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

Implementation Strategy

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Introduction

This document supplements the white paper titled *CBS Integrated Research Plan: Problem Statement*. The ***Problem Statement*** describes ***why*** it is important to implement a fully integrated research plan to derive risk estimates for the combined, potentially synergistic, effects of the three major spaceflight hazards (space radiation; isolated, confined, and extreme environments; altered gravity). These risk estimates will help establish acceptable maximum decrement or change in a physiological or behavioral parameter during or after spaceflight, and the acceptable limit of exposure to the combined spaceflight hazards. This ***Implementation Strategy*** describes ***how*** the research plan will accomplish the CBS Integrated Research Plan goals. The Implementation Strategy includes approaches to evaluate relationships among biological responses underlying three risks that are managed by three of NASA's Human Research Project (HRP) organizational "elements":

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

This **CBS** (Acute effects of radiation on **C**NS, **B**Med, **S**ensorimotor) Integrated Research Plan also identifies strategies to monitor and mitigate decrements to operationally relevant performance. Currently, the strategy that was initiated in 2018, includes an eight-year research plan and a four-year validation plan that extend to the year 2030. Once the monitoring tools and countermeasures are developed, they will be validated and refined during four years of early exploration missions. The planned tasks and their associated research products and deliverables have been mapped to the individual research emphases to clearly demonstrate how each research area helps ensure crew health and safety during exploration missions.

CBS Integrated Research Plan Approach, and Strategy

The *CBS Integrated Research Plan* describes a strategy to evaluate and mitigate any decrements to operationally relevant performance that could result from the combined exposure to spaceflight hazards. The overall approach is designed to accomplish the items below:

- Be an integrated research effort that is transdisciplinary and translational in nature, as well as multi-center in its approach.
- Review, verify, and include tasks that are planned or already selected to address the three individual CBS based risks (CNS, BMed, Sensorimotor) and include them as dependencies to the CBS Integrated Research Plan.
- Leverage ongoing tasks and supplement active grants to accelerate CBS based risk mitigation.
- Proactively include CBS-specific topics and aims to solicitations sponsored by the HHC, HFBP, and SR elements.
- Standardize animal models, with the goal of producing higher fidelity models, facilities and spaceflight simulation conditions for translating research outcomes and observations in animals, identify and vet scaling relationships to operational significance for CBS health and behavioral performance risks for humans.
- Include datamining efforts to identify brain performance pathways and biomarkers that are common to animals and humans and that can be used to extrapolate animal measures to predict performance outcomes for astronauts.
- Identify biomarkers related to adverse outcome pathways that result from exposure to space radiation, isolation and confinement, and altered gravity. These biomarkers will help to assess mission related outcomes and performance standards, and to develop monitoring tools and countermeasures.
- Develop computational models that use the identified biomarkers to predict and validate operationally relevant performance outcomes as a function of mission phases.
- Systematically assess effects of radiation exposure on operationally relevant brain performance pathways and mechanisms.
- Regularly synchronize project schedules and deliverables for the CNS, BMed, Sensorimotor risks to ensure transparency and integration of all CBS related content.
- Regularly socialize the integration plan with key stakeholders and encourage adaptation and implementation of the integrated research strategy with technical interchange meetings to cross-educate stakeholders and subject matter experts.

Successful implementation of this approach should result in a suite of validated monitoring tools and countermeasures that can mitigate the combined impact of spaceflight stressors on operationally relevant performance domains.

A conceptual overview of the implementation strategy for the CBS Integrated Research Plan is outlined in Figure 1. This figure is delineated into five functional work areas. Figure 1(I)—*Review Evidence Base/Datamining & Shape Policy*—highlights our current knowledge of biological effects induced by the three individual spaceflight hazards. The figure also identifies areas that have not been sufficiently characterized (red boxes), i.e., direct, non-targeted, and multiple exposure effects, and are a focus of the research plan. The red arrow with blue outline extending from "radiation exposure" to "biological effects" depicts that the risks of radiation exposure have been partially defined (indicated by red), however the blue outline depicts that more research is required in this area. A review of evidence from individually characterized risks (dark blue boxes) will determine the state of collective knowledge and help clarify the objectives of the overall plan. For example, these datamining tasks will identify relevant standards for astronaut's operational performance during a mission, will uncover translational models to help identify the brain domain/pathways related to performance, and will provide information to help interpret how brain domains/pathways are related to operational performance (with the cross-walk from animal models to humans). Each yellow box depicts a needed "knowledge" or "method" and they include *Objectives for Working Groups* (Upper left) that will be engaged in conjunction with transdisciplinary datamining to identify knowledge gaps that will guide forward work. These datamining efforts will focus on operationally relevant performance outcomes with associated brain performance pathways and biomarkers. Policies will also be established to implement standardized research methods and analyses that will optimize translation of animal data to human outcomes.

The CBS Integrated Research Plan includes computational modeling efforts (as depicted in Figure 1(II)—C*omputational Modeling)* to develop tools that will predict and validate research results, and will eventually be used to predict performance decrements for astronauts. The model will help determine the need for preventative measures and/or countermeasures. The gold clouds depict the need for "big data" related to both translational modeling and computational modeling. The translational modeling support is a cross-cutting effort; the Space Biology group at NASA Ames will identify all the "biomarkers" currently assessed for the three individual risk areas (CNS/SM/BMed) and assess "effects" or "outcomes" of various levels of exposures for each of the three hazards. The Space Biology groups' efforts focus on operationally relevant brain performance pathways linked to operational performance. The intent is to capture the "biomarkers" and "effects" for use in heuristic models to more effectively target and accelerate research in this area. NASA Glenn Research Center will utilize the data pipeline provided by NASA Ames to build predictive models through a variety of data driven modeling techniques.

