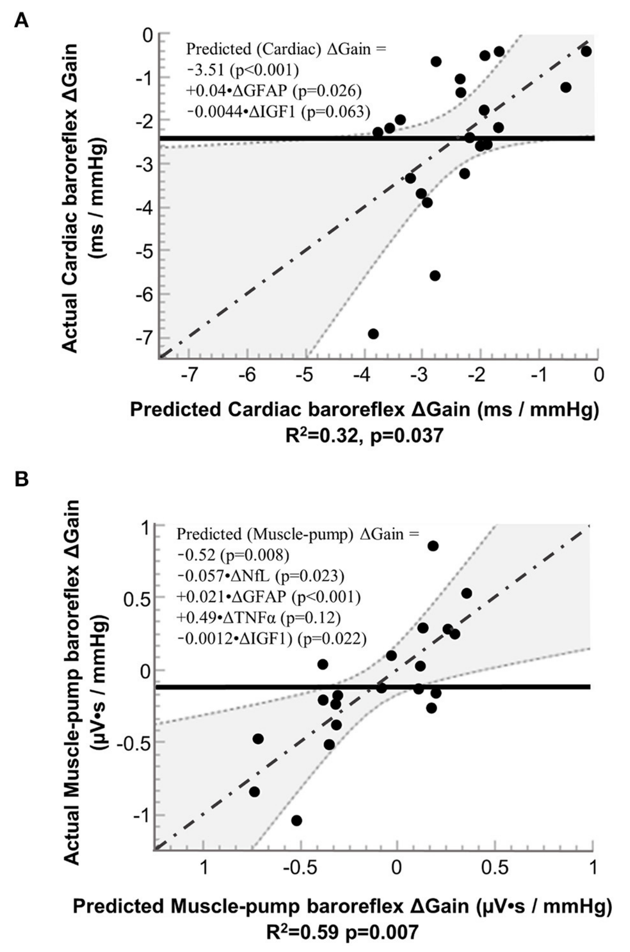

FIGURE 5
Results from stepwise regression analysis of pre-to-post (R+0 – BDC-2) changes (Δ) in neural injury biomarkers with pre-to-post (R+0 – BDC-1) changes in the gain of **(A)** cardiac baroreflex and **(B)** muscle-pump baroreflex. NfL, neurofilament light chain; GFAP, glial fibrillary acidic protein; TNF-α, tumor necrosis factor alpha; and IGF-1, insulin-like growth factor 1. Solid line (———): mean value of actual; dashed lines and shaded areas (……): 95% confidence area; dash dotted line (-·-·-·-·): regression line.

longer than our older participants spent in HDBR. Furthermore, the effect of the spaceflight and its analog HDBR on overall NfL levels could be a cause for concern. Rising serum NfL levels with reduced activity have been associated with cognitive decline (Desai et al., 2022) and all-cause mortality in older adults (Nguyen et al., 2022).

Considering that rising NfL levels signal the early onset of neural injury as well as many neurological complications (Ferreira-Atuesta et al., 2021; Verde et al., 2023), these data indicate that the HDBR is an effective model for weightlessness exposure in relation to neurological insults to the brain. We hypothesized that the headward fluid shifts observed in HDBR would predispose participants to this type of injury. The elevations in NfL we observed in older adults after 2 weeks of HDBR and those observed in five cosmonauts (Zu Eulenburg et al., 2021) are not unlike the reported changes in NfL from athletes with concussions (Shahim et al., 2017). One consideration for investigation should be the relationship between the headward fluid shift experienced in both HDBR and spaceflight by test participants and the brain, which may be a physical link between microgravity and concussion.

GFAP

The results from five male cosmonauts showed a 20% increase in GFAP levels (169–215 pg/mL) (Zu Eulenburg et al., 2021), which were similar in magnitude to the HDBR participants. The elevation in GFAP in our older adults in HDBR is notable in that it not only confirms, in a spaceflight analog, the cosmonaut results, but that similar increases are emerging as a useful prognostic and diagnostic marker for multiple neurological diseases (Abdelhak et al., 2022). Prior to the latest human spaceflight results (Zu Eulenburg et al., 2021), investigations of GFAP levels in altered gravity had shown varying results. After 14 days of microgravity exposure, the expression of astrocyte-specific GFAP was observed to decrease significantly (Day et al., 1998); however, the same effect was not observed with long-term microgravity exposure (Bellone et al., 2016). In an animal study (Grigoryan et al., 2012), GFAP levels increased during exposure to long-term microgravity. Mao et al. reported an increase in perivascular reactive GFAP astrocytes in the hippocampus of mice who had spent 35 days on the International Space Station when compared to control mice on the ground (Mao et al., 2020). Future research should examine the correlation of GFAP levels with long-term human spaceflight and physical inactivity and determine the directionality of such correlation.

