Integrated Research Plan to Assess the Combined Effects of Space Radiation, Altered Gravity, and Isolation and Confinement on Crew Health and Performance: *Problem Statement*

We are not students of some subject matter, but students of problems. And problems may cut right across the borders of any subject matter or discipline.

--Karl Popper

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Summary

Future crewed exploration missions to Mars could last up to three years and will expose astronauts to unprecedented environmental challenges. Challenges to the nervous system during these missions will include factors of: space radiation that can damage sensitive neurons in the central nervous system (CNS); isolation and confinement can affect cognition and behavior; and altered gravity that will change the astronauts' perception of their environment and their spatial orientation, and will affect their coordination, balance, and locomotion. In the past, effects of spaceflight stressors have been characterized individually. However, long-term, simultaneous exposure to multiple stressors will produce a range of interrelated behavioral and biological effects that have the potential to adversely affect operationally relevant crew performance. These complex environmental challenges might interact synergistically and increase the overall risk to the health and performance of the astronaut. Therefore, NASA's Human Research Program (HRP) has directed an integrated approach to characterize and mitigate the risk to the CNS from simultaneous exposure to these multiple spaceflight factors. The proposed research strategy focuses on systematically evaluating the relationships among three existing research risks associated with spaceflight: Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation (CNS), Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (BMed), and Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Spaceflight (SM).

NASA's HRP approach is intended to identify the magnitude and types of interactions as they affect behavior, especially as it relates to operationally relevant performance (e.g., performance that depends on reaction time, procedural memory, etc.). In order to appropriately characterize this risk of multiple spaceflight environmental stressors, there is a recognition of the need to leverage research approaches using appropriate animal models and behavioral constructs. Very little has been documented on the combined effects of altered gravity, space radiation, and other psychological and cognitive stressors on the CNS. Preliminary evidence from rodents suggest that a combination of a minimum of exposures to even two of three stressors of: simulated space radiation, simulated microgravity, and simulated isolation and confinement, have produced different and more pronounced biological and performance effects than exposure to these same stressors individually. Structural and functional changes to the CNS of rodents exposed to transdisciplinary combined stressors indicate that important processes related to information processing are likely altered including impairment of exploratory and risk taking behaviors, as well as executive function including learning, memory, and cognitive flexibility — all of which may be linked to changes in related operational relevant performance.

The fully integrated research plan outlines approaches to evaluate how combined, potentially synergistic, impacts of simultaneous exposures to spaceflight hazards will affect an astronaut's CNS and their operationally relevant performance during future exploration missions, including missions to the Moon and Mars. The ultimate goals are to derive risk estimates for the combined, potentially synergistic, effects of the three major spaceflight hazards that will establish acceptable maximum decrement or change in a physiological or behavioral parameters during or after spaceflight, the acceptable limit of exposure to a spaceflight factor, and to evaluate strategies to mitigate any associated decrements in operationally relevant performance.

Background

The Problem

During future crewed exploration missions to Mars, astronauts will be exposed to prolonged periods of microgravity and space radiation exposure, abrupt gravity transitions, and multiple other stresses including isolation and confinement that will challenge their nervous system and may affect their cognition and behavior. The effects of prolonged exposure to space radiation will accumulate with time during the mission and can damage sensitive neural cells. Gravity transitions, which will occur at specific times during the mission after prolonged exposure to weightlessness, will change the astronaut's interpretation and response to their environment and their spatial orientation, and will affect their coordination, balance, and locomotion. The psychological stresses of a Mars mission could affect the astronaut's cognition and behavior; these stresses may be non-linear, occurring first with the abrupt transition into the small spaceflight living volume, then influenced by factors such as time in space, limited social interactions, lack of meaningful work, and increasing delay in communications with Earth. Combined exposure to these complex environmental challenges could result in effects that act synergistically on the CNS, may differ in their dose/exposure rates depending on mission phase, and may increase the overall risk to the health and performance of the astronaut. Representation of the three spaceflight hazards that pose risk to the CNS, and some of the effects that may be associated with these hazards are discussed in more detail below.

Radiation Environment

Outside the protection of the Earth's geomagnetic field, astronauts will be exposed to levels of heavy-charged particle radiation from interplanetary galactic cosmic rays (GCR) that exceed those in low earth orbit, and to the potential risk of radiation exposure from solar particle events (SPEs).

GCR are composed of protons, helium nuclei, and high charge and energy (HZE) nuclei. The maximum annual radiation exposure from GCR during a Mars mission is predicted to be of the order of 200 mGy a year with less than 50% of the dose from HZE particles [*1*]. One estimate is depicted in the Mars: GCR exposure tables shown in Figure 1A in terms of the physical dose (mGy) as well as in dose equivalents (mSv). The precise dose is dependent on details of spacecraft design, mission operations, shielding and time in solar cycle. Also shown in Figure 1a are the detailed breakout of U.S. astronaut mission doses through 2002, organized sequentially by astronaut's order of flight [*2*].

SPEs occur when the sun ejects large quantities of charged particles consisting mostly of protons, and the potential exists for significant acute radiation exposures from SPEs: an astronaut could potentially be exposed to over 1 Gy, for example if they are performing an extended spacewalk during a SPE. The frequency of SPEs is unpredictable but they are more likely to occur near solar maximum and less likely to occur near solar minimum.

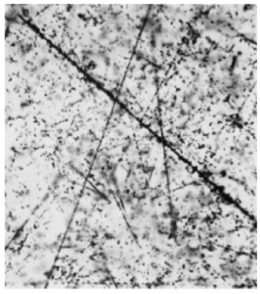
The Ilford G.5 nuclear emulsion that Neil Armstrong wore on his ankle during the Apollo 11 lunar landing mission in July, 1969 (shown in Figure 1A) gives an illustration of the complexity of the space radiation environment: the background of silver grains on this image are likely caused by gamma

A.

Human Space Radiation Exposure

Radiation Exposure GCR (HZE nuclei, Protons)

- **Direct Effects**
- **Non-Targeted Effects**
- **Multiple Exposures**



An illustration of the ambient radiation exposure in deep space as *a microscopic field of view of an Ilford G.5 nuclear emulsion* that was worn on the ankle of Neil Armstrong during the Apollo 11 lunar landing mission in July, 1969 (shown to the left).

Opposition Class: Earth and Mars *not aligned* leading to short transit times and long return times with 60 day stay time; total 520 to 840 days

Conjunction Class: Earth and Mars *aligned* for equal transition and return time with ~540 day stay time; total 910 to 1000 (940 average) days

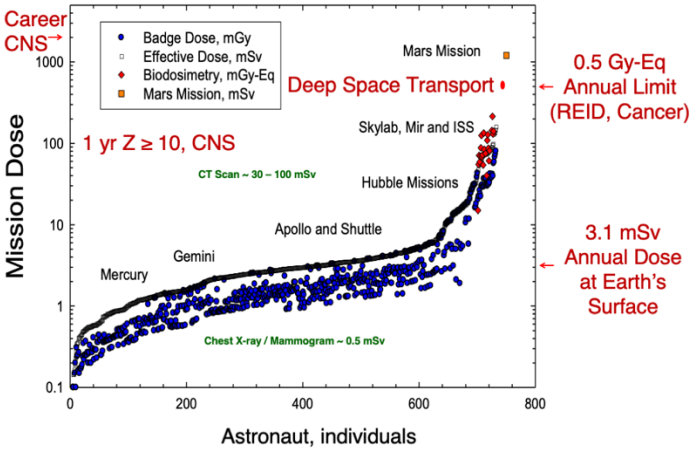
Example exposure estimate by particle type (10g/cm^2, solar min, many assumptions)

Mars: GCR exposure	Mars: GCR exposure
130 mGy to 180 mGy protons	185 mSv to 210 mSv protons
45 mGy to 70 mGy alphas	140 mSv to 160 mSv alphas
20 mGy to 40 mGy 3<Z<9	130 mSv to 145 mSv 3<Z<9
30 mGy to 40 mGy Z>10	515 mSv to 590 mSv Z>10
20 mGy to 30 mGy Z<1 (neutrons, pions,etc.)	80 mSv to 95 mSv Z<1 (neutrons, pions,etc.)
Physical Dose (mGy)	Dose Equivalent (mSv)
Total: 245 mGy to 360 mGy	Total: 1050 mSv to 1200 mSv

Exposure estimate of 1.0 – 1.2 Sv

Mars Exposure Estimates: approximately three times greater than current Permissible Exposure Limits (%REID)

Adapted from L. Simonsen

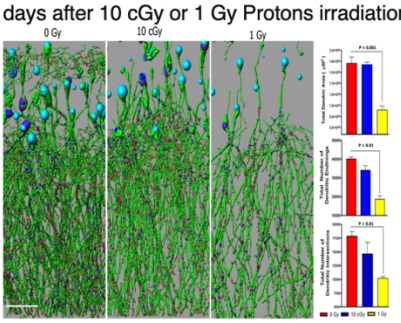


Modified from Cucinotta et al. (2002) [2]

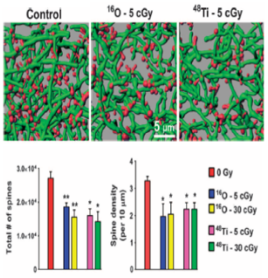
B.

GCR Exposure – Rodent studies

Altered Dendritic Complexity Hippocampal Neurons, 30 days after 10 cGy or 1 Gy Protons irradiation.



Dendritic Spine # and Density, 8 weeks after ^{16}O and ^{48}Ti ions irradiation.



Parihar VK, et al. What happens to your brain on the way to Mars. *Sci Adv.* 1;1(4), 2015 [3],[6]

Figure 1: *Example representation of the risk posed by acute effects of space radiation spaceflight hazard to the CNS* (A), *and some of the associated effects* (B).

rays and electrons, with numerous proton tracks and one HZE particle track also evident. In general, translational research using ground models has demonstrated that charged particles can disrupt the neural circuitry of the brain and compromise cognitive function over surprisingly protracted intervals after exposure [3]. Electrophysiological parameters in animals irradiated with various doses of radiation show altered excitability, plasticity, and intrinsic membrane properties in hippocampus, prefrontal cortex and perirhinal cortex, along with associated short and longer term deficits in cognitive functioning [4], [5]. As shown in the Figure 1B, accelerated titanium and oxygen particles at doses as low as 5 cGy can reduce the complexity of dendrites in mice (image of the effects are shown, and plots quantify changes for 5 cGy and 30 cGy of oxygen and titanium [6]). Hence, NASA sponsored research, predominantly with single ion acute exposures within the radiation biology community, has identified radiation-induced synaptic and neurophysiological changes in cortical neurons and neuron ensembles associated with decrements in behavioral performance. However, the biological consequences of complex mixed-radiation exposures during long-duration deep space missions is still uncertain. Biological impacts have been assessed based on single species of mono-energetic (i.e., single ion) particles. Only recently (i.e., 2019) have capabilities become available to simulate a GCR mixed field (e.g., five or more ions) simulation. This now allows investigation of the combined biological effect from simultaneous exposure to different radiation types. Further evidence of changes to the CNS associated with space radiation exposures are documented in the HRP Evidence Report, *Risk of Acute and Late Central Nervous System Effects from Radiation Exposure [7]*.