The CBS Integrated Research Plan includes strategies to accelerate the accumulation of knowledge using translational models that quantify the effects of the three main space hazards (as depicted in Figure 1(III)—*Translational Models to Accelerate Building Knowledge Base of CBS Combinatorial Effect)*. The light blue boxes in Figure 1 depict "known" (but incompletely understood) variables that could affect operationally relevant performance. The need for operationally relevant monitoring tools and standards to characterize the effects of these variables are denoted. Each yellow box in this functional area depict a needed "knowledge" or "method", and some include objectives for research focused in multiple contributing areas (an example of an area of research is "Brain Performance Pathways"). These studies will focus on how dose-rate and order of stressor exposures—how radiation exposure interacts with effects induced by isolation, confinement and altered gravity. Further, these studies will identify biomarkers via brain performance pathways associated with operationally relevant performance, with direct contributions to identifying performance outcome levels (as depicted by dark blue arrows originating from brain performance pathways passing through

CBS Integrated Research Plan: Implementation Strategy

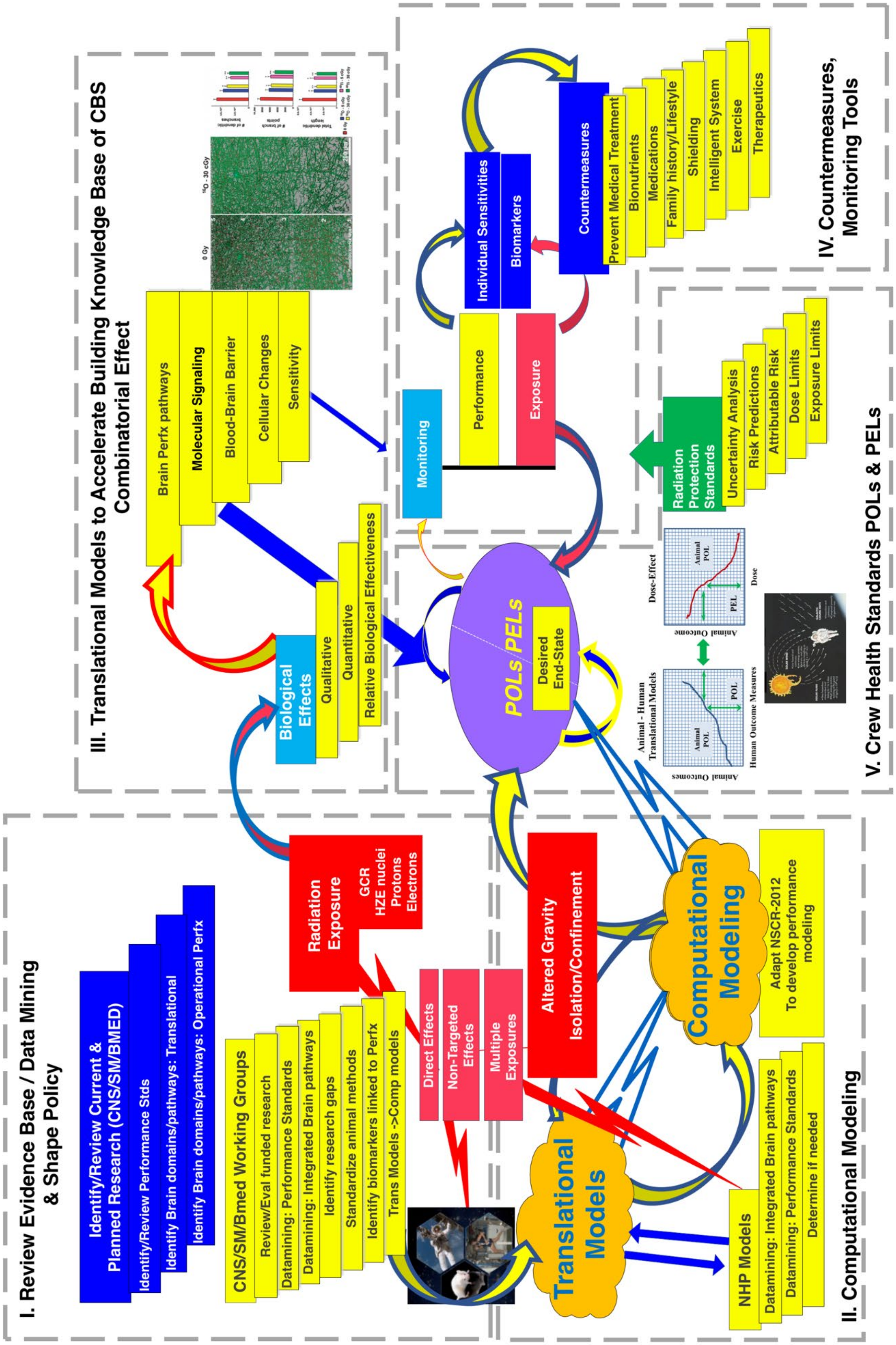

Figure 1: The overall strategy for the CBS Implementation Plan. To read the CBS Integrated Research Plan strategy, print on 11x17 format paper, or zoom in when displayed in a pdf document.

biological effects of multiple stressors with smaller dark blue arrow emphasizing importance of monitoring these effects on performance and exposures).

The CBS Integrated Research Plan includes approaches to develop countermeasures that can improve an astronaut's performance and enable them to stay within newly established permissible outcome levels (POLs) and permissible exposure limits (PELs) for operationally relevant performance (as depicted in Figure 1(IV)—*Countermeasures, Monitoring Tools*). Under the dark blue box in the lower right, titled *Countermeasures*, is a list of those areas where countermeasures are already demonstrating some benefit but clearly more effort is needed to determine if they can counteract the performance deficits from exposure to combined spaceflight hazards, if these hazards interact in a synergistic manner. Just above *Countermeasures* are *Individual Sensitivities* and *Biomarkers* both of which feed into *Countermeasures*. Inter-individual sensitivity to spaceflight stressors has already been reported, and a significant number of biomarkers have already been identified for each of three CBS based risk areas; however, as depicted by the yellow arrow with blue outline, more relevant and focused research is required. The light blue boxes represent the need for additional knowledge and monitoring capability to determine "what" the operationally relevant and "acceptable" level of performance is, and "how" (i.e., via monitoring, testing, etc) we will determine that level of performance for establishing POLs and PELs. Each yellow box depicts a needed "knowledge" or "method", some of which include further understanding, refinement and integration of existing efforts on developing integrated countermeasures.

The purple center (representing the "regal" or most important outcome— *Crew Health Standards POLs & PELs*) relates to developing operational performance standards for human performance effects from combined exposure to space radiation, altered gravity and isolation and confinement. As noted above, each yellow box depicts a needed "knowledge" or "method", some of which relate to adjustment of current radiation protection standards for "operationally relevant performance" (e.g., see green box lower right and yellow needed "knowledge" or "method" boxes for the operationally relevant risk predictions, dose limits, etc.).