Growth factors (IGF-1)

In a study of four male and four female astronauts, Hughson et al. (2016) reported elevated IGF-1 following 6 months on the International Space Station (ISS). However, they indicated that female participants tended to have smaller changes. In the current study, we found a reduction in IGF-1 in the female participants, with no change in the males. The results from the analog and space environments suggest that sex differences reduce the gravitational influence on IGF-1. Bed rest is analogous and does not completely match the spaceflight environment. Although the exercises were space-based, they were not the same, and the duration of bed rest was ∼10% of that of the average crewmember's flight.

Previous animal models in microgravity research had suggested that a suppression in the production of IGF-1 is most common when bones are not exposed to mechanical loading (Kumei et al., 2002). In particular, Kumei et al. (2002) observed reduced mRNA levels for IGF-1 in rat osteoblast cultures during spaceflight compared to ground controls. They also found that microgravity completely suppressed the expression of insulin receptor substrate-1, a molecule involved in IGF-1 signaling. The results from our study may suggest that HDBR inactivity in older adults promotes physical deconditioning (Aagaard et al., 2010; Jasim et al., 2017), and the reduction in IGF-1 in the female participants suggests a greater or earlier susceptibility of older females to bed rest.

Pro-inflammatory cytokines (TNF-α and IL-6)

We observed significant increases in TNF-α and IL-6 following HDBR. Previous studies investigating the levels of TNF-α and IL-6 during bed rest have indicated an increase in overall levels of these cytokines. Notably, bed rest is often associated with bone and muscle mass loss and is an overall stressor on the cardiovascular system. Previous investigations have also shown that both young and older populations have an increase in overall TNF-α and IL-6 levels. However, the older population showcases even more pronounced levels of TNF-α and IL-6, which can potentially signal an increase in inflammatory markers with immobility and increasing age.

Although the results of serum and urinary data for cytokines in astronauts are mixed, there is evidence of their elevation during space missions (Thiel et al., 2017). A study of endothelial cell cultures has shown a marked increase in IL-6 production up to 3 months post-flight (Muid et al., 2013).

In a study of mice exposed to 35 days of microgravity, Mao et al. (2020) described a relationship between pro-inflammatory cytokines and damage to the blood–brain barrier (BBB) and related pathways to spaceflight. The study found evidence of elevated proteins associated with apoptosis and a decrease in tight junction proteins. The combination of decreased tight junction proteins, increased GFAP, and the presence of apoptosis markers could have led to damage to the BBB. Mao et al. also found that the Cdk5 signaling pathway, which is essential for the cellular mechanisms behind cognition and regulation of neural cell death and is associated with the NfL, Tau, and BDNF pathways (Pao and Tsai, 2021), showed remarkable downregulation after exposure to spaceflight (Mao et al., 2020).

With the similarity between HDBR and data collected from human and animal models in space, we recommend integrating measures of neural function with biomarkers of neural injury into mission planning and as a component of exercise prescription. The parallels in neurodegenerative markers and inflammatory proteins with the animal models could indicate that the cerebral impact of the head-down position may not only mimic fluid shifts in spaceflight but may also provoke BBB damage. Further research into the Cdk5 pathway in HDBR and spaceflight is recommended.

Serum markers and physiological measurements

Four of eight serum markers showed consistent change with bed rest independent of sex and intervention, while a fifth changed in females but not males and independent of intervention. To further investigate the significance of all eight serum markers, we examined their relationship with changes in cardiovascular and muscular system physiology. Did physiological function change over bed rest in a manner consistent with the change (positive or negative) in a serum marker? With intra-individual variability associated with differences in participant physiology, it was expected that responses to bed rest may not have been similar in magnitude or direction and that this would mask biomarker–physiological function relationships when investigated as group effects. However, if the underlying physiological processes were similar, then any changes observed in physiological function would be reflected in consistent changes in their associated biomarkers and could be tested with correlation analyses.