Sensorimotor Changes Due to Altered Gravity

Astronauts experience sensorimotor alterations predominantly during gravitational transitions, which generally occur at critical periods during space travel such as entry and reentry into microgravity and immediately after landing on a planet as shown in the Figure 2A. The more time astronauts spend in space, the more intensely they experience sensorimotor disturbances. Sensorimotor disturbances pose a significant challenge for future long-term space exploration missions in various gravitational environments. As shown in the Figure 2A, in one potential mission profile astronauts will be exposed to several months of 0g (or microgravity) during the trip to Mars, on arriving at Mars they will have to adapt to Martian gravity (0.38g), then readapt to 0g (or microgravity) for the trip home, and finally re-adapt to 1g when they return to Earth. In an alternate mission profile, they may be exposed to periods of microgravity on the way to Moon, experience and adapt to Lunar gravity (1/6g), and then be exposed to the above profile of adaptation and readaptation to 0g, Martian gravity and 1g. The sensorimotor disturbances that astronauts experience during a typical long-duration low Earth orbit spaceflight include (a) space motion sickness; (b) spatial disorientation; (c) difficulty acquiring and tracking visual targets; (d) dynamic vision changes due to alterations in the vestibular ocular reflex; (e) modification of vestibular and proprioception interpretations (e.g., pointing, sense of limb position); (f) modifications in vestibulo-spinal reflexes; (h) loss of muscle tissue and motor efference; (g) reduced cognitive reserve; (h) reduced manual and fine motor control [8]–[10]. After they return to Earth, astronauts experience (a) Earth motion sickness lasting from a few hours to more than a week; (b) hypo- or hypertonia of the major postural skeletal muscles, which alters locomotion; (c) early muscle fatigability and potentiation of major postural muscle reflexes, which can lead to falls or other accidents; (d) frequent under- or overshooting when reaching for an object; (e) unilateral gaze nystagmus, which is associated with dizziness and vertigo; (f) saccadic intrusion during smooth pursuit tracking; and (g) postural ataxia[8], [10]. Astronauts rely significantly on visual feedback when walking after they return from space and it is likely that astronauts will experience similar sensorimotor issues when they arrive on Mars. These changes are most prominent after g-transitions, however the extent of change is a function of flight duration [8], [11].

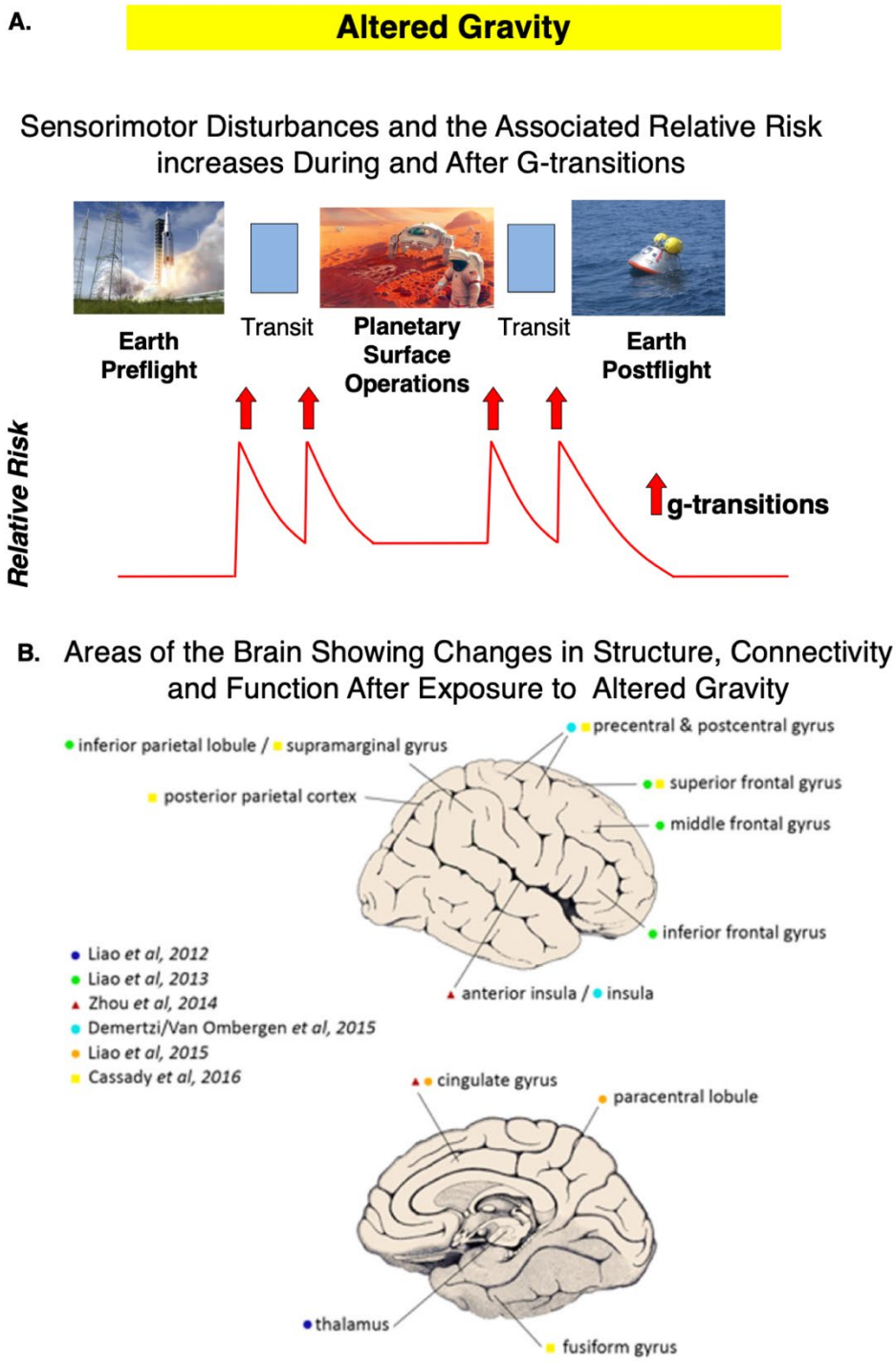


Figure 2: *Example representation of the risk posed by altered gravity spaceflight hazard to the CNS* (A), *and some of the associated effects* (B).

The cortical network integrates sensory inputs (vestibular, visual, proprioceptive), processes self-motion, spatial orientation, and memory, and provides a perception of vertical alignment using visual and gravitational cues. Adaptation to altered gravity affects: the structure, connectivity and functioning of focal grey matter (as shown in Figure 2B) [**12**]–[**14**], the integrity of white matter in several neural pathways [**11**], redistribution of cerebrospinal fluid compartments [**12**], [**15**], central reinterpretation of both vestibular and proprioception inputs [**16**]–[**19**]. Although, for example, changes in hair cells in the rat utricular macula undergo extensive plasticity as a result of spaceflight, with a large (40-55%) increase in synapse number [**20**], and studies have shown changes in properties of otoconia from exposure to hyper- and hypo- gravity [**21**]–[**22**], the spaceflight-induced performance changes seem to predominantly originate from alterations at the cortical level. Further evidence of the changes to the sensorimotor system associated with spaceflight factors and its effects on operationally relevant performance tasks are provided in the HRP Evidence Report, *Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Space flight [**8**].*

Isolation and Confinement

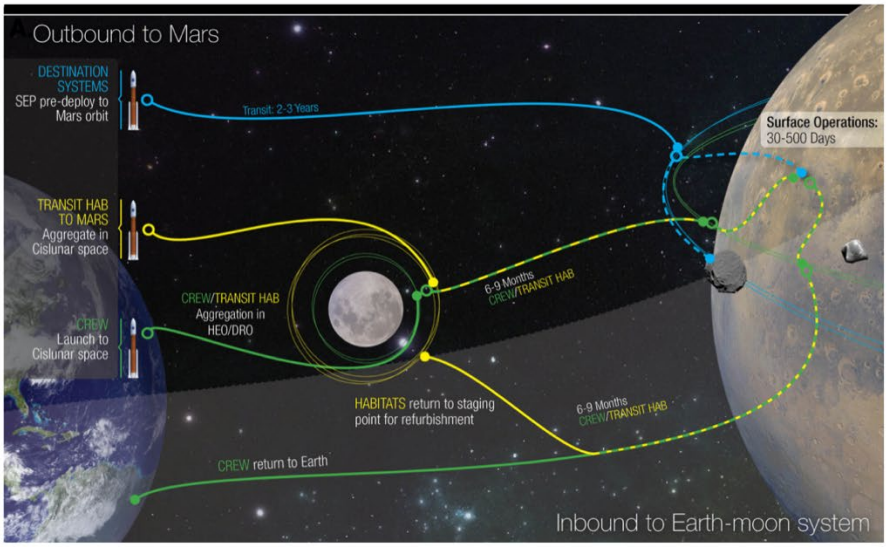
Spaceflight exploration missions will present challenges to crewmembers' behavioral health and performance that are much greater than those currently faced by astronauts working and living in the International Space Station (ISS). That is primarily because deep space missions will include unprecedented duration, distance, isolation, and confinement under increasingly autonomous operations such as depicted in the journey to Mars in Figure 3A.

The extended distance from Earth will expose the astronauts to a unique combination of stressors: exploration vehicles will have very limited habitable volume and little privacy; the crew will be unable to see Earth and they won't receive resupply and care packages; there will be periods of monotony, limited social, physical, and sensory stimulation, and with an estimated 20-22 minute delay (one-way) with mission support on Earth. In addition, medical care will be limited and there will be no evacuation options. Psychophysiological "*adaptations*" to spaceflight include disruptions in circadian rhythm and associated sleep loss, hormonal changes, and cognitive changes (e.g., reduced reaction time).

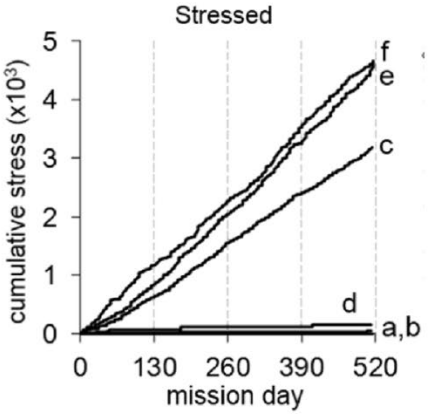
Evidence that long-duration spaceflight on the ISS alters cognitive functioning is equivocal. When they reviewed extensive cognition data from studies conducted in space and in analog environments, Strangman et al. [**23**] found no consistently predictable decrements in cognitive performance for the areas of emotion and social processing, attention, memory, learning, and executive or higher order functioning, (although it should be noted that these studies were limited by small samples and inconsistent measurement methods). Findings from these studies are in contrast to anecdotal reports that astronauts commonly experience "space fog"—cognitive and perceptual changes that manifest as attention-lapses, short-term memory problems, spatial disorientation, and confusion when performing tasks—especially during the period of adaption to spaceflight [**24**]. Further, preliminary data from a more recent study conducted on the ISS [**25**] suggests that stress increases during the mission, with stress ratings the highest in the 4th quarter of the flight relative to the 1st and 2nd quarters.