Identifying and Organizing the CBS Integrated Research Priorities

The CBS Integrated Research Plan schedule is displayed in Figure 2 showing the sequence of research tasks and logical dependencies. The plan is organized into the six research emphases shown along the left column (as described in the *Problem Statement* document). Unique CBS funded tasks are displayed as green bars (for ground studies) or blue bars (for flight studies). Research products and deliverables owned by the three individual risk areas are displayed as purple pentagons throughout the integrated project plan. These deliverables are necessary for full success of the CBS Integrated Research Plan. Blue arrows show where content from one task feeds into a future task. Major milestones are displayed at the top of the schedule. These include (1) Characterization of the synergistic effects of CNS/BMed/SM (Fiscal Year [FY]21); (2) Initial Countermeasures (CMs) and Standards Updates recommended (FY22); (3) CMs Validated and Standards Updated (FY26); and (4) Updated CMs Validated (FY30). The orange bars at FY22, FY26, and FY30 indicate review of the recommended CMs and POLs/PELs by the Office of the Chief Health and Medical Office (OCHMO).

CBS Integrated Research Plan: Implementation Strategy

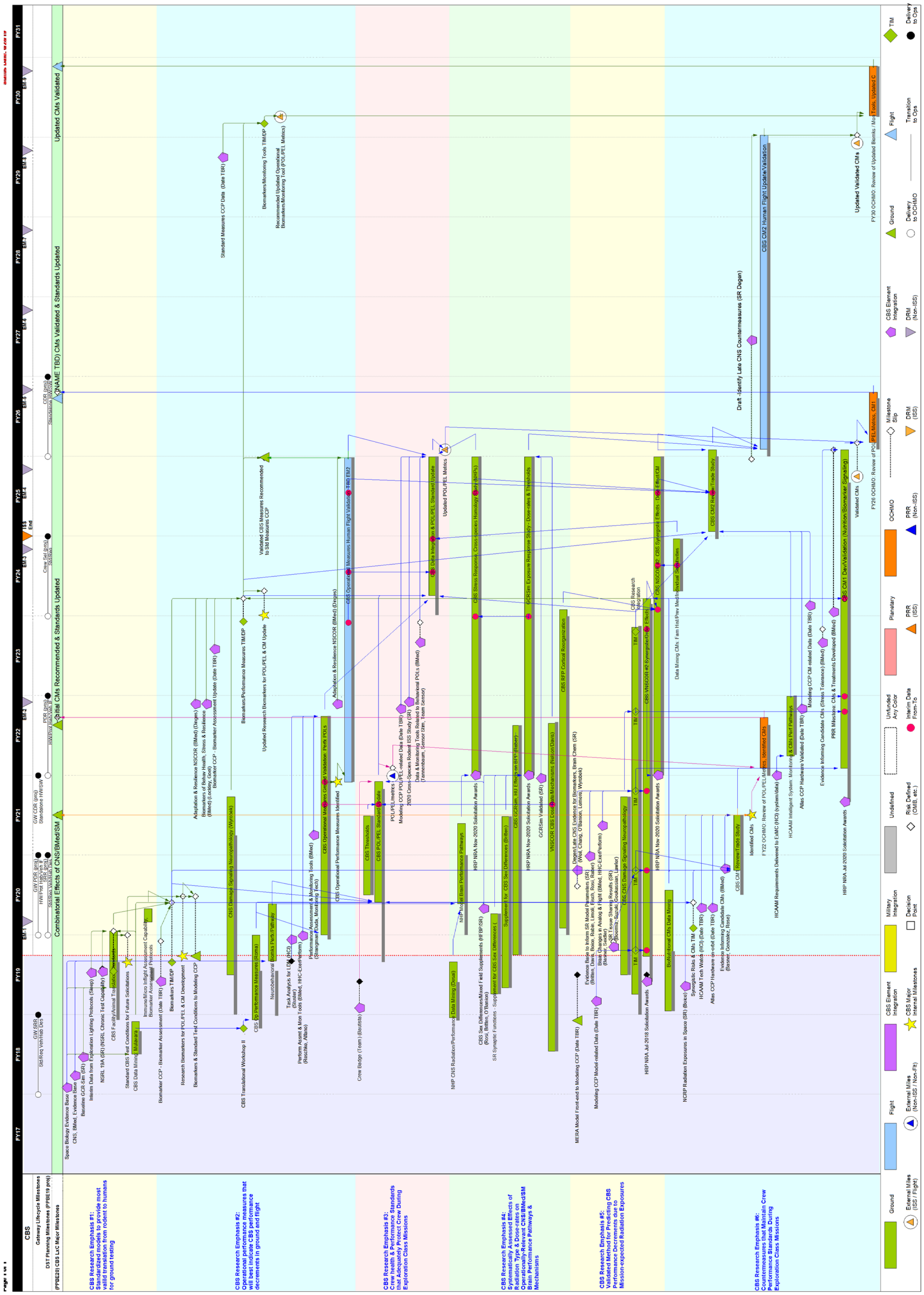

Figure 2: CBS Integrated Research Plan Schedule. (Note: To read the CBS Integrated Research Plan schedule, print on 11x17 format.)

The CBS Integrated Research Plan was designed to accelerate delivery of research products that will allow updates to CNS, BMed, and SM standards, as required, and using the eight year research plan to establish new POLs and PELs for operationally relevant performance by the year 2026. The CBS Integrated Research Plan is integrally dependent on the established pathways to risk reduction (i.e. project schedules) to mitigate the CNS, BMed, and SM risks. Tasks funded through the HFBP, the HHC, and the SR Elements are linked to the CBS Integrated Research Plan schedule. The final deliverables to the three individual organizational Elements are assigned as hard dependencies within the CBS Integrated Research Plan schedule, and the integration of these are critical to the overall success of the CBS strategy. These tasks are represented as purple pentagons in the CBS Integrated Research Plan schedule (Figure 2). Examples of these tasks, one from each of the CBS risk areas, are shown in Appendix A.

The HRP prioritizes research in part through characterization of human spaceflight risk. The HRP identifies individual risks, which are assigned to specific organizational "elements" within the program that are responsible for identifying gaps in knowledge required to characterize the risk, and this in turn drives solicited or directed research that will partially or completely close the knowledge gap, and ultimately the entire risk. The gaps associated with the CBS based HRP risks are described in Table 1of the accompanying document *CBS Integrated Research Plan: Problem Statement*. The CBS Integrated Research Plan is still formulating a knowledge base, and is not a stand-alone risk at this time. To ensure that CBS tasks map back to existing risks and gaps, the content in the CBS portfolio was organized into 6 Research Emphases, which emulate knowledge gaps. The Research Emphases are also depicted in Figure 2, CBS Integrated Research Plan Schedule (see far left of multiple colored column of Figure 2). The *CBS Integrated Research Plan: Problem Statement*, which is the companion document to this *CBS Integrated Research Plan: Implementation Plan*, provides the rationale, goals, and detailed knowledge gaps for each Research Emphasis.