Spearman's ranked test was first applied to find the directionality and strength of correlation. Given the large number of multiple comparisons, false discovery rate analysis (FDR) was used. The robust Huber M-estimation was used due to non-normally distributed data and outlier effects. Because of the complexity of conducting a bed rest project involving older people, only a small number of participants in each subgroup was feasible. Therefore, we have limited in-depth discussion of the effects associated with bed rest, with links to possible sex or intervention differences. Finally, Spearman's rank test, FDR, discriminant, and multiple regression analyses are inferential, not causal, and are used to identify areas of interest for future targeted research.

Heart rate and blood pressure

Two serum markers, namely TNF-α and BDNF, were associated with the cardiovascular system when all participants were grouped together. Changes in TNF-α were correlated with elevated cardiovascular stress during standing, while BDNF may have had a repairing role in the presence of cardiovascular stressors.

TNF-α is secreted by several cardiovascular cells (endothelial, smooth muscle, and cardiac muscle) and has wide-ranging effects on these systems through cardiac muscle function and vasodilation (Urschel and Cicha, 2015). The involvement of TNF-α with both HR and blood pressure is therefore consistent with its sites of secretion and action. Increases in TNF-α were correlated with decreases in blood pressure and increases in HR. The behavior of TNF-α was consistent with this hypothesis as HR and blood pressure are inversely related through the baroreflex; decreases in blood pressure led to increases in HR. Those participants with the greatest increase in orthostatic challenge (i.e., largest drop in blood pressure upon standing) had the largest increase in TNF-α.

Although we did not observe a significant change in BDNF with bed rest, we detected a positive correlation between BDNF levels and blood pressure. This would suggest that while the BDNF response to bed rest was variable between participants, it changed in the same direction with a similar relative order of magnitude as blood pressure in these participants.

BDNF is secreted by the central nervous system, lungs, heart, and liver and plays a key role in protecting neurons in both the central and peripheral nervous systems. Responses to orthostatic stress are most characterized by alterations in HR via vagal withdrawal and increased involvement of vasoconstrictor tone (Blaber et al., 2022). Previous research has shown that a decrease in overall BDNF levels has been associated with neurodegenerative disorders such as Alzheimer's and Parkinson's disease (Phillips et al., 1991; Levivier et al., 1995; Connor et al., 1997; Parain et al., 1999; Howells et al., 2000; Michalski and Fahnestock, 2003). Further research has shown that when exposed to acute stressors, after an initial decrease, an increase in BDNF levels is observed. Such a pattern was observed with 14 days of bed rest (Soavi et al., 2016). The increase in BDNF levels was thought to act as a restorative to combat the stressor and was shown to partially repair the metabolic damages caused by inactivity (Soavi et al., 2016).

The current study is consistent with the hypothesis that BDNF has a repairing role. The positive correlation with blood pressure levels could suggest the factor's repair effect to combat the physiological downsides caused by 14 days of head-down bed rest, especially to the blood pressure regulating mechanisms. For example, participants with larger secretions of BDNF would be associated with smaller decreases or even increases in BP upon standing. Participants with lower or reduced BDNF, and therefore less protection, would be more susceptible to blood pressure declines with standing.

Cardiac and muscle-pump baroreflex

The results from this study show an interaction between the individual cytokines and neural injury biomarkers with cardiac and muscle-pump baroreflexes, which could provide insight into the potential role of inflammatory responses and neurodegeneration in spaceflight and aging. Changes in NfL and GFAP were significantly correlated with baroreflex function, while NfL, GFAP, IGF-1, and TNF-α emerged as multiple regression coefficients for baroreflex gain.

In our previous analyses of cardiovascular control in the same participants, we showed a degradation in the neural and not the mechanical components of the cardiac and muscle-pump blood pressure feedback loop, which was not improved with exercise (Sadeghian et al., 2022). We reported similar cardiac muscle-pump baroreflex impairments with long-term (60 days) bed rest (Xu et al., 2020) and cardiac baroreflex with short-duration (8–16 days) spaceflight (Blaber et al., 2022). We proposed that these could result from both inactivity and cephalad fluid shifts associated with HDBR and weightlessness.