The ISS provides an unique environment through which to assess physiological stressors related to weightlessness. However, terrestrial platforms can offer a more exploration like psychological analog for evaluating the effects of prolonged isolation and confinement. In a study conducted to simulate 520 days of isolation simulation of a mission to Mars (the Mars 520-day simulation study), crewmembers' subjective ratings demonstrated significant increases in stress. More importantly, there were individual differences in these responses that were measured across crewmembers in the Mars

A. **Isolation and Confinement**

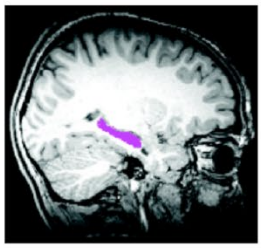


B. Cumulative Crews' Stress Levels During Confinement in a 520-Day Simulated Interplanetary Mission to Mars



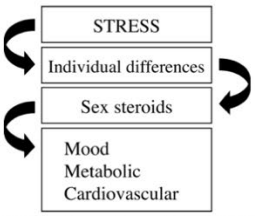
Basner M, Dinges DF, Mollicone DJ, Savelev I, Ecker AJ, et al. Psychological and Behavioral Changes during Confinement in a 520-Day Simulated Interplanetary Mission to Mars. PLoS ONE (2014); 9(3): e93298 [***26***].

C. Neurostructural, Cognitive, and Physiological Changes During a 1-year Antarctic Winter-Over Mission



M. Basner et al.: Neurostructural, Cognitive, and Physiologic Changes During a 1-Year Antarctic Winter-Over Mission. Poster at NASA's Human Research Program Investigators' Workshop, Galveston, TX, February 9, 2016 [***35***]

D. Factors Affecting Individual Differences in Response to Repeated Exposure to Stress



Radley J, et al, Chronic stress and brain plasticity: mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders. Neuroscience and biobehavioral reviews. 2015;58:79-91 [***29***].

Figure 3: *Example representation of the risk posed by isolation and confinement spaceflight hazard to the CNS for an example mission profile* (A), *and some of the associated effects* (B-C).

520 - day simulation study as shown in the example depicted in Figure 3B (for example, of the six total subjects, subjects c, e and f show increasing levels of cumulative stress in comparison to subjects a, b and d who show little to no accumulation of self reported stress levels) [26]. A separate analysis of physiological effects showed among others, increasing levels of cortisol and number of lymphocytes over the duration of the mission [27]. Stress during aging is associated with both memory impairment and reduced hippocampal volume [28]. However, as depicted in the Figure 3C preliminary results that showed significant changes in the somatosensory cortex after a 1-year Antarctic winter-over mission in subjects participating in a study investigating the effects of simulated long duration isolation and confinement [35]. Radley et al. (2015) as depicted in the Figure 3D, specifically highlight the contributions of various factors including individual differences in gonadal hormone variations and have reviewed various factors including individual changes of hippocampal and other brain structures and in resilience that can potentially contribute to the individual differences in adaptive, maladaptive responses to repeated stress exposure [29].

It is very difficult to determine whether outcomes seen in isolation, confinement and extreme environments are additive or synergistic, and how much of the effect can be attributed to specific risk factors such as workload, fatigue, CO_2 levels, lighting, and noise. In addition, the crewmembers can vary considerably in their response to the stress and the environmental demands [30]. A crewmember's psychological well-being during a long-duration space mission will depend on multiple factors. Astronauts must have the ability to self-regulate the range and intensity of their affective states and sustain an emotional state (i.e., mood) that does not interfere with or deteriorate their functioning (e.g., cause other physical or cognitive symptoms). A full range of affects (e.g., happiness, elation, calmness, anxiety, irritability, anger, sadness) might occur over a long-duration mission. A comprehensive review of this risk and mitigation efforts is compiled at in the HRP evidence report Evidence *of the Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders* [31].

Brain Structure Changes

Long-duration spaceflight alters the structure and function of the brain. Many spaceflight stressors including altered gravity, sleep loss, radiation, and isolation and confinement may dysregulate the brain's structure and microenvironment, leading to imbalance in the function of neuronal and glial networks and the neurovascular unit [14], [32]. The volume of gray matter decreases in many areas, which may reflect an upward shift of the brain within the skull and redistribution of intracranial fluids during spaceflight [11], [33], [34], [36]. In addition, gray matter increases within the medial primary somatosensory and motor cortices—the cerebral areas where the lower limbs are represented—suggesting adaptive sensorimotor plasticity during spaceflight [12]. The structural connectivity of white matter is altered in regions involved in visuospatial processing, vestibular function, and movement control, suggesting that processes requiring prefrontal multimodal integration of sensory inputs may be at risk during spaceflight [11]. Cerebellar afferent connections change during spaceflight, and after spaceflight white matter structural integrity has been shown to have been changed in the right inferior and posterior parietal lobe—areas involved in body spatial perception and central proprioceptive processing[11]. However, little is known about the complex interplay between adaptions of the various sensory inputs (e.g. vestibular, visual, somatosensory, etc.) and the psychological and behavioral effects that are anticipated during long-duration spaceflight. We cannot underestimate the importance of understanding how the sensorimotor and cognitive processing systems interact during dangerous or threatening situations (e.g., the effects of fight-or-flight responses when precise vestibular perceptions are needed to drive adaptive motor responses during landing). The hippocampus, important for cognition and spatial memory, is very sensitive to both radiation and

chronic stress. For example, mice exposed to charged particles with space relevant fluences, showed significant hippocampal-based cognitive deficits [6]. Most effects are related to synaptic efficacy and plasticity rather than abilities of neurons to conduct signals. Spaceflight-induced changes in peripheral and central vestibular neurotransmission may decrease vestibular inputs to areas of the hippocampus, and this may impair spatial learning and cognition abilities [37]–[39]. In addition, the otoliths help tune the function of head direction cells, which process information required for spatial orientation, making 3-dimensional visuospatial navigation difficult without the anchor of gravity [40]–[42]. Furthermore, neuroimaging reveals that vestibular-induced nausea influences the same prefrontal areas of the brain [43] that are associated with autonomic regulation of emotions[44], which implies that vestibular-induced motion sickness can "stress" prefrontal areas of the brain and disrupt autonomic mechanisms. Emotional processing signal and mobilize the crewmember for action [45]–[47], whereas, precise vestibular processing help drive their adaptive motor responses. Given this commonality of purpose, it is not surprising that the vestibular and emotion systems share parts of the insular and anterior cingulate cortex[48]–[50]. If the brain performance pathways related to cognition and processing of sensory inputs (e.g., vestibular) are degraded, then the areas of the brain that are important for piloting, operating, or docking the vehicle, procedures that also require spatial memory and perspective, may be adversely affected as well.

Performance Decrements

Sensorimotor and cognitive responses during and after spaceflight are related to the length of the mission [8], [11], [51]–[54]. A number of acute and chronic performance changes related to changes in brain performance pathways may occur during an exploration mission, potentially impacting operator proficiency after landing, piloting performance, and operating remote vehicles and devices in space and on the ground [55]. Operating telerobotically-controlled systems on a spacecraft or a surface-rover requires significant sensorimotor and cognitive proficiency [56]–[58]. In fact, deficits in sensorimotor performance and cognition probably contributed to the collision of the Progress 234 resupply ship with the Mir space station during a manual docking practice session [55], [59]. Adaptation of physiological systems during spaceflight can compromise a crewmember's ability to optimize the integration of multi-sensory information, and lead to perceptual illusions and reduced cognitive reserve that can further compromise their ability to perform mission tasks such as driving a vehicle on the lunar or Mars surface [8]. Astronauts will likely find it very challenging to manually land a vehicle on Mars. After the long transit they will be profoundly adapted to microgravity and may also have difficulty recalling their training [8]. Tilt-translation disturbances following G-transitions, incorrect perceptions of vehicle accelerations, tilted terrain, and uneven (bumpy) surfaces may all cause inappropriate responses. Although automated control systems can compensate for some deficiencies in human performance, lessons learned from the Apollo missions [60] suggest that manual takeover is required as a minimum safe guard, and therefore countermeasures must concentrate on mitigating risks associated with manual operation of the Mars vehicles. Some astronauts also experience sensorimotor and cognitive decrements after they return to Earth. Astronauts returning from a 6 month spaceflight on the ISS, showed a significant median decrease in performance of functional tasks that required the most body coordination and postural stability control: egressing a vehicle, recovering from a fall to a standing position, translation of objects from one place to another, jumping down from a height of 30 cm, and climbing ladders [18].

HRP Risk Mitigation Strategy for the combined CBS risk

NASA's HRP investigates and mitigates the greatest risks to human health and performance during spaceflight, providing essential countermeasures and monitoring technologies for human space exploration. The CBS Integrated Research Plan is a portfolio within HRP's Integrated Research Plan (IRP). HRP's IRP identifies 32 individual risks, which are assigned to specific organizational elements within the program, and HRP's IRP describes the approach and research activities to mitigate each of these individual risks. This specialized single risk approach has proven very productive; however, there is an increasing recognition of the importance of characterizing the risks in a completely integrated manner with transdisciplinary expertise. For example, given that the behavioral medicine risk focuses on changes to cognitive functioning, there is a need to determine if spaceflight stressors interact in a synergistic manner and increase the risk [***61***] to the astronauts' health and performance when they are isolated and confined while simultaneously exposed to space radiation. In addition, we must determine whether CNS alterations and sensorimotor adaptations that occur due to altered gravity affect brain structure and function [***33***], [***62***]–[***64***], and the potential synergistic impacts of these changes when astronauts have also been isolated and confined, and chronically exposed to space radiation.

As a first step in designing an integrated risk approach, the HRP has directed the integration of research efforts to evaluate the impact of simultaneous exposures to spaceflight hazards that could affect the CNS and operationally relevant behavior and performance. The intent of this integrated approach is to systematically identify and investigate the relationships amongst three risks:

- Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation (CNS), assigned to the Space Radiation Element
- Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (BMed), assigned to the Human Factors and Behavioral Performance Element
- Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Spaceflight (SM), assigned to the Human Health Countermeasures Element

The proposed integrated research plan—the **CBS** (**C**NS, **B**Med, **S**ensorimotor) Integrated Research Plan, outlines approaches to evaluate the combined, potentially synergistic, impacts of simultaneous exposures to spaceflight hazards that affect the CNS and operationally relevant behavior and performance. These research results are needed to derive risk estimates for use in establishing initial POLs and PELs linked to operationally relevant performance in consideration of the three integrated risks that comprise the CBS Integrated Research Plan.