Tables 1- 6 below describe the discreet tasks in the CBS portfolio organized by Research Emphasis depicted in green and blue bars in Figure 2, provide the sequence of research tasks via the periods of performance within each Research Emphasis, milestones and the anticipated final deliverables (research products, end-state or final outcomes) to characterize and mitigate the CBS based risks presented in the CBS Integrated Research Plan. The discreet tasks are organized and listed by Research Emphasis highlighting the periods of performance, the gaps each address, and the deliverables for each task. The set of tasks within each Research Emphasis is chronologically ordered by their period of performance. These tasks are directly funded and managed by the CBS portfolio as compared to the hard dependency tasks that are funded and managed by the individual organizational Elements (see examples of tasks - hard dependencies in Appendix A).

CBS Research Areas, Techniques and Strategies

Table 1: Two discreet CBS portfolio tasks under Research Emphasis 1 highlighting the periods of performance, CBS related gaps, and the deliverables for each task (See Figure 2, first row).

Research Emphasis 1 **Standardized Models to Provide Most Valid Translation from Rodent to Humans for Ground Testing**
Task 1: CBS Sensorimotor Datamining & Technical Interchange Meeting (TIM) **Period of Performance:** 4/2/2018-8/31/2018 **Gaps Addressed:** CBS-CNS-1, CBS-CNS-8, CBS-SM7.1, CBS-SM2.1, CBS-SM28 , CBS-CNS-2, CBS-CNS-5, CBS-BMed3, CBS-BMed2 **Task Aims:** 1. Review and assess current and completed research findings from relevant NASA-funded studies. Identify behaviors and physiological changes (biomarkers) in cells, molecules, and brain regions that are linked to specific effects of space radiation exposure, simulated altered gravity, and/or spaceflight, and can be translated to operational performance measures. 2. Determine the neural circuitry of brain performance pathways responsible for maintaining operationally relevant behavior and cognitive functions by reviewing studies of behavioral responses to artificial stimulation of networks that are sensitive to radiation, isolation and confinement, or altered gravity; and identify biomarkers of the network activity (neurotransmitters and changes associated with messenger activity) that predict behavioral changes. **Deliverable Description:** • Summary of existing research results • Descriptions of brain performance pathways and brain regions that influence operationally relevant performance • Description of knowledge gaps • Recommendations for specific areas needing further research • Identified biomarker candidates to modeling project
Task 2: CBS Facility/Animal Translation Standards **Period of Performance:** To Be Determined (TBD) **Gaps Addressed:** CBS-CNS-1, CBS-CNS-8, CBS-SM (26) , CBS-CNS-2, CBS-CNS-5, CBS-BMed3, CBS-BMed2 **Task Aim:** Determine and develop standards and recommendations related to animal handling, research facility (e.g., volume, lighting, sound, etc.), and animal/rodent type (species/strains) to increase reliability and validity of animal to human translational research yields. **Deliverable Description:** Recommendations for • Standard testing conditions and tissue handling procedures for future CBS research (focus on translational models to increase confidence in animal to human predictive models) • Biomarkers of brain performance pathways linked to operationally relevant performance • Testing/measurements/questionnaires linked to operational performance • Standardized animal conditions and models that will be used to assess effects of space radiation exposure on CNS during isolation and confinement and altered gravity, and to advance computational models to translate animal data to human outcomes • Robust methods that use biomarker and computational modeling to validate translation of neurophysiological insights in animals and predict effects on astronauts' operational performance

Table 2: Five discreet CBS portfolio tasks under Research Emphasis 2 highlighting the periods of performance, CBS related gaps, and the deliverables for each task (See Figure 2, second row).

Research Emphasis 2

Operational Performance Measures that will Best Indicate CBS Performance Decrements on the Ground and in Flight

Task 1: CBS Operational Performance Measures

Period of Performance: 9/1/2018-8/31/2019

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM26 , CBS-SM2.1, CBS-BMed2

Task Aims:
Review NASA technical and internal documents, the scientific literature, and input from NASA operations experts to identify and assess the following:

1. Core tasks, individual and team performance abilities, and behavioral health and performance competencies that are required for long-duration space exploration.
2. The constituent neurobehavioral processes (e.g., attention, short-term memory, verbal communication), brain performance pathways, and neurobehavioral, neuroanatomical, and neurochemical substrates underlying the tasks identified in Aim 1.
3. The sensitivity, reliability, validity, translational potential, and redundancy of existing research measures of constituent neurobehavioral processes, brain performance pathways, and neurobehavioral, neuroanatomical, and neurochemical substrates identified in Aim 2.

Deliverable Description:

- Summary of the findings identifying relative strengths and weaknesses of potential operational performance measures and potential redundancy of measures as determined by overlapping brain performance pathways
- Summary of other CBS operational performance measures and CBS integrated datamining tasks including CBS Datamining, CBS Nonhuman Primate CNS Radiation/Performance Datamining, and CBS Research Review (RR): Neurobehavioral Biomarkers Performance/Pathway
- Recommendations of evidence-based set(s) of brain performance pathways measures applicable to multiple risk areas to assess the integrated effects of radiation, isolation and confinement, and altered gravity
- Recommendation for a concise set of operationally relevant human performance measures to assess the combined effects of radiation, stress, and altered gravity
- Description of brain performance pathways that could be related to operationally relevant measures and could inform translational models that link animal performance and changes in brain function and structure changes to human performance measures (behavior, biomarker, predictive models)
- Recommend changes to NASA standards and guidelines for operational performance (e.g., monitoring frequency based on length/amount of radiation exposure along with cumulative effects of other spaceflight stressors).