Correlation analysis indicated a significant positive relationship between NfL and cardiac baroreflex FTA, which were significantly reduced after bed rest. We also observed a significant increase in NfL with bed rest. The production of NfL occurs within the cell bodies of neurons located in the central nervous system (CNS) and peripheral nervous system (PNS), and its production is triggered by neuronal damage or dysfunction (Yuan et al., 2012; Khalil et al., 2018). While the specific triggers for NfL production are not fully understood, it is known that various pathological processes affecting neurons, such as neurodegenerative diseases (Rosengren et al., 1996; Gaiottino et al., 2013; Khalil et al., 2018; Gaetani et al., 2019), traumatic brain injury (Snowdon et al., 1997; Thelin et al., 2017), or neuronal damage (Strydom et al., 2018), can lead to increased production and the release of NfL into the surrounding tissues and blood. Elevated levels of NfL in the blood are indicative of neuronal injury or degeneration, as the protein leaks out from damaged neurons (Gaetani et al., 2019). In addition to the CNS, peripheral neuropathies and injuries affecting peripheral nerves can also result in elevated NfL levels (Strydom et al., 2018).

GFAP had a positive coefficient with muscle-pump baroreflex gain. Like NfL, the production of GFAP occurs predominantly in the brain and spinal cord (Huang et al., 2019). Astrocytes are the main source of GFAP synthesis (Rodnight et al., 1997); however, GFAP expression is not exclusive to astrocytes, as it can also be found in other glial cell types (Eng et al., 2000). Triggers that upregulate the expression of GFAP (Rodnight et al., 1997) include brain injury (Thelin et al., 2017), neuroinflammation, ischemia, infection, neurodegenerative diseases (Pelinka et al., 2004), and other insults that lead to astrocyte activation or reactive gliosis.

Elevated levels of GFAP can be detected in cerebral spinal fluid (CSF) and blood following CNS injuries or neurodegenerative conditions (Middeldorp and Hol, 2011), indicating astrocyte reactivity and the extent of CNS damage. GFAP expression and reactivity in astrocytes can be both beneficial and detrimental, depending on the context (Escartin et al., 2021). In this study, we observed a global increase in GFAP along with a positive correlation with muscle-pump baroreflex gain. This could indicate a possible neurological injury associated with skeletal muscle activation in the blood pressure control system, for which GFAP may have been beneficial since a higher astrocyte response was associated with better baroreflex gain than a lower response.

To further explore the interaction of inflammation, neural injury, and blood pressure regulation, we performed multiple regression analysis of the serum biomarker data with cardiac and muscle-pump baroreflex gain.

Multiple regression analysis for cardiac baroreflex gain showed a positive relationship with GFAP and a negative relationship with IGF-1, variables not seen with FDR. However, the assumptions for the two statistical procedures are different. The former looks at the probability of correlation between paired variables over multiple comparisons, and the latter determines the relative contribution of a specific combination of variables to predicting a change in a single variable. These results indicate a possible relationship between neurodegenerative effects on cardiac baroreflex function and the observed increase in GFAP, similar to the FDR analysis of muscle-pump baroreflex. The negative IGF-1 relationship parallels aging effects (Aagaard et al., 2010; Jasim et al., 2017).

Multiple regression analysis of the muscle-pump baroreflex indicated the additional involvement of NfL and TNF-α compared to the cardiac baroreflex. This may reflect additional complexity, as the muscle-pump baroreflex involves both autonomic and motoneuron recruitment. The positive coefficient for TNF-α on baroreflex gain is consistent with its relationship with the cardiovascular system observed in the correlational analysis, where it was related to increased HR and reduced blood pressure during standing. The negative coefficient for NfL with muscle-pump gain is consistent with the hypothesis of neurological insult, resulting in a reduced reflex response to blood pressure.

Although our previous results indicated no effect of bed rest on the causal relationship between muscle activity and blood pressure (EMG→SBP, muscle-pump mechanics) (Sadeghian et al., 2022), a correlational analysis of NfL showed a significant negative correlation. These data suggest neural degradation, which impacts afferent and efferent components of the reflex, and may explain the extended time for muscle-pump reflex deficits following bed rest when compared to the cardiac baroreflex (Xu et al., 2020).

Muscle contraction, postural sway, and jump test

An examination of tests of postural sway and muscle strength, control, and power revealed significant correlations with neurodegenerative and pro-inflammatory markers following HDBR. Together, these biomarkers could be leading indicators for the onset of degenerative processes in the skeletal muscle pathways related to reduced motor unit recruitment and/or remodeling during inactivity.