Goals of the CBS Integrated Research Plan

The HRP's integrated approach will help answer the following important questions:

- Do the spaceflight hazards underlying the three risks impinge on the human system in a synergistic manner and elevate risk to astronauts' operationally relevant performance?
- Can we identify brain performance pathways that are impacted by these risks?
- Are there neurobehavioral biomarkers associated with dynamic changes in those pathways that will help predict when (and then potentially help to prevent) one or more of these integrated effects that are likely to adversely affect crew health and performance?
- Can we leverage past research results from the three risk areas to develop computational models that can identify these relationships?
- Can we then leverage those models to develop translational models of integrated risks that can help characterize the inter-relationships of the risks from animal to human models, and to help determine efficacy of countermeasures to reduce their effects?
- Do identified countermeasures in one risk area "cross-walk" to the other two risks, thereby reducing overall risk of adverse outcomes?

The overall goal of the CBS Integrated Research Plan is to identify biomarkers and operationally relevant performance metrics to determine and establish permissible outcome levels (POLs) and permissible exposure limits (PELs) for astronauts. POLs are defined as the maximum acceptable performance decrements or changes in physiological or behavioral parameters, during or after a spaceflight mission, as the result of exposure to the space environment, and PELs are defined as quantifiable limits of exposure to a space flight factor over a given length of time. The identification of the POLs and PELs will contribute to both monitoring to characterize the risks and the identification of countermeasures to mitigate the risk posed to the astronaut's CNS related to operationally-relevant performance as a result of spaceflight.

Research Emphases

This white paper describes the conceptual framework for the CBS Integrated Research Plan. This plan will lead to benchmark criteria for identifying risks to performance of critical spaceflight activities that have the greatest potential for compromising mission success and/or crewmember safety. Potential criteria might include measures of alterations in cognition and sensorimotor performance that will be used to determine the astronauts' proximity to POLs. Further, this CBS Integrated Research Plan will also lead to the development of monitoring capabilities and of countermeasures to mitigate the changes associated with the combined exposure to the CBS stressors of spaceflight.

The CBS Integrated Research Plan proposes plausible, consistent, and scientifically demonstrable ways to determine if simultaneous exposure to the three major spaceflight stressors affects astronaut performance. This integrated research approach, focused on these combined spaceflight stressors affect astroanut performance, is designed to help determine and if evident, quantify how exposure to any one specific CBS related hazard further modulates, interacts with, and/or amplifies the risk to operationally relevant performance that can be mapped to the underlying neural circuitry and

mechanisms related to other spaceflight hazards (e.g., isolation, confinement, space radiation, circadian dysregulation, sleep deprivation, and altered gravity).

The CBS research plan includes a set of synthesized areas of major "Research Emphases" (REs) that are associated with the individual risks that comprise the CBS Integrated Research Plan, their associated gaps of research knowledge (see Table 1 below) and are listed below in the same sequence as they are arranged in the companion document describing the CBS Implementation Strategy.

Research Emphases:

1. Standardized models to provide most valid translation from rodent to humans for ground testing
2. Operational performance measures that will best indicate CBS performance decrements in ground and flight
3. Crew health & performance standards that adequately protect crew during exploration class missions
4. Systematically assess effects of radiation type & dose-rates on operationally relevant CBS brain performance pathways & mechanisms
5. Validated method for predicting CBS performance decrements due to mission-expected radiation exposures
6. Countermeasures that maintain crew performance standards during exploration class missions

These areas of Research Emphases in the CBS Integrated Research Plan includes identified research areas outlined in item #4 of the 'Statement of Task' to the SRP as follows:

a. Translation of animal results to humans (Research Emphasis 1)
b. Datamining efforts in biomarkers relevant to these risks (Research Emphasis 2)
c. Identification of common brain performance pathways (Research Emphasis 4)
d. Operational performance domains (Research Emphasis 2)
e. Identification and monitoring of actionable biomarkers (Research Emphases 2 and 4)
f. Computational modeling (Research Emphasis 5)
g. Development/adaptation of CBS Integrated Risk radiation-based Permissible Outcome Levels (POLs) and Permissible Exposure Limits (PELs) (Research Emphasis 3)
h. Countermeasure development (Research Emphasis 6)

The specific research tasks in the CBS Integrated Research Plan (for list of research tasks see accompanying document, CBS Integrated Research Plan: Implementation Strategy) are aligned with individual research emphases, and their specific objectives address gaps (see Table 1), for each risk.

Table 1: Description of the gaps within each of the three existing HRP defined risks (Acute CNS, Behavioral Medicine, and Sensorimotor) that are associated with the CBS Integrated Research Plan.

CNS: Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure
CBS CNS - 1: Are there significant adverse changes in CNS performance in the context and time scale of spaceflight operations? If so, how is significance defined, and which neuropsychological domains are affected? Is there a significant probability that space radiation exposure would result in adverse changes? What are the pathways and mechanisms of change?
CBS CNS - 2: Does space radiation exposure elicit key events in adverse outcome pathways associated with neurological diseases? What are the key events or hallmarks, their time sequence and their associated biomarkers (in-flight or post-flight)?
CBS CNS - 3: How does individual susceptibility including hereditary pre-disposition (e.g. Alzheimer's, Parkinson's, apoE allele) and prior CNS injury (e.g. concussion, chronic inflammation or other) alter significant CNS risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?
CBS CNS - 4: What are the most effective medical or dietary countermeasures to mitigate CNS risks? By what mechanisms are the countermeasures likely to work?
CBS CNS - 5: How can new knowledge and data from molecular, cellular, tissue and animal models of acute CNS adverse changes or clinical human data, including altered motor and cognitive function and behavioral changes be used to estimate acute CNS risks to astronauts from GCR and SPE?
CBS CNS - 8: Are there significant CNS risks from combined space radiation and other physiological or space flight factors, e.g., psychological (isolation and confinement), altered gravity (micro-gravity), stress, sleep deficiency, altered circadian rhythms, hypercapnea, altered immune, endocrine and metabolic function, or other?
BMed: Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders
CBS BMed1: We need to identify and validate countermeasures that promote individual behavioral health and performance during exploration class missions.
CBS BMed2: We need to identify and validate measures to monitor behavioral health and performance during exploration class missions to determine acceptable thresholds for these measures.
CBS BMed3: We need to identify and quantify the key threats to and promoters of mission relevant behavioral health and performance during autonomous, long duration and/or long distance exploration missions.
CBS BMed5: We need to identify and validate measures that can be used for the selection of individuals that are highly resilient to the key behavioral health and performance threats during autonomous, long duration and/or long distance exploration missions.
CBS BMed6: We need to identify and validate effective treatments for adverse behavioral conditions and psychiatric disorders during exploration class missions.
SM: Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Spaceflight
CBS SM2.1: Determine the changes in sensorimotor function over the course of a mission and during recovery after landing.
CBS SM6.1: Determine if sensorimotor dysfunction during and after long-duration spaceflight affects ability to control spacecraft and associated systems.
CBS SM7.1: Determine if there are decrements in performance on functional tasks after long-duration spaceflight. Determine how changes in physiological function, exercise activity, and/or clinical data account for these decrements.
CBS SM24: Determine if the individual capacity to produce adaptive change (rate and extent) in sensorimotor function to transitions in gravitational environments can be predicted with preflight tests of sensorimotor adaptability.
CBS SM26: Determine if exposure to long-duration spaceflight leads to neural structural alterations and if this remodeling impacts cognitive and functional performance.
CBS SM28: Develop a sensorimotor countermeasure system integrated with current exercise modalities to mitigate performance decrements during and after spaceflight.

RE 1: Standardize Models to Provide Most Valid Translation from Rodent to Human for Ground Testing

This research emphasis is linked to the following existing gaps: CNS (1,2,3,4,5,8); BMed (1,2,3,5,6) and SM (2.1, 6.1, 7.1, 24,26,28)

Due to the need to irradiate subjects with simulated space radiation, we must use translational models (e.g., rodents) to study the effects of the neurochemical, functional alterations, and structural changes in the brain, and to assess how these functional, structural, and biochemical alterations relate to operationally relevant performances associated with radiation exposures similar to space flight missions. Extrapolating observations in animals to operational significance for CNS health risks in humans is challenging and further complicated by different experimental conditions for radiobiological and neurobehavioral studies. Factors that vary in these studies include animal handling, facilities (e.g., environmental controls, volume, lighting, sound, etc.), animal type (species/strains/sex/age), sensitivity of biomarker responses, and regional pathophysiology related to brain and operational performance pathways. Therefore, translational models (facilities, strains, approaches, etc.) must be "standardized" to ensure the reproducibility, reliability, robustness, and validity of tests, and to enhance and accelerate efforts to translate from animal models to humans and reverse translate when appropriate. Furthermore, no single spaceflight analog exits that can simultaneously induce all the spaceflight-induced sensorimotor effects. For example, hind limb unloading may simulate some effects of microgravity on the CNS [**65**] but it does not affect the vestibular organs that contribute to operationally relevant performance changes during spaceflight. This limits the translational approach because radiation may directly impact sensorimotor function and also the animal's ability to adapt their sensorimotor response to altered gravity.

The association between altered neuronal function and cognitive and behavioral processes is complex; the characteristics of the nervous system and the type of behavioral testing affect the experimental results [**66**]. Animal tests to study the relationship between changes in the brain and behavior is affected by many factors including the animal type, variability in environmental conditions during the testing, and the ability of the animal to respond to a stimulus and perform complex tests. A workshop that focused on improving the utility and translation of animal models for cognition, behavior, and neurodegenerative diseases, and implementing best practices for animal studies of diseases such as Alzheimer's, highlighted a number of the same challenges of our proposed research plan [**67**], [**68**]. For example, the panel identified the importance and advantages of including automated multidimensional testing of animals, standardizing the length of acclimatization periods and handling of animals, understanding the effects of using different species and strains, and adopting standard models of stressors. In addition, they emphasized the importance of using tests that are as similar as possible to tests that simulate the operationally relevant tasks (e.g., in our case, astronaut testing). Interestingly, and relevant to our current proposed approach, they also recommended matching brain performance pathways involved for cross walking forward and reverse translation of results between human and translational models. As this panel also pointed out, animal models can only provide limited information; we are unable to assess all aspects of exposure to spaceflight, since scaling effects seen in animal models may not be equivalent to that seen in humans (see e.g.,[**67**]–[**69**]). To address some of these issues, NASA's CBS Integrated Research team has conducted two technical interchange meetings (TIMs) with external and internal subject matter experts to help compile the state-of-knowledge to "integrate" approaches using animal models for translation of cognitive and physiological effects of individual spaceflight hazards, and to synthesize information related to some of the aspects of standardization highlighted above. These TIMs have been very productive, achieving their intended purpose to inform the program for future work related to the characterization

and mitigation of the individual and combined effects of CBS stressors (See Appendix B in CBS Integrated Research Plan: Implementation Strategy)

RE 2: Operational Performance Measures that will Best Indicate CBS Performance Decrements in Ground and Flight