Task 2: CBS CNS Damage Signaling Neuropathology

Period of Performance: 4/1/2019-3/31/2021

Gaps Addressed: CBS-CNS-1, CBS-CNS-2

Task Aims:

1. Characterize the persistence of radiation-induced molecular abnormalities in cortex and hippocampus after low-dose exposures to 56Fe particles, and compare the predictions for CNS tissue damage and late-onset neuropathologies in similarly irradiated mice and rats.
   1a: Use archived CNS tissue from Sprague Dawley® (SD) rats collected at 4 and 9 months after low-dose exposures, and generate new transcriptomics (3'TAGseq) and new metabolomics profiles (untargeted

metabolism and targeted complex lipids) from cortex and hippocampus. These data will be integrated with prior proteomics profiles from hippocampus at 9 months after exposure to build a predictive model of CNS tissue damage and risks for neuropathology, with emphasis on vascular and immune abnormalities.

1b: Compare molecular responses in cortex and hippocampus of mice and rats at 9 months after radiation exposure to evaluate cross-species consistency. The predictive model will be built using integrating bioinformatics and biostatistical approaches.

2. Identify persistent bio-effect markers in peripheral blood and cerebrospinal fluid (CSF) that correlate with molecular damage in CNS vascular or immune functions.

   2a: Investigate the metabolomics profiles of archived CSF and archived peripheral blood plasma from the same animals.

   2b: Determine whether the blood metabolities associated with CNS tissue damage correlate with individual variation in radiation-susceptibility for anxiety as measured in the elevated plus maze.

Deliverable Description:

- Molecular information on the effects of age at radiation exposure, time of tissue collection after exposure, and effects of genomic background on dose response and thresholds for CNS pathways associated with radiation-damage response and neuropathology
- Description of CNS subregion-specific responses, common radiation responses, and mouse-rat cross-genome-risk biomarkers and pathways that can be used for developing of molecular countermeasures

Task 3: Neurobehavioral Biomarkers Performance/Pathway

Period of Performance: 5/31/2019-5/30/2020

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-S24 , CBS-SM7.1 , CBS-SM2.1, CBS-SM28 , CBS-CNS-2, CBS-BMed3, CBS-BMed2

Task Aims:

1. Review research of neurobehavioral biomarkers, integrating past radiation research with current and cutting-edge neuroscience results from psychopathology related to stress and vulnerabilities to psychiatric disorders, to identify correlative contributions of brain regions relevant to operational performance.
2. Determine specific neurobehavioral biomarkers of dose variation from radiation, altered gravity, and isolation and confinement, and biomarkers associated with both human and rodent cognition and performance.

Deliverable Description:

- Identified neurobehavioral biomarkers (blood, behavioral, etc.) linked to past CBS research that correlate with human behavior and performance
- Description of biomarkers associated with behavioral decrements and/or greater risk of developing neurocognitive disorders
- Conceptual model and heuristic method to determine dose effects
- Computational models to identify potential linkage between operationally relevant performance and the organization of brain modular networks that support complex behavioral adaption during exposure to novel environments, and sub-networks that support "associative" processes such as executive function

Task 4: CBS Operational Measures Ground Validation: Performance Permissible Outcome levels (POLs)

Period of Performance: Planned: 10/01/2020-08/31/2022

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM24 , CBS-SM7.1 , CBS-SM2.1, CBS-SM28 , CBS-CNS-2, CBS-CNS-3, CBS-BMed3, CBS-BMed2

Task Aims:

1. Validate human performance measures in appropriate spaceflight analogs to assess the integrated effects of radiation, isolation and confinement, and altered gravity.

Deliverable Description: • Ground validated recommendations for in-flight performance measures and thresholds for POLs that are linked to mission operations milestones (i.e., exploration missions) and will provide preliminary information that represents a significant step toward recommendation of POL/PEL standards
Task 5: CBS Operational Measures Human Flight Validation **Period of Performance**: Planned: 08/01/2021-09/30/2025 **Gaps Addressed:** CBS-CNS-1, CBS-CNS-8, CBS-SM24 , CBS-SM7.1 , CBS-SM2.1, CBS-SM28 , CBS-CNS-2, CBS-CNS-3, CBS-BMed3, CBS-BMed2 **Task Aims:** 1. Monitor astronauts during their missions on board the International Space Station to link brain performance pathways with performance tasks sensitive to combined exposure to radiation, isolation and confinement, and altered gravity. **Deliverable Description:** • Results of in-flight monitoring of astronaut performance and biomarkers associated with combined exposure to radiation, isolation and confinement, and altered gravity • Calculations of the effect of deep space radiation on operationally relevant crew performance during relatively short mission durations that could be extrapolated to effects of exploration missions

Table 3: Two discreet CBS portfolio tasks under Research Emphasis 3 highlighting the periods of performance, CBS related gaps, and the deliverables for each task (See Figure 2, third row).

Research Emphasis 3 **Crew Health and Performance Standards that Adequately Protect Crew during Exploration Class Missions**
Task 1: CBS POL/PEL Standard Update **Period of Performance:** 06/30/2020-08/31/2021 **Gaps Addressed:** CBS-CNS-1, CBS-CNS-3, CBS-CNS-8, CBS-BMed2, CBS-BMed3, CBS-SM6.1, CBS-SM24 **Task Aims:** 1. Use initial research results from the CBS research studies to draft POLs for use in developing PELs for CNS effects from combined exposure to radiation, isolation and confinement, and altered gravity, and initiate review through the required control boards. **Deliverable Description:** • Initial POLs linked to operationally relevant performance tasks with identified decrements of performance used to establish PELs.
Task 2: CBS Data Integration and POL/PEL Standard Update **Period of Performance:** 02/01/2024-09/30/2025 **Gaps Addressed:** CBS-CNS-1, CBS-CNS-8, CBS-SM24 , CBS-SM7.1 , CBS-SM2.1 , CBS-SM28 , CBS-CNS-2, CBS-CNS-3, CBS-BMed2, CBS-BMed3

Task Aims:

1. Use research results to update POLs and PELs for CNS effects from combined exposure to radiation, isolation and confinement, and altered gravity as needed, and gain approval for the updated POLs and PELs through the required review processes. The study aims address operationally relevant fitness for duty standards within the context of NASA Standard 3001, 4.2.2.2 Space Permissible Exposure Limits (SPEL) - Quantifiable limit of exposure to a space flight factor over a given length of time, e.g., lifetime radiation exposure. Physical/chemical agent measured, and 4.2.2.3 POL - Acceptable maximum decrement or change in a physiological or behavioral parameter, during or after a space flight mission, as the result of exposure to the space environment. Biological/clinical parameter measured, e.g., bone density.