Like the cardiovascular system, changes in TNF-α, BDNF, and GFAP were correlated with a wide variety of muscular variables. TNF-α was positively correlated with changes in muscle EMG, soleus MVC, and COPr. GFAP was associated with soleus MVC, isotonic contraction EMG, and postural sway (COPr, COPrv). BDNF was significantly correlated with EMG during standing and soleus MVC. paired with in relation to We also observed significant decreases in these same physical and physiological responses with bed rest. This may indicate a strong influence of inflammation (TNF-α) and the recruitment of neural restorative measures (BDNF), as well as MVC of the soleus.

The neural injury marker, t-Tau, correlated negatively with the MVC of the medial gastrocnemius. Tau is a protein that stabilizes the structure of neurons in the brain. Total tau is a biomarker that measures the total amount of tau protein in the blood or cerebrospinal fluid. Although there is limited prior research on how t-Tau levels may change after bed rest, studies have shown that t-Tau increases with age and may be a marker of age-related cognitive decline and neurodegeneration (Harrison et al., 2019; Huseby et al., 2019). Regarding neurodegenerative diseases, t-Tau levels tend to be elevated in the cerebrospinal fluid of affected individuals (Harrison et al., 2019). This increase is believed to be due to the release of tau protein from degenerating neurons in the brain (Huseby et al., 2019).

We found that UCH-L1 was positively correlated with the change in isotonic contraction. Ubiquitin C-terminal hydrolase L1 (UCH-L1) is a protein that is primarily expressed in neurons and plays an important role in development. UCH-L1 has been identified as a potential biomarker for traumatic brain injury and other neurological conditions (Yang et al., 2023). There is limited research on how UCH-L1 levels may change after bed rest or with aging specifically. However, studies have shown that UCH-L1 levels can be affected by a variety of factors, including traumatic brain injury, neurodegenerative diseases, and aging (Reinicke et al., 2019). In the case of traumatic brain injury, UCH-L1 levels may increase due to neuronal damage. Similarly, in neurodegenerative diseases, UCH-L1 levels may increase as a result of neuronal damage and loss (Vinciguerra, 2019). UCH-L1 levels tend to decrease with age (Reinicke et al., 2019), possibly due to a decline in the activity of the ubiquitin-proteasome system in neurons. This decline in UCH-L1 activity may contribute to age-related cognitive decline and an increased risk of neurological disorders (Yang et al., 2023).

Interleukin-6 had its primary interaction with the jump test. It was significantly and negatively correlated with peak velocity, flight time, and flight height, which all had significant reductions after bed rest while also being positively correlated with soleus MVC. Immune cells (Ferguson-Smith et al., 1988) are the primary source of IL-6; however, IL-6 can also be secreted by endothelial cells, fibroblasts, and certain tumor cells (Ferguson-Smith et al., 1988). The effects of IL-6 are diverse and context-dependent, involving the regulation of inflammation, hematopoiesis (the production of blood cells), and the acute-phase stress response. Additionally, it impacts multiple organ systems, such as the immune system, cardiovascular system (Kanda and Takahashi, 2004), nervous system (Zhou et al., 2021), musculoskeletal system (Muñoz-Cánoves et al., 2013), and the liver (Hsieh et al., 2019). Bed rest, in general, can lead to muscle wasting and atrophy, resulting in a decrease in the production of anti-inflammatory cytokines (Drummond et al., 2013). This can cause an imbalance in the inflammatory response, potentially leading to increased levels of pro-inflammatory cytokines such as IL-6 (Drummond et al., 2013).

IL-6 plays a significant role in regulating muscle power and strength (Park et al., 2013) and is crucial for the body's inflammatory and immune response to stress (Ferguson-Smith et al., 1988). Some studies indicate that moderate increases in IL-6 can enhance muscle force production and overall performance (Ferrucci et al., 2002; Pereira et al., 2009; Park et al., 2013), likely due to its ability to facilitate glucose uptake, providing more energy to the working muscles (Park et al., 2013) (measured in this study by the MVC test). This may explain the positive correlation between IL-6 and the soleus MVC test. On the other hand, maintaining a balance in IL-6 levels is essential because chronic elevation caused by inflammation can have adverse effects on muscle power and function (Haddad et al., 2005). In the current study, IL-6 had the most interactions with the jump test, which is a measure of muscle power.