Research Emphasis identified research areas

- Identify potential decrements (and impairments) in operational performance
- Identify biomarkers linked to performance standards
- Identify molecular/cellular pathways linked to performance
- Identify "integrated" Brain/Behavior domains/pathways linked to performance
- Identify adverse outcome pathways (if present) linked to performance and influenced by multiple stressors

This research emphasis is linked to the following existing gaps: CNS (1,3,4,5,8); BMed (1,2,5,6) and SM (7.1, 24,26)

The CBS Integrated Research Plan seeks to identify biomarkers that are linked to in-flight and postflight decrement in an astronauts' operationally relevant performance as a result of simultaneous exposures to the CBS-relevant spaceflight hazards. In this context, a biomarker is defined as a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention[***70***]. It is unlikely that a single biomarker will adequately predict risk of spaceflight-induced performance deficits. Multi-modal approaches assessing longitudinal changes in biochemical, cognitive, electrophysiological, genetic, and neuroimaging tests will likely be more reliable (and discriminating) than cross-sectional studies. Biomarkers must be useful for bi-directional translation of homologous human and animal measures, a cornerstone of the CBS plan. For example, the CBS Integrated Research Plan focusses on (a) outcomes of homologous, vetted behavioral tests, (b) adverse outcome pathways (AOPs) that show high homology between animals and humans–thus indicating that underlying processes elicited by various stressors are similar, and (c) biomarkers that report the magnitude of exposure to a stressor, and that correlate with pathophysiological processes (in the AOP context this would link biomarkers to "key events" in a pathway). Biomarkers could be metabolites, cytokines, etc. in saliva, urine or blood that can indicate neuroinflammatory processes, imbalances in signaling molecules such as neurotransmitters or precursors, glucocorticoids, or oxidative stress. Parameters measured by noninvasive imaging could also serve as biomarkers.

In addition, following the research domain criteria outlined by Sanislow et al, 2019 [***71***], the CBS plan seeks to identify changes in DNA, cells, molecules, physiology, or neurocircuitry that are linked to performance and physiological effects (e.g., neurological disorders)—linking the probability for performance decrement to the level of exposure (during and/or after mission). For example, HZE particles in the form of cosmic rays can trigger a multitude of cellular changes, depending on the particle type, energy/fluence/dose, rate of exposure, and individual susceptibility. Example biomarkers of radiation exposure include radiation-induced DNA damage and chromosome aberration frequency and spectra, which are good predictors of the radiation dose that can be assessed before, during and after spaceflight.

An ideal biomarker should reflect individual differences in susceptibility to radiation-induced damage, and predict the risk of radiation-associated health effects. If biomarkers of radiation exposure persist, they can help determine the late effects of radiation exposure and its influence on cell fate. However, heterogeneity in dose, dose-rate, radiation quality, energy, and particle flux complicate assessments of risk [72]. Early changes to biomarkers may portend inflammatory processes that lead to significant performance decrements [e.g. [73], [74]. Biomarkers that link to deficits in operationally relevant performance are of particular interest for translational and computational modeling efforts to determine when to apply a countermeasure and to assess the efficiency of countermeasures, while also helping to characterize the risk from multiple stressors depending on the specificity of a biomarker. For example, activated microglia can shift between pro-inflammatory (e.g. via the release of several pro-inflammatory mediators) and neuroprotective (e.g. that which promote the production of neurotrophic factor) phenotypes, depending on the environment in the brain [75], [76]. Stress may alter metabolic processes (that may be derived from the activated microglia) that could signal inflammation, cognitive impairment, and activation of neurodegenerative disease processes [77]. Blood levels of vitamins B1 and B6 are related to cognitive performance, cortical folding, and functional resting state connectivity [78], all of which have important implications for potential biomarkers for assessing the synergistic effects of space radiation on the CNS of an isolated, confined crewmember operating in an altered gravity environment.

RE 3: Crew Health and Performance Standards that Adequately Protect Crew during Exploration Class Missions

Research Emphasis identified research areas

- Determine/Identify relevant performance standards and acceptable impairment thresholds
- Development of quantitative measures of accreditation and human performance

This research emphasis is linked to the following existing gaps: CNS (3); BMed (2); and SM (2.1, 7, 6.1)

This research emphasis seeks to develop recommendations for acceptable levels of changes in performance that are linked to probability of mission success. These recommendations are especially important given clear evidence that astronauts have inter-individual changes in a variety of physiological effects during and after spaceflight [7], [8], [18], [31], [79], due to the risks posed by radiation, isolation and confinement, and gravity changes. NASA has standard recommendations for astronauts' health and performance that are reevaluated as additional data becomes available to warrant updates[80].

The NASA Space Flight Human System Standard [80] defines the short-term and career dose limits for noncancer effects of space radiation. These short-term limits are intended to prevent clinically significant noncancer health effects including performance degradation, or sickness or death inflight. However, the types and magnitudes of the space radiation risks to the CNS are largely unknown but are of great concern during the mission and after return to Earth.

These levels of space radiation exposures, and the potential for synergistic affects when combined with the other two risks, are important for establishing POLs and PELs. The HRP risk of impaired a human health and performance tied to muscle strength provides an example of the processes that may be used to set up the POLs. This risk is titled *Risk of Impaired Performance Due to Reduced Muscle Mass, Strength, and Endurance*[81]. Research to understand and mitigate this risk determined whether various measures of muscle strength could predict a subjects ability to complete a variety of

operationally relevant tasks within an acceptable amount of time. All the tasks evaluated in the study were simulations of tasks that astronauts will have to perform during exploration missions. The greater challenge in establishing fitness standards is often not simply characterizing the relationship between fitness and performance, but rather determining the acceptable cut-off times (performance) for completion of the tasks. Numerous tasks have a natural physiological breakpoint [**82**]. That is, when normalized strength is below the breakpoint threshold, change in time to perform a task as a factor of strength is greater than when one's normalized strength is above the strength threshold. Presumably, this phenomenon occurs because functional reserve is not challenged when strength is above the threshold value. The practical application of a threshold is that for many occupational settings the time taken to perform the task at this threshold can be considered "an acceptable amount of time". The rationale here is that being stronger than the threshold is of marginal to no benefit to being able to do the job. Therefore, in this example, a breakpoint whereby task completion time more markedly increases with a decrease in strength can be considered as a threshold for "impaired performance". Similar approaches and others may be used for the definition of the POLs and PELs for the combined effects of the three CBS stressors.

To establish the POLs and PELs related to the combined CBS stressors, as for example for space radiation, exposure data from existing data sets using single ions provides a starting point and template for the focus of our research related to performance outcome levels. We will need to focus the CBS Integrated Research Plan on translation of results from animal research models to likely impacts on human CNS as expressed through a combinatorial effect of radiation, cognitive, sensorimotor, and behavioral health domains and associated impairments potentially faced by crew exposed to the types of space radiation and other spaceflight hazards. We need to establish dose-effects linked to performance for the CBS risks to establish these thresholds, a process addressed in the next section.

RE 4: Systematically Assess Effects of Radiation Type and Dose-rates on Operationally Relevant CBS Brain Performance Pathways and Mechanisms

Research Emphasis identified research areas

- Performance linked dose-effects, GCR simulations, mixed field vs single ion exposures, males & females in combination with "doses" of other spaceflight hazards (Altered Gravity, Isolation and confinement)

This research emphasis is linked to the following existing gaps: CNS (1,5,8); BMed (3) and SM (24, 26)

The CBS Integrated Research Plan proposes appropriate animal models and behavioral constructs that will characterize interactions between multiple spaceflight stressors and contribute to NASA's objectives of (a) Identifying CNS effects, functional properties, and pathways that are affected by the duration/doses of exposure to individual spaceflight stressors that are likely to result in cognitive performance and sensorimotor changes; (b) Identifying adverse outcome pathways and improving risk estimation for performance outcome levels based on the magnitude and (c) identifying the effect of the sequence of exposure to the stressors (e.g., altered gravity exposure then irradiated vs. irradiated and then stressed, etc.).

The conceptualization of brain performance pathways (BPP) is based on how the architecture of brain networks at rest guide the connectivity patterns that emerge during the performance of various tasks

(i.e., modularity measured during "resting states" predicts working memory performance and stimulus detection in a perceptual task) [32], [83]–[88]. Individuals who score higher on intelligence quotient (IQ) tests have less change in functional connectivity between "resting state" and "task performance states" (suggesting more efficient adaptation to task demands). Spaceflight and simulated microgravity activates cortical re-organization[51], [89], and it is important to determine the specific areas of the brain that are affected by spaceflight because cortical organization has "between-module connectivity" that, when disrupted, is associated with widespread cognitive dysfunction. Importantly, in a similar manner, long-duration spaceflight alters vestibular/sensorimotor function, which manifests as changes in several areas linked to BPPs (e.g., in eye-head-hand control, postural or locomotor ability, gaze function, and perception). These changes have not specifically been correlated with real-time performance decrements[33]. The risk of impairment is greatest during and soon after g- transitions (hours to weeks) when performance decrements and may have high operational impact (landing, immediate egress, and extravehicular activities following landing). Learning-related increases in cerebral blood flow in contralateral motor effector areas, including the motor cortex, the supplementary motor area, and the putamen, are consistent with the hypothesis that nondeclarative motor learning occurs in cerebral areas that control limb movements [90]. This research also identified additional cortical sites: rostral prefrontal cortex and parietal cortex, right dorsolateral prefrontal and parietal areas (associated with spatial working memory) and right prefrontal cortex (implicated in retrieval tasks of verbal episodic memory—areas of great importance to the BMed risk). Awareness and sequence of learning is also associated with greater activity in bilateral parietal, superior temporal, and right premotor cortex. Therefore, the attentional demands of learning a new motor task may activate different cerebral areas, which is relevant for the three CBS related risk areas to assess decrements to performance in translational models after irradiation. A neural substrate exists for both perceptive and constructive object-oriented sensorimotor cognition, with asymmetry of the inferior parietal activations, including the angular gyrus, during imagery of modelling along with the ventral premotor activations, emphasizing the close proximity of the circuitry for cognitive manipulative motor behavior and language [91]. Hence, it is imperative that we understand to what extent structural changes in the brain are associated with long-term alterations in sensorimotor performance (e.g., such as during a Mars missions) may be increased due to combined exposure to prolonged microgravity, stress, and radiation [51].