Deliverable Description:

- Approved POLs and PELs for CNS effects from combined exposure to radiation, isolation and confinement, and gravity

Table 4: Ten discreet CBS portfolio tasks under Research Emphasis 4 highlighting the periods of performance, CBS related gaps, and the deliverables for each task (See Figure 2, row four).

Research Emphasis 4

Systematically Assess Effects of Radiation Type and Dose-Rate on Operationally Relevant CBS Brain Performance Pathways and Mechanisms

Task 1: CBS VNSCOR #1 - Mechanisms of Radiation-Induced Neurobehavioral Deficits

Period of Performance: 4/15/2018-8/31/2022

Gaps Addressed: CBS-CNS-1, CBS-CNS-5, CBS-BMed3

Task Aims:

1. Investigate the time course of radiation-induced deficits in sustained attention and social processing after protracted exposure to the follow types of exposures: five-ion simulated galactic cosmic ray spectrum of charged particles (‘5-ion GCR simulation’ or ‘simplified GCR sim’: standardized radiation field consisting of 5 accelerated ion species: $^{1}H^{1+}$, $^{4}He^{2+}$, $^{16}O^{8+}$, $^{28}Si^{14+}$ and $^{56}Fe^{26+}$ with energies in the 250 to 1000 MeV/n range and in balanced proportions designed to roughly approximate the galactic cosmic ray environment); galactic cosmic ray simulation (GCR sim: a standardized radiation field consisting of 7 accelerated ion species: $^{1}H^{1+}$, $^{4}He^{2+}$, $^{12}C^{6+}$, $^{16}O^{8+}$, $^{28}Si^{14+}$, $^{48}Ti^{22+}$ and $^{56}Fe^{26+}$ with 33 ion + energy combinations up to 1000 MeV/n in proportions designed to approximate the galactic cosmic ray environment on the basis of LET distribution and relative fluence, total dose: 0.5 Gy); heavy ions only in the “five-ion” GCR simulation (^{4}He, ^{28}Si, ^{16}O, and ^{56}Fe only: total dose: 0.5 Gy); protons (total dose: 0.5 Gy); ^{4}He ions (250 MeV/n) at two different exposure doses (5 and 25 cGy).
2. Investigate the time course of neuronal and other molecular markers after exposure to the GCR sim or ^{4}He. The time points for testing include 7 days, 1 month, 3 months, and 6 months after irradiation.
3. Investigate the effects of silencing the regions of the medial prefrontal cortex, including the prelimbic, infralimbic and the anterior cingulate cortices, on sustained attention and social processing to determine possible mechanisms of radiation-induced changes in these behaviors.

Deliverable Description:

- Description of the effects of acute and fractionated high charge and energy (HZE) exposures on cognitive domains relevant to astronaut performance (e.g., attention, social cognition)
- Description of the effects of other spaceflight factors in combination with HZE exposure on neurobehavioral performance
- Description of the effects of HZE exposure on neuronal activation in behavioral task-specific brain regions, including the medial pre-frontal cortex (mPFC), a region important for numerous cognitive domains and executive function

- Description of the severity of HZE induced deficits during to pharmacogenetic silencing of the different sub-regions of the mPFC

Task 2: CBS VNSCOR #1 - Radiation Dose Rate Effectiveness Factors

Period of Performance: 4/15/2018-8/31/2022

Gaps Addressed: CBS-CNS-1, CBS-CNS-2, CBS-CNS-5, CBS-BMed3

Task Aims:

1. Determine responses for an interrelated set of CNS outcome measures in mice exposed to acute or protracted exposures of protons (0.5 Gy), GCR sim radiation (0.25 or 0.5 Gy), and gamma radiation (0.75 and 2.0 Gy).
2. Derive dose-rate effectiveness factors for the set of outcome measures and determine relative biological effects for the set of outcome measures for protracted GCR sim exposure.

Deliverable Description:

- Dose-rate effectiveness factors and relative biological effectiveness factors for an interrelated set of CNS outcome measures in mice after protracted exposures to protons or a simulated galactic cosmic ray spectrum of charged particles that can be used to extrapolate dose-response measurements from acute laboratory exposures to the protracted exposure condition of spaceflight

Task 3: SR Synaptic Functions - Supplement for CBS Sex Differences

Period of Performance: 7/31//2018-1/5/2020

Gaps Addressed: CBS-CNS-2

Task Aims:

1. Determine why female mice are more resistant than males to the effects of GCR exposure by examining how sex influences synaptic composition and microglia activation and repopulation of microglia after GCR exposure.
2. Determine if sex affects changes in the N-methyl-D-aspartate (NMDA) receptor after GCR exposure.
3. Determine if microglia depletion and repopulation is able to correct cognitive deficits in male and female mice after GCR exposure.
4. Map molecular changes to brain performance areas that are known to be associated with in molecular pathways for brain structure changes that predict performance decrements.

Deliverable Description:

- Description of male and female synaptic composition and microglia activation in the various brain regions involved in cognitive deficits after GCR exposure
- Data to determine a genetic signature of microglia in male and females after acute or chronic exposure to GCR
- Data to determine if microglia depletion and repopulation in male and female mice is able to rescue cognitive deficits after GCR exposure and the sex differences in the genetic signature of the repopulated microglia population

Task 4: CBS Nonhuman Primate (NHP) CNS Radiation/Performance Datamining

Period of Performance: 9/17/2018-5/30/2019

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM26 , CBS-SM24 , SM27, CBS-CNS-2, CBS-CNS-5, CBS-CNS-3, CBS-BMed2, CBS-CNS-4

Task Aims:
1. Conduct a comprehensive and systematic evaluation of existing research on the acute and long-term effects of exposure to spaceflight stressors on NHP CNS function.
2. Identify gaps in the knowledge of applied and mechanistic effects from acute and long-term exposure to spaceflight stressors on CNS function that need to be studied in NHPs and for which rodent studies are inadequate.
3. Assess the validity and limitations of using non-human primates in future targeted research to address critical gaps in knowledge.

Deliverable Description:
- A comprehensive and systematic evaluation of existing research on the acute and long-term effects of exposure to spaceflight stressors on NHP CNS-related neurobiological, neurochemical, neurobehavioral and cognitive function
- Description of critical research gaps that cannot be determined by translation of rodent data to humans
- Recommendations regarding the validity, strengths, and limitations of using NHP in future targeted research

Task 5: Supplement for CBS Sex Differences

Period of Performance: 1/1/2019- 12/31/2020

Gaps Addressed: CBS-CNS-1, CBS-CNS-3, CNS-6

Task Aims:
1. Establish the impact that re-irradiation with 10 cGy of 5-ion simplified GCR sim beam has on the Attentional Set shifting (ATSET) performance of male and female Wistar rats that maintained a functional ATSET performance after initial exposure to 10 cGy of either He or GCR sim.