Sex and exercise

In our previous publication (Sadeghian et al., 2022), we found that the reduction in baroreflex was not affected by exercise. Following bed rest, similar numbers of females and males presented with presyncopal symptoms during the 5-min stand (Sadeghian et al., 2022) and 15-min tilt test (Hajj-Boutros et al., 2023). Given the small number of participants, we therefore examined the effects of sex by combining control and exercise participants within sex and intervention by combining male and female participants within intervention. The biomarker correlations displayed different patterns when examined by sex, although most biomarkers were found to be significantly related to a physical/physiological variable in either one. The males had a greater number of negative interactions compared to the females, with the majority being inflammatory proteins (IL-6, TNF-α, and IGF-1) in blood pressure, muscle-pump baroreflex, and jump test results. This may indicate a greater inflammatory response to HDBR in males compared to females. In our article on baroreflex function in these participants (Sadeghian et al., 2022), we found a greater reduction in muscle activation and muscle-pump control during standing in the males. This is evident in the data presented here, where male participants had twice the reductions in muscle-pump baroreflex indices compared to females.

When we compared control with exercise participants, we observed a reduction in the number of significant correlations. Both control and exercise groups had fewer correlations than either the female or male groupings. In the control group, the inflammatory marker TNF-α was associated with cardiac control, while IGF-1 and IL-6 were associated with the muscle-pump baroreflex. The neurodegenerative markers GFAP, UCH-L1, and NfL were correlated with reflex mechanisms: cardiac and muscle-pump baroreflexes, and postural sway. The exercise group, on the other hand, only had minimal neurodegenerative biomarker correlations: NfL with cardiac baroreflex and t-Tau with the jump test and postural sway. These data support the hypothesis that the exercise program would reduce the effects of bed rest on neural injury. However, the correlation of NfL with cardiac baroreflex and sway, along with the lack of protection against orthostatic intolerance (Sadeghian et al., 2022), are strong indicators that these exercises were not effective for maintaining the cardio-postural control system (Xu et al., 2017, 2020).

Several serum and physical/physiological markers were identified through discriminant analysis. These could provide further information on the whole-body impact of bed rest in relation to sex and exercise intervention in older persons. Unlike correlational analysis, where we obtained data on links between biomarkers and physical outcomes, discriminant analysis provides an avenue to investigate distinguishing characteristics related to specific groups. With main effects and all subgroup comparisons, cardiac-specific variables were not returned as discriminatory measures. This may indicate that their responses were similar across all groups. Indeed, we previously reported that these participants' HR and cardiac baroreflex responses were universally impacted (Sadeghian et al., 2022) by bed rest.

Instead, serum markers and muscle-related measures were highlighted, with each containing at least one biomarker, one muscle-pump variable, and a muscle strength measurement. These data show that the male and female participants responded differently to bed rest in combination with the intervention. These differences were related to a greater negative effect of t-Tau and IGF-1 and the combined effects of motor control associated with muscle-pump baroreflex, calf muscle contractions, jumping power, and postural sway.

Strengths and limitations

Through quantitative serum analysis, we showed significant increases in inflammatory and neurodegenerative biomarkers over a 14-day exposure to HDBR in otherwise healthy 55- to 65-year-olds. Our data are consistent with recently reported data from cosmonauts, and we have provided additional markers to be considered. The exercise intervention had no significant impact on these changes, nor did it prevent a significant loss of orthostatic tolerance. Because of the logistical complexities of mounting a study like this, only a few male or female participants (4–6) were in each category. This limited our ability to investigate the sex/intervention interactions for the biomarkers from the ANOVA analysis; however, we have presented the means (95% CI) as pilot data for future comparisons.

For the first time, we had the opportunity, as part of a dedicated head-down tilt bed rest study with older persons, to investigate cardio-postural control and biomarkers of neural injury in males and females with an exercise intervention. This provided unique data in relation to post-HDBR and possible insights into spaceflight neural deconditioning. We examined the correlation between the changes in these biomarkers with a robust false discovery rate analysis correcting for multiple comparisons. This revealed relationships between neurodegenerative biomarkers and blood pressure and posture control, providing evidence in support of cardio-postural impairment through HDBR-associated neural injury. The association of neural injury (GFAP, NfL), growth factors (IGF-1), and pro-inflammatory (TNF-α) markers was also supported through multiple regression analysis. Both correlational and multiple regressions do not indicate causal relationships and are only used here to provide support to hypothesize and form the base for future studies.