RE 5: Validated Method for Predicting Performance Decrements due to Mission-Expected Radiation Exposures

Research Emphasis identified research areas

- Integrate data derived from high-fidelity performance simulations
- Adapt recent breakthroughs in neuroscience computational models for heuristic predictions
- Translational animal laboratory analogs to "translate" performance demands from animal models to humans performance

This research emphasis is linked to the following existing gaps: CNS (3,5,8); BMed (1,2,3,5,6) and SM (24,26)

Computational models will leverage large research databases of neurophysiological and behavioral changes associated with the three CBS risk areas and integrate neural model simulations and simplified brain models that help provide insights into complex neural functions of relevance to

BPP and operational performance [92]. The CBS Integrated Research Plan will thus leverage previously funded research in the individual risks areas and use computational modeling in an effort to identify forward and reverse translatational relationships of order and duration effects of the magnitude and quality of exposure to hazards to biomarkers and operationally relevant performance. An integrated modeling approach requires an understanding of associated mechanisms and must include variables and features that can be used to estimate risk and validate countermeasures. Biophysically informed computational models will help elucidate the neurophysiological basis of changes in neural circuitry in an effort to determine how changes in brain structure and function induced by spaceflight, links to BPPs. This computational model will leverage research data that has already been compiled in support of the three risk areas, and model the function of neural circuitry for relevant BPPs by taking into consideration biological mechanisms, neural dynamics, and biomarkers that are involved in the specific cortical circuit functions impacted by the combined stressors of spaceflight. In addition, such models will help extrapolate and interpolate exposures of longer or greater levels, facilitate characterization of interactions between multiple stressors, help translate animal-based data to humans, and identify credible candidate biomarkers and common AOPs for various stressors.

This modelling effort is intended to produce relevant information that can be used for developing integrated methods to determine how the combined effects of spaceflight stressors affect performance. Integrated methods may include the use of existing computational neuroscience tools, event driven pathway structures, and other mathematical methods. For example, Broderson et al.[93] developed a "generative embedding" approach model to identify subgroups of patients who were diagnosed with a range of psychiatric disorders. *Generative embedding modeling* is an approach to translate dynamic causal models into clinical applications by conceptually developing a model-based classification system that is based on the combination of a generative model and a discriminative classifier. *Dynamic causal models* have been increasingly used to shed light on the mechanisms behind multivariate time series of brain activity acquired in the healthy and the diseased human brain [94]. In their study, Magnetic Resonance Imaging (MRI) data obtained from 41 schizophrenia patients and 42 healthy subjects while they performed memory tasks were used to measure parameters in the prefrontal brain that were then used to define a model-based feature space for the subsequent application of supervised and unsupervised learning techniques [93]. This proof-of-concept study was able to identify subgroups of individuals within the spectrum of psychiatric disorders using dynamical system models that infer neuronal circuit mechanisms from neuroimaging data. Another example of a modelling approach that uses biomarkers to predict performance outcomes in patients with traumatic brain injury[95] used principal component analysis to identify biomarkers (proteins from saliva samples) associated with positive CT findings for cognitive recovery.

In summary, an important component of these research emphases is to data mine research results and literature to uncover relevant biomarkers associated with exposure to individual stressors and combined hazards that relate to changes in operationally relevant performances. This data will assist in developing predictive, heuristic computational models to assess and validate changes in risk status and in identifying biomarkers associated with operational performance changes due to varying types and amounts of space radiation exposures, psychological stress, and sensorimotor changes resulting from microgravity of differing amounts of time. The monitoring of biomarkers, to include monitoring of operationally relevant performance, is then used to activate countermeasures to mitigate risks to mission or crew health.

RE 6: Countermeasures that Maintain Crew Performance Standards during Exploration Class Missions

Research Emphasis identified research areas:

- Identify new concepts and paradigms for intelligent systems and human-computer interfaces for use in designing countermeasures
- Pharmacological, nutritional, and adaptability approaches

This research emphasis is linked to the existing following gaps: CNS (4); BMed (5,6) and SM (24,28)

The CBS Integrated Research Plan requires a focused effort to identify countermeasures (for example: Astronaut selection process, medications, nutrition, exercise, therapeutics, sensorimotor training) that mitigate the integrated effects of space radiation, isolation and confinement, and altered gravity on the CNS. Countermeasures research will identify connections between combined exposures to CBS stressors and operationally relevant brain and behavioral performance pathways. For example, bionutritional countermeasures (alone or in combination with another countermeasure) could alter the neurophysiology, structure, or function of the CNS. Both spaceflight and radiation exposure affect neuroinflammatory processes that produce CNS alterations. Neuroinflammatory pathways are believed to track to brain performance domains/areas that are putatively associated with changes in biomarkers. These biomarkers, in turn, reflect associated alterations (molecular, cellular, neural circuitry, physiological, behavioral changes) from acute CNS effects of radiation and/or isolation and confinement (and potential stress leading to cognitive/behavioral changes).

Increased neuroinflammation is associated with progressive neuronal loss (similar to that from radiation exposure), which increases risk of decrements in cognitive performance. Nutrition has an important role in maintaining cognitive functioning [**96**]. Nutritional status has an important protective role for mental and behavioral functions [**97**]. Consumption of certain types of foods is known to exacerbate neuroinflammation, neurodegeneration, and cognitive impairment (e.g., high fat diets activate microglia, and can result from exposure to either low doses of HZE particles, or isolation and confinement). In addition, microglia are highly responsive to changes throughout the brain and are crucial in maintaining homeostasis. These are also associated with cytokines that serve as convenient biomarkers. In addition, elevated neuroinflammation may have an acute effect on food intake, favoring fat storage. Targeted countermeasures could be developed that stem the inflammatory processes and reactions and reduce inflammation in the brain and microglial activation associated with acute radiation exposure and isolation and confinement. Resolvin D1 (RvD1) and resolvin E1(RvE1), both of which are derived from n-3 long chain polyunsaturated fatty acids, offer promising countermeasures because they can "turn off" systemic inflammatory responses [**98**] (as well as biomarkers for that activation—TNF-a, IL-6, & IL-1B).

Stress is associated with increased microglia motility in the sensorimotor cortex of adult mice, which could influence sensorimotor function. In addition, radiation exposure is linked to reduction in dendritic spines in the hippocampus and imaging has determined that spine remodeling (i.e., the addition and elimination of individual spines from the dendritic field) occurs within hours of radiation exposure. In some rodent models of neuroinflammation associated brain injury, the rates of spine remodeling continually increase during the first two weeks after injury, then gradually decline (especially in the peri-infarct regions, but not in distant brain regions [**99**], which could be a "translational model" and a potential model to validate countermeasures. This may also offer insight into a critical period for

re-stabilization (i.e., countermeasure intervention) to help accelerate replacement or restoration of diminished or damaged areas of the brain.

Identifying some countermeasures will require investigating relevant immune system responses because microglia are activated by exposures to the integrated effects of spaceflight. For example, as noted earlier, recent research has demonstrated that the brain environment influences shifts between pro-inflammatory and neuroprotective microglia [*75*], [*76*]. In addition, both acute and chronic stress can lead to inflammatory biomarkers that signal potential cognitive impairment and the activation of neurodegenerative disease processes [*77*]. As noted in the biomarker section, the integrated approach seeks to leverage blood levels of vitamins B1 and B6 as biomarkers of cognitive performance, cortical folding, and functional resting state connectivity[*78*]. Identifying and linking biomarker changes to countermeasure delivery has important implications for countering the potential synergistic effects of space radiation on the CNS of an isolated, confined crewmember exposed operating in an altered gravity environment. For example, while there is a broad range of promising countermeasure approaches (e.g., therapeutics, exercise, pharmacological and bionutritional); they need to be assessed for their ability to drive a shift from proinflammatory to neuroprotective. The HRP has engaged NASA's Space Biology Program in a cross-cutting effort to help identify relevant biomarkers to mitigate the integrated CBS stressors.

Conclusion

This CBS Integrated Research Plan has thus been developed to meet the HRP guidance. The plan proposes plausible, consistent, and scientifically demonstrable ways to determine if simultaneous exposure to the three major spaceflight stressors affects astronaut performance; and if so, to determine and to quantify how, if at all, exposure to any one specific CBS related spaceflight hazard further modulates, interacts with, and/or amplifies the risk to operationally relevant performance that can be mapped to the underlying neural circuitry and mechanisms related to other spaceflight hazards (e.g. space radiation, isolation, confinement, circadian dysregulation, sleep deprivation, and altered gravity). Further, this CBS Integrated Research Plan will also lead to the development of monitoring capabilities and of countermeasures to mitigate the changes associated with the combined exposure to the CBS stressors of spaceflight.

The CBS Integrated Research Plan will require each of the three organizational elements (Space Radiation, Human Factors and Behavioral Performance, and Human Health Countermeasures Elements) to bring their unique capabilities, experience, and perspectives into an integrative, collaborative and formalized risk mitigation strategy, with efforts and timelines fully integrated. This approach allows a broad, evidenced-based, collaborative, and coordinated HRP research effort to maximize opportunities for learning about the physiological and psychological adaptations to long-duration space travel in the unique environment of deep space. That is, this integrated plan allows HRP to characterize and identify strategies to mitigate risk for in-mission and postlanding performance decrements and/or injuries that are due to the integrated effects of exposure to space radiation, isolated and confined environmental factors, and altered gravity [*100*].

References

[1] F. A. Cucinotta, M. Alp, F. M. Sulzman, and M. Wang, "Space radiation risks to the central nervous system," *Life Sci. Space Res.*, vol. 2, pp. 54–69, Jul. 2014.

[2] F. Cucinotta *et al.*, "Space Radiation Cancer Risk Projections for Exploration Missions: Uncertainty Reduction and Mitigation," p. 63, 2002.

[3] V. K. Parihar *et al.*, "Persistent nature of alterations in cognition and neuronal circuit excitability after exposure to simulated cosmic radiation in mice," *Exp. Neurol.*, vol. 305, pp. 44–55, 2018.

[4] J. S. Jewell, V. D. Duncan, A. Fesshaye, A. Tondin, E. Macadat, and R. A. Britten, "Exposure to ≤15 cGy of 600 MeV/n 56Fe Particles Impairs Rule Acquisition but not Long-Term Memory in the Attentional Set-Shifting Assay," *Radiat. Res.*, vol. 190, no. 6, pp. 565–575, 2018.

[5] B. M. Rabin *et al.*, "Acute Effects of Exposure to (56)Fe and (16)O Particles on Learning and Memory," *Radiat. Res.*, vol. 184, no. 2, pp. 143–150, Aug. 2015.

[6] V. K. Parihar *et al.*, "What happens to your brain on the way to Mars," *Sci. Adv.*, vol. 1, no. 4, pp. e1400256–e1400256, May 2015.

[7] G. A. Nelson, L. Simonsen, and J. L. Huff, "Evidence Report: Risk of Acute and Late Central Nervous System Effects from Radiation Exposure," Human Research Program, Space Radiation Program Element, NASA, Houston, TX, Evidence Report, Apr. 2016. https://humanresearchroadmap.nasa.gov/evidence/reports/cns.pdf

[8] J. J. Bloomberg, M. F. Reschke, G. R. Clement, A. P. Mulavara, and L. C. Taylor, "Evidence Report: Risk of Impaired Control of Spacecraft/Associated Systems and Decreased Mobility Due to Vestibular/Sensorimotor Alterations Associated with Space flight," Human Research Program, Human Health Countermeasures Element, NASA, Houston, TX, Evidence Report, Jun. 2016. https://humanresearchroadmap.nasa.gov/evidence/reports/SM.pdf

[9] O. Bock, C. Weigelt, and J. J. Bloomberg, "Cognitive demand of human sensorimotor performance during an extended space mission: a dual-task study," *Aviat. Space Environ. Med.*, vol. 81, no. 9, pp. 819–824, Sep. 2010.