Deliverable Description:
- Information on the robustness of single-exposure experiments to predict the impact of repeated episodic radiation exposures (such as will be encountered on the mission to Mars) on neurocognition
- ATSET performance after a single exposure (He or GCR sim) and after a second exposure (~6 months later) to the 5-ion GCR sim beam

Task 6: CBS GCR sim, Hindlimb Unloading (UH) Effects on Brain Performance Pathways

Period of Performance: 5/1/2019-3/1/2021

Gaps Addressed: CBS-CNS-8, CBS-CNS-2, CBS-CNS-5

Task Aims:
1. Determine the effects of mixed beam irradiation in the presence and absence of hindlimb unloading on behavioral and cognitive performance and determine whether these effects are associated with alterations in metabolic pathways in two pertinent brain regions in WAG rats (WAG rats are a strain of rats that exhibit depression-like symptoms).

Deliverable Description:
- Metabolomics analysis of the two pertinent brain regions (all likelihood, hippocampus and cortex)

Task 7: CBS Cortical Reorganization

Period of Performance: 01/01/2020-01/31/2024

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM26 , CBS-SM24, CBS-CNS-2, CBS-CNS-5, CBS-CNS-3, CBS-BMed2

Task Aims:
1. Assess the connection patterns in the brain as represented by brain performance pathways to determine differential vulnerabilities of modular networks.
2. Determine how a more modular brain network may reorganize.

3. Identify and potentiate countermeasures to mitigate risk associated with decrements in operationally relevant performance (e.g., the potential for up-regulation in neurotrophic factors that have been associated with greater exercise-related changes in brain connectivity).

Deliverable Description:
- Description of specific focal impacts on brain regions and "between-module connectivity" that are linked to operationally relevant behavior and cognitive functioning
- Explanation of how these connectivity patterns represent brain performance pathways and reflect differential vulnerabilities to brain changes that are linked to performance

Task 8: NHP Model Brain Performance Pathways

Period of Performance: Planned: 06/01/2020-06/30/2021

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM26 , CBS-SM24 , CBS-SM2.1 , CBS-CNS-2, CBS-CNS-5, CBS-CNS-3, CBS-BMed3, CBS-BMed2

Task Aims:
1. Perform a research review of prior studies of performance outcomes in NHP from exposure to space-like stressors.
2. Identify available biomarkers or performance measures collected after exposure to space-like stressors.

Deliverable Description:
- Report on brain performance pathways and connectivity patterns observed in past research of radiation, stress, and sensorimotor adaption in NHP
- Descriptions of NHP models of brain performance pathways that could be associated with decrements in operationally relevant performance from combined exposure to radiation, isolation and confinement, and altered gravity

Task 9: CBS GCR sim Exposure Response Study

Period of Performance: HRP NRA Nov-2020 Solicitation Awards

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM26, CBS-SM24 , CBS-CNS-2, CBS-CNS-5, CBS-CNS-3, CBS-BMed2

Task Aims:
1. Use standardized animal models including behavioral tests to assess brain physiology (including patency and function of the blood-brain barrier), molecular signaling, and biomarker changes.
2. Inform computational modeling to characterize and predict changes in brain performance pathways associated with operationally relevant performance.

Deliverable Description:
- GCR sim exposure response for selected measures
- Experimental evidence and predictive models for brain performance pathways affected by space-like radiation, stress, and altered gravity, with associated exposure-level effects, compensatory pathways, and adverse outcome mechanistic pathways that can inform heuristic computational models and countermeasure development

Task 10: CBS Stress Response, Cross-species Homology Study NHPs

Period of Performance: HRP NRA Nov-2020 Solicitation Awards

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM26 , CBS-SM24, SM27, CBS-CNS-2, CBS-CNS-5, CBS-CNS-3, CBS-BMed2, CBS-CNS-4

Task Aims:

1. Develop scientifically plausible, heuristic, validated computational models linked to Research Emphasis 5 that can assess, characterize, and validate operationally relevant spaceflight performance using data derived from NHP and radiation exposures (both clinical and space relevant doses) in combination with other CBS related spaceflight stressors.

Deliverable Description:

- Description of integrated stress response linked to alteration in behavior
- List of cross-species homology of selected behaviors
- Description of early markers of molecular and/or cellular changes to elucidate the molecular cascades linked to behavior changes that result from combined exposure to radiation, isolation and confinement, and altered gravity

Table 5: Seven discreet CBS portfolio tasks under Research Emphasis 5 highlighting the periods of performance, CBS related gaps, and the deliverables for each task (See Figure 2, Row 5).

Research Emphasis 5

Validated Method for Predicting CBS Performance Decrements due to Mission-Expected Radiation Exposures

Task 1: CBS Research Integration

Period of Performance: 09/01/2019-08/31/2023

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM24, CBS-SM7.1, CBS-SM2.1, CBS-SM28, CBS-CNS-2, CBS-CNS-5, CBS-BMed1, CBS-BMed2, CBS-BMed3, CBS-CNS-4

Task Aims:

1. Review research from the three CBS risk areas (i.e., CNS, BMed, and SM) when the studies are completed and assess relation to operationally relevant performance areas.
2. Assess the feasibility and acceptability of current research in addressing operational performance constructs.
3. Identify iterative processes for selecting relevant research data to incorporate into a thematic analysis.
4. Assess implications of research to date as it relates to development of standards and performance and countermeasures.
5. Determine quality of research needed to form an integrated approach to assess the three risks.

Deliverable Description:

- Report summarizing the extent, range, and nature of three (CNS, BMed, and SM) research activities that includes rationale for integrated approach and implications related to operational performance and research, practice, and development/refinement of relevant standards
- Assessment of quality of methods used in studies
- List of research gaps covering mechanisms, pathways, and validation of order effects

Task 2: CBS VNSCOR#2: Impact of Galactic Cosmic Radiation simulation (GCR sim) /Hindlimb Unloading (HU) /Isolation Confinement Extreme (ICE) environment /Sleep on Brain Function

Period of Performance: 10/1/2019-9/30/2023

Gaps Addressed: CBS-CNS-1, CBS-SM26, CBS-SM6.1, CBS-CNS-2, IM8, CBS-BMed2, CBS-BMed3

Task Aims:

1. This project aims to determine the individual and synergistic effects of simulated microgravity (hindlimb suspension (HLS)), social isolation (SI) and space radiation (SR) on sleep, ability to cope with additional stress, and on temporal perception and sensorimotor function in male and female Wistar rats that show individual differences in stress resilience and vulnerability.