As with the analysis of biomarkers by ANOVA, we were limited in our ability to test relationships between biomarkers and physiological measurements at the sex/intervention level. However, the use of discriminant analysis, which used the full data set, provided important information regarding the influence of serum markers and physiological outcomes in relation to both sex and exercise and their respective combinations.

This study was one of eight research groups embedded in the HDBR project. Our hypotheses focused on cardio-postural control declines with bed rest, making many measurements beyond the scope of our study. For example, we were unable to relate the changes observed with the neurodegenerative biomarkers to associated cognitive and psychological outcomes. Furthermore, the multi-modal exercise intervention was designed by an external expert committee (Hedge et al., 2022), within whose framework all funded research programs functioned. As such, it is difficult to relate current observations to specific exercises. Analyses exploring these aspects will be pursued in future publications from us and the other teams participating in the first Canadian aging and inactivity study.

Conclusion

These data suggest that even a short period (9–14 days) of HDBR in older persons can elevate major protein markers of neural injury, which were correlated with changes in the cardiovascular and muscular systems, and in particular those systems involving the baroreflex and postural sway. Additionally, discriminant and multiple regression analyses point to neurodegenerative components associated with baroreflex impairment following HDBR that exercise was unable to halt. This raises significant concerns regarding post-bed rest recovery and its long-lasting effects, particularly in the elderly. Finally, these results highlight the need for neurological monitoring of astronauts as space missions become longer.

Data availability statement

The datasets presented in this article are not readily available because data may only be shared for the use under which it was ethically approved. Requests to access the datasets should be directed to andrew_blaber@sfu.ca.

Ethics statement

The studies involving humans were approved by McGill University Health Centre Research Ethics Board, Office of

Research Ethics at Simon Fraser University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

AB had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. AB and IS contributed to the concept and design and after obtaining funding, AB coordinated and supervised data acquisition and statistical analysis. FS and DN conducted all sit-to-stand tests and collected and analyzed muscle activity, jump test, and baroreflex function data. All contributed to interpreting the data and drafting the manuscript. All authors contributed to the article and approved the submitted version.

Funding

The bed rest study was conducted as a collaborative effort by the Canadian Space Agency, the Canadian Institutes of Health Research (CIHR), and the Canadian Frailty Network (CFN). This research was funded by the CIHR grant UH1-161691, with AB as the principal investigator and IS as the co-investigator. The funders had no role in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, the preparation, review, or approval of the manuscript, or the decision to submit the manuscript for publication.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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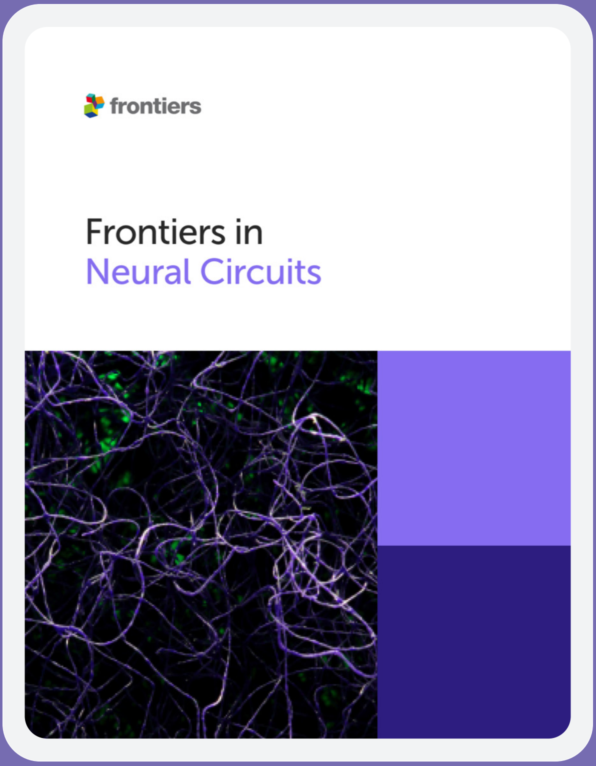

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