[10] J. R. Lackner and P. DiZio, "Audiogravic and oculogravic illusions represent a unified spatial remapping," *Exp. Brain Res.*, vol. 202, no. 2, pp. 513–518, Apr. 2010.

[11] J. K. Lee *et al.*, "Spaceflight-Associated Brain White Matter Microstructural Changes and Intracranial Fluid Redistribution," *JAMA Neurol.*, vol. 76, no. 4, pp. 412–419, Apr. 2019.

[12] V. Koppelmans, J. J. Bloomberg, A. P. Mulavara, and R. D. Seidler, "Brain structural plasticity with spaceflight," *Npj Microgravity*, vol. 2, no. 1, Dec. 2016.

[13] V. Koppelmans *et al.*, "Exercise effects on bed rest-induced brain changes," *PLOS ONE*, vol. 13, no. 10, p. e0205515, Oct. 2018.

[14] A. Van Ombergen, S. Laureys, S. Sunaert, E. Tomilovskaya, P. M. Parizel, and F. L. Wuyts, "Spaceflight-induced neuroplasticity in humans as measured by MRI: what do we know so far?," *Npj Microgravity*, vol. 3, no. 1, Dec. 2017.

[15] D. R. Roberts *et al.*, "Effects of Spaceflight on Astronaut Brain Structure as Indicated on MRI," *N. Engl. J. Med.*, vol. 377, no. 18, pp. 1746–1753, Nov. 2017.

[16] M. F. Reschke, D. L. Harm, D. E. Parker, and W. H. Paloski, "DSO 459: Otolith

Tilt-Translation Reinterpretation," in *Results of Life Sciences DSOs Conducted Aboard the Space Shuttle, 1988–1990*, Houston, TX: NASA Johnson Space Center, 1991, pp. 33–50.

[17] J. P. Roll *et al.*, "Sensorimotor and perceptual function of muscle proprioception in microgravity," *J. Vestib. Res. Equilib. Orientat.*, vol. 3, no. 3, pp. 259–273, 1993.

[18] A. P. Mulavara *et al.*, "Physiological and Functional Alterations after Spaceflight and Bed Rest," *Med. Sci. Sports Exerc.*, Jun. 2018.

[19] R. A. Ozdemir, R. Goel, M. Reschke, S. Wood, and W. Paloski, "Critical Role of Somatosensation in Postural Control Following Spaceflight: Vestibularly Deficient Astronauts Are Not Able to Maintain Upright Stance During Compromised Somatosensation," *Front. Physiol.*, vol. 9, Nov. 2018.

[20] M. D. Ross and J. Varelas, "Synaptic ribbon plasticity, ribbon size and potential regulatory mechanisms in utricular and saccular maculae," *J. Vestib. Res. Equilib. Orientat.*, vol. 15, no. 1, pp. 17–30, 2005.

[21] R. Boyle *et al.*, "Neural readaptation to Earth's gravity following return from space," *J. Neurophysiol.*, vol. 86, no. 4, pp. 2118–2122, Oct. 2001.

[22] R. Boyle, R. Ehsanian, A. Mofrad, Y. Popova, and J. Varelas, "Morphology of the utricular otolith organ in the toadfish, Opsanus tau," *J. Comp. Neurol.*, vol. 526, no. 9, pp. 1571–1588, 15 2018.

[23] G. E. Strangman, W. Sipes, and G. Beven, "Human cognitive performance in spaceflight and analogue environments," *Aviat. Space Environ. Med.*, vol. 85, no. 10, pp. 1033–1048, Oct. 2014.

[24] K. J. Slack, W. Sipes, and A. Holland, "Selecting Astronauts: The Role of Psychologists," in *In Keeton KE (Chair), I-O Psychology and Astronauts---Work on Behavioral Health and Performance at NASA(High-Risk/Extreme-Environments)*, Washington, DC: Symposium conducted at the annual convention of the American Psychological Association, 2014.

[25] D. F. Dinges *et al.*, "PVT on ISS: Reaction Self-Test (RST) from 6-month missions," presented at the NASA Human Research Program Investigators' Workshop, 2017.

[26] M. Basner *et al.*, "Psychological and Behavioral Changes during Confinement in a 520-Day Simulated Interplanetary Mission to Mars," *PLOS ONE*, vol. 9, no. 3, p. e93298, Mar. 2014.

[27] B. Yi *et al.*, "520-d Isolation and confinement simulating a flight to Mars reveals heightened immune responses and alterations of leukocyte phenotype," *Brain. Behav. Immun.*, vol. 40, pp. 203–210, Aug. 2014.

[28] S. J. Lupien, B. S. McEwen, M. R. Gunnar, and C. Heim, "Effects of stress throughout the lifespan on the brain, behaviour and cognition," *Nat. Rev. Neurosci.*, vol. 10, no. 6, pp. 434–445, Jun. 2009.

[29] J. Radley, D. Morilak, V. Viau, and S. Campeau, "Chronic stress and brain plasticity: Mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders," *Neurosci. Biobehav. Rev.*, vol. 58, pp. 79–91, Nov. 2015.

[30] K. J. Borle *et al.*, "Intra-individual variability in cerebrovascular and respiratory chemosensitivity: Can we characterize a chemoreflex 'reactivity profile'?," *Respir. Physiol. Neurobiol.*, vol. 242, pp. 30–39, Aug. 2017.

[31] K. J. Slack, T. J. Williams, J. S. Schneiderman, A. M. Whitmire, and J. J. Picano, "Evidence Report: Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorder," Human Research Program, Behavioral Health and Performance, NASA, Houston, TX, Evidence Report, Apr. 2016. https://humanresearchroadmap.nasa.gov/evidence/reports/BMed.pdf

[32] K. Cassady *et al.*, "Effects of a spaceflight analog environment on brain

connectivity and behavior," *NeuroImage*, vol. 141, pp. 18–30, Nov. 2016.

[33] V. Koppelmans *et al.*, "Brain plasticity and sensorimotor deterioration as a function of 70 days head down tilt bed rest," *PLOS ONE*, vol. 12, no. 8, p. e0182236, Aug. 2017.

[34] V. Koppelmans *et al.*, "Intracranial Fluid Redistribution But No White Matter Microstructural Changes During a Spaceflight Analog," *Sci. Rep.*, vol. 7, no. 1, Dec. 2017.

[35] M. Basner et al.: Neurostructural, Cognitive, and Physiologic Changes During a 1-Year Antarctic Winter-Over Mission. Poster at NASA's Human Research Program Investigators' Workshop, Galveston, TX, February 9, 2016.

[36] D. R. Roberts, X. Zhu, A. Tabesh, E. W. Duffy, D. A. Ramsey, and T. R. Brown, "Structural Brain Changes following Long-Term 6° Head-Down Tilt Bed Rest as an Analog for Spaceflight," *AJNR Am. J. Neuroradiol.*, vol. 36, no. 11, pp. 2048–2054, Nov. 2015.

[37] T. Brandt *et al.*, "Vestibular loss causes hippocampal atrophy and impaired spatial memory in humans," *Brain J. Neurol.*, vol. 128, no. Pt 11, pp. 2732–2741, Nov. 2005.

[38] N. Sugaya, M. Arai, and F. Goto, "Changes in cognitive function in patients with intractable dizziness following vestibular rehabilitation," *Sci. Rep.*, vol. 8, no. 1, Dec. 2018.

[39] E. Vitte, C. Derosier, Y. Caritu, A. Berthoz, D. Hasboun, and D. Soulié, "Activation of the hippocampal formation by vestibular stimulation: a functional magnetic resonance imaging study," *Exp. Brain Res.*, vol. 112, no. 3, pp. 523–526, Dec. 1996.

[40] C. M. Oman, "Spatial Orientation and Navigation in Microgravity," in *Spatial Processing in Navigation, Imagery and Perception*, Springer, Boston, MA, 2007, pp. 209–247.

[41] R. W. Stackman, A. S. Clark, and J. S. Taube, "Hippocampal spatial representations require vestibular input," *Hippocampus*, vol. 12, no. 3, pp. 291–303, 2002.

[42] J. S. Taube, R. W. Stackman, J. L. Calton, and C. M. Oman, "Rat Head Direction Cell Responses in Zero-Gravity Parabolic Flight," *J. Neurophysiol.*, vol. 92, no. 5, pp. 2887–2997, Nov. 2004.

[43] A. D. Miller, H. A. Rowley, T. P. Roberts, and J. Kucharczyk, "Human cortical activity during vestibular- and drug-induced nausea detected using MSI," *Ann. N. Y. Acad. Sci.*, vol. 781, pp. 670–672, Jun. 1996.

[44] H. A. Demaree and D. W. Harrison, "Physiological and neuropsychological correlates of hostility," *Neuropsychologia*, vol. 35, no. 10, pp. 1405–1411, Oct. 1997.

[45] N. H. Frijda, *The Emotions*. Cambridge University Press, 1986.

[46] N. H. Frijda, *The laws of emotion*. Mahwah, NJ, US: Lawrence Erlbaum Associates Publishers, 2007.

[47] P. J. Lang, M. M. Bradley, B. N. Cuthbert, and C. J. Patrick, "Emotion and psychopathology: a startle probe analysis," *Prog. Exp. Pers. Psychopathol. Res.*, vol. 16, pp. 163–199, 1993.

[48] J. E. Carmona, A. K. Holland, and D. W. Harrison, "Extending the functional cerebral systems theory of emotion to the vestibular modality: A systematic and integrative approach," *Psychol. Bull.*, vol. 135, no. 2, pp. 286–302, 2009.

[49] N. Preuss, G. Hasler, and F. W. Mast, "Caloric vestibular stimulation modulates affective control and mood," *Brain Stimulat.*, vol. 7, no. 1, pp. 133–140, Feb. 2014.

[50] N. Preuss, F. W. Mast, and G. Hasler, "Purchase decision-making is modulated by vestibular stimulation," *Front. Behav. Neurosci.*, vol. 8, p. 51, 2014.

[51] A. Demertzi *et al.*, "Cortical reorganization in an astronaut's brain after long-duration spaceflight," *Brain*

Struct. Funct., vol. 221, no. 5, pp. 2873–2876, Jun. 2016.

[52] J. R. Lackner and P. DiZio, "Multisensory, cognitive, and motor influences on human spatial orientation in weightlessness," *J. Vestib. Res. Equilib. Orientat.*, vol. 3, no. 3, pp. 361–372, 1993.

[53] A. B. Newberg and A. Alavi, "Changes in the central nervous system during long-duration space flight: implications for neuro-imaging," *Adv. Space Res. Off. J. Comm. Space Res. COSPAR*, vol. 22, no. 2, pp. 185–196, 1998.

[54] M. E. Vazquez, "Neurobiological problems in long-term deep space flights," *Adv. Space Res.*, vol. 22, no. 2, pp. 171–183, Jan. 1998.

[55] S. T. Moore, V. Dilda, T. R. Morris, D. A. Yungher, H. G. MacDougall, and S. J. Wood, "Long-duration spaceflight adversely affects post-landing operator proficiency," *Sci. Rep.*, vol. 9, no. 1, pp. 1–14, Feb. 2019.

[56] Currie NJ and Peacock B, "International Space Station robotic systems operations - A human factors perspective," in *HFES (ed)*, Baltimore, MD, 2001.

[57] M. A. Menchaca-Brandan, A. M. Liu, C. M. Oman, and A. Natapoff, "Influence of perspective-taking and mental rotation abilities in space teleoperation," *2007 2nd ACMIEEE Int. Conf. Hum.-Robot Interact. HRI*, pp. 271–278, 2007.

[58] M. R. Tracey and C. E. Lathan, "The interaction of spatial ability and motor learning in the transfer of training from a simulator to a real task," *Stud. Health Technol. Inform.*, vol. 81, pp. 521–527, 2001.

[59] S. R. Ellis, "Collision in space," *Ergon. Des. Mag. Hum. Factors Appl.*, vol. 8, no. 1, pp. 4–9, 2000.

[60] D. A. Mindell, *Digital Apollo: Human and Machine in Spaceflight*, Later prt. edition. Cambridge, MA: MIT Press, 2008.

[61] W. R. Greco, G. Bravo, and J. C. Parsons, "The search for synergy: a critical review from a response surface perspective," *Pharmacol. Rev.*, vol. 47, no. 2, pp. 331–385, Jun. 1995.

[62] J. A. Bellone, P. S. Gifford, N. C. Nishiyama, R. E. Hartman, and X. W. Mao, "Long-term effects of simulated microgravity and/or chronic exposure to low-dose gamma radiation on behavior and blood–brain barrier integrity," *Npj Microgravity*, vol. 2, no. 1, Dec. 2016.

[63] X. W. Mao *et al.*, "Simulated Microgravity and Low-Dose/Low-Dose-Rate Radiation Induces Oxidative Damage in the Mouse Brain," *Radiat. Res.*, vol. 185, no. 6, pp. 647–657, Jun. 2016.

[64] A. Pulga, Y. Porte, and J.-L. Morel, "Changes in C57BL6 Mouse Hippocampal Transcriptome Induced by Hypergravity Mimic Acute Corticosterone-Induced Stress," *Front. Mol. Neurosci.*, vol. 9, Dec. 2016.

[65] E. Cekanaviciute, S. Rosi, and S. V. Costes, "Central Nervous System Responses to Simulated Galactic Cosmic Rays," *Int. J. Mol. Sci.*, vol. 19, no. 11, p. 3669, Nov. 2018.

[66] B. Rabin, "An introduction to behavior testing for the radiobiologist.," *Three Health Risks Extraterr. Environ.*, p. 11, Jan. 2012. https://three.jsc.nasa.gov/articles/Three

[67] I. of Medicine, *Improving the Utility and Translation of Animal Models for Nervous System Disorders: Workshop Summary*. 2013.

[68] D. W. Shineman *et al.*, "Accelerating drug discovery for Alzheimer's disease: best practices for preclinical animal studies," *Alzheimers Res. Ther.*, vol. 3, no. 5, p. 28, Sep. 2011.

[69] M. J. Bissell *et al.*, "Animal experimentation at the frontiers of molecular, Cellular and tissue radiobiology," Ernest Orlando Lawrence Berkeley National Laboratory, University of California, Berkeley, CA, Oct. 1996.

https://three.jsc.nasa.gov/articles/Three

[70] I. of Medicine, *Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease*. 2010.

[71] C. A. Sanislow, M. Ferrante, J. Pacheco, M. V. Rudorfer, and S. E. Morris, "Advancing Translational Research Using NIMH Research Domain Criteria and Computational Methods," *Neuron*, vol. 101, no. 5, pp. 779–782, Mar. 2019.

[72] D. M. Sridharan *et al.*, "Evaluating biomarkers to model cancer risk post cosmic ray exposure," *Life Sci. Space Res.*, vol. 9, pp. 19–47, Jun. 2016.

[73] S. G. Snowden *et al.*, "Association between fatty acid metabolism in the brain and Alzheimer disease neuropathology and cognitive performance: A nontargeted metabolomic study," *PLoS Med.*, vol. 14, no. 3, p. e1002266, Mar. 2017.

[74] V. R. Varma *et al.*, "Brain and blood metabolite signatures of pathology and progression in Alzheimer disease: A targeted metabolomics study," *PLoS Med.*, vol. 15, no. 1, p. e1002482, 2018.

[75] M. V. Catani, V. Gasperi, T. Bisogno, and M. Maccarrone, "Essential Dietary Bioactive Lipids in Neuroinflammatory Diseases," *Antioxid. Redox Signal.*, vol. 29, no. 1, pp. 37–60, 01 2018.

[76] L. E. Peña-Altamira *et al.*, "Release of soluble and vesicular purine nucleoside phosphorylase from rat astrocytes and microglia induced by pro-inflammatory stimulation with extracellular ATP via P2X7 receptors," *Neurochem. Int.*, vol. 115, pp. 37–49, 2018.

[77] L. Hoeijmakers, A. Amelianchik, F. Verhaag, J. Kotah, P. J. Lucassen, and A. Korosi, "Early-Life Stress Does Not Aggravate Spatial Memory or the Process of Hippocampal Neurogenesis in Adult and Middle-Aged APP/PS1 Mice," *Front. Aging Neurosci.*, vol. 10, p. 61, 2018.

[78] K. Jannusch, C. Jockwitz, H.-J. Bidmon, S. Moebus, K. Amunts, and S. Caspers, "A Complex Interplay of Vitamin B1 and B6 Metabolism with Cognition, Brain Structure, and Functional Connectivity in Older Adults," *Front. Neurosci.*, vol. 11, Oct. 2017.

[79] K. L. English, S. M. C. Lee, J. A. Loehr, R. J. Ploutz-Snyder, and L. L. Ploutz-Snyder, "Isokinetic Strength Changes Following Long-Duration Spaceflight on the ISS," *Aerosp. Med. Hum. Perform.*, vol. 86, no. 12 Suppl, pp. A68–A77, 2015.

[80] "NASA Space Flight Human-System Standard Volume 1, Revision A: Crew Health," 2015. [Online]. Available: https://standards.nasa.gov/standard/nasa/nasa-std-3001-vol-1.

[81] J. W. Ryder *et al.*, "A novel approach for establishing fitness standards for occupational task performance," *Eur. J. Appl. Physiol.*, vol. 119, no. 7, pp. 1633–1648, Jul. 2019.

[82] J. W. Ryder *et al.*, "Influence of muscle strength to weight ratio on functional task performance," *Eur. J. Appl. Physiol.*, vol. 113, no. 4, pp. 911–921, Apr. 2013.

[83] D. S. Bassett, N. F. Wymbs, M. A. Porter, P. J. Mucha, J. M. Carlson, and S. T. Grafton, "Dynamic reconfiguration of human brain networks during learning," *Proc. Natl. Acad. Sci.*, vol. 108, no. 18, pp. 7641–7646, May 2011.

[84] N. U. F. Dosenbach *et al.*, "Distinct brain networks for adaptive and stable task control in humans," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 104, no. 26, pp. 11073–11078, Jun. 2007.

[85] D. A. Fair *et al.*, "Functional Brain Networks Develop from a 'Local to Distributed' Organization," *PLOS Comput. Biol.*, vol. 5, no. 5, p. e1000381, May 2009.

[86] M. D. Fox, A. Z. Snyder, J. L. Vincent, and M. E. Raichle, "Intrinsic fluctuations within cortical systems account for intertrial

variability in human behavior," *Neuron*, vol. 56, no. 1, pp. 171–184, Oct. 2007.

[87] M. P. van den Heuvel, C. J. Stam, R. S. Kahn, and H. E. H. Pol, "Efficiency of Functional Brain Networks and Intellectual Performance," *J. Neurosci.*, vol. 29, no. 23, pp. 7619–7624, Jun. 2009.

[88] D. Meunier, R. Lambiotte, A. Fornito, K. D. Ersche, and E. T. Bullmore, "Hierarchical Modularity in Human Brain Functional Networks," *Front. Neuroinformatics*, vol. 3, Oct. 2009.

[89] G. Pani *et al.*, "Morphological and Physiological Changes in Mature In Vitro Neuronal Networks towards Exposure to Short-, Middle- or Long-Term Simulated Microgravity," *PLOS ONE*, vol. 8, no. 9, p. e73857, Sep. 2013.

[90] S. T. Grafton, E. Hazeltine, and R. Ivry, "Functional mapping of sequence learning in normal humans," *J. Cogn. Neurosci.*, vol. 7, no. 4, pp. 497–510, 1995.

[91] L. Jäncke, N. Gaab, T. Wüstenberg, H. Scheich, and H. J. Heinze, "Short-term functional plasticity in the human auditory cortex: an fMRI study," *Brain Res. Cogn. Brain Res.*, vol. 12, no. 3, pp. 479–485, Dec. 2001.

[92] X.-J. Wang and J. H. Krystal, "Computational psychiatry," *Neuron*, vol. 84, no. 3, pp. 638–654, Nov. 2014.

[93] K. H. Brodersen *et al.*, "Dissecting psychiatric spectrum disorders by generative embedding," *NeuroImage Clin.*, vol. 4, pp. 98–111, 2014.

[94] K. H. Brodersen, "Generative embedding and variational Bayesian inference for multivariate time series," ETH, Zurich, 2012.

[95] J. R. Huie, C. A. Almeida, and A. R. Ferguson, "Neurotrauma as a big-data problem," *Curr. Opin. Neurol.*, vol. 31, no. 6, pp. 702–708, 2018.

[96] S. L. Gardener and S. R. Rainey-Smith, "The Role of Nutrition in Cognitive Function and Brain Ageing in the Elderly," *Curr. Nutr. Rep.*, vol. 7, no. 3, pp. 139–149, 2018.

[97] J. M. Bourre, "Effects of nutrients (in food) on the structure and function of the nervous system: update on dietary requirements for brain. Part 1: micronutrients," *J. Nutr. Health Aging*, vol. 10, no. 5, pp. 377–385, Oct. 2006.

[98] C. Rey *et al.*, "Resolvin D1 and E1 promote resolution of inflammation in microglial cells in vitro," *Brain. Behav. Immun.*, vol. 55, pp. 249–259, 2016.

[99] C. E. Brown and T. H. Murphy, "Livin' on the edge: imaging dendritic spine turnover in the peri-infarct zone during ischemic stroke and recovery," *Neurosci. Rev. J. Bringing Neurobiol. Neurol. Psychiatry*, vol. 14, no. 2, pp. 139–146, Apr. 2008.

[100] I. of Medicine, *Safe Passage: Astronaut Care for Exploration Missions*. 2001.