2. Effects of SI, HLS and SR on sleep architecture, activity, stress system responsivity, extinction learning, and anticipatory activity.
3. Determine synergistic effects of SR and SI and of SR and HLS on sleep architecture, activity, stress system responsivity, extinction learning, and anticipatory activity.
4. Determine synergistic effects of SR and SI and of SR and HLS on neural communication.
5. Determine synergistic effects of SR, SI and HLS on immune system.

Deliverable Description:

- Functional assessment of alterations in multiple systems (sleep and arousal, stress, sensorimotor, central and peripheral immune system, brain cognitive and emotional regulatory systems, and ability to perceive time) in response to space radiation and environmental challenges astronauts may encounter
- Assessment of whether the order of exposure to stressors alters health and performance outcomes
- Data to determine whether resilience or vulnerability in the sleep and arousal system affects ability to perform, and whether sex affects the results
- Assessment of peripheral brain derived neurotropic factor as a predictor of resilience and vulnerability
- Assessment of functional and structural changes in neurocircuitry that regulates important cognitive, memory, and emotional behaviors
- Foundational data for multi-factorial models predictive of functional and structural changes in systems important for astronaut health and performance

Task 3: CBS VNSCOR#2: Effects of GCR sim/Hindlimb Unloading/Isolation and Confinement on Immune, Performance with Dietary countermeasure (CM) Development

Period of Performance: 10/1/2019-9/30/2023

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM26, CBS-CNS-2, CBS-CNS-5, CBS-CNS-4

Task Aims:

1. Determine dose dependence of acute 'Five-Ion GCR Simulation' exposure for immune, brain, and behavioral performance responses in crew age-matched adult male and female mice.
2. Determine effects of acute 'Five-Ion GCR Simulation' exposure singly and in combination with simulated microgravity and social isolation, on immune and nervous system responses in crew age-matched male and female mice mimicking deep space missions.
3. Determine efficacy of the dietary antioxidant, nicotinamide mononucleotide (NMN) in reversing immune, brain and behavioral/cognitive performance effects after acute 'Five-Ion GCR Simulation' exposure in socially isolated, ionizing radiation, and simulated microgravity exposed male and female mice, mimicking deep space missions.

Deliverable Description:

- Data to address fundamental questions regarding rodent sex differences in response to major environmental factors associated with deep space
- Does exposure to radiation, either alone or in combination with simulated microgravity and social isolation, result in an elevation of brain reactive oxygen species (ROS), immune dysfunction, altered morphology and function in brain areas related to cognition and behavior?
- What is the preferred reference dose of the 'Five-Ion GCR Simulation' GCR simulation at the NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratories (BNL) that can confirm increased or decreased combinatorial effects of radiation with other deep space factors (i.e., microgravity and social isolation)?
- Can immune and inflammatory markers serve as biomarkers of alterations in the structure and function of the CNS?
- What is the time course for emergence of immune, brain, and performance alterations after exposure to radiation, simulated microgravity and social isolation?
- Do the observed CNS alterations lead to behavioral and cognitive impairments?
- What brain performance pathways are implicated after exposure to radiation or simulated microgravity, either alone or in combination?

- Can administration of the dietary antioxidant, nicotinamide mononucleotide (NMN), a key intermediate in nicotinamide adenine dinucleotide (NAD+) biosynthesis, ameliorate these changes?

Task 4: CBS VNSCOR#2: Effects of GRCsim/Hindlimb Unloading/Isolation and Confinement on Behavior with Risk Prediction Model

Period of Performance: 10/1/2019-9/30/2023

Gaps Addressed: CBS-CNS-1, CBS-SM26, CBS-CNS-2, CBS-CNS-5

Task Aims:
1. Characterize the relative contributions of radiation and social and gravity stressors on sensorimotor, behavioral, and cognitive functions and their possible synergistic interactions.
2. Investigate the quantitative relationships between neuro-inflammation and synaptic changes in mice with sensorimotor, behavioral, and cognitive deficits after exposure to combined spaceflight stress.
3. Characterize the molecular profiles in peripheral blood of mice exposed to combined CBS stressors to develop surrogate blood biomarkers of susceptibility and resistance to specific behavioral impairments.
4. Integrate the relationships between tissue damage markers and behavior phenotypes in male and female mice exposed to space stressors, and develop multivariate models that predict impaired performance for behaviors that are relevant to astronauts on deep space missions.

Deliverable Description:
- Data from combined and individual effects of radiation exposure (e.g. GCR sim), isolation confinement stress, and altered gravity on behavioral, cognitive and sensorimotor performance
- Data to determine if there are sex-dimorphic responses
- Recommendation of predictive biomarkers for individual sensitivity
- Predictive statistical model for the extrapolation of performance decrements
- Estimate of risks to astronauts' CNS

Task 5: NSCOR #1: CBS Synergistic Effects Study - Dose Effect/Countermeasures

Period of Performance: HRP NRA Nov-2020 Solicitation Awards

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM24, CBS-SM7.1, CBS-SM2.1, CBS-SM28, CBS-CNS-2, CBS-CNS-5, CBS-BMed1, CBS-BMed2, CBS-BMed3, CBS-CNS-4

Task Aims:
1. Assemble an NSCOR with multiple research arms that will use a standardized GCR sim radiation field and experimental design that leverages previous research focused on combined, and order-effects of radiation exposure, isolation and confinement stress, and hindlimb unloading using standardized handling and behavioral tests, and will assess biomarker changes, and brain physiology changes that predict changes in operationally relevant brain performance pathways.

Deliverable Description:
- Computational models that predict brain pathways (with mapping to compensatory pathways) affected by combined exposure to space-like radiation, stress, and altered gravity
- Report of dose effects of exposures
- Report of countermeasures

Task 6: Computational Modeling for CBS Synergistic/Order Effects of Spaceflight Hazards

Period of Performance: HRP NRA Nov-2020 Solicitation Awards

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM24, CBS-SM7.1, CBS-SM2.1, CBS-SM28, CBS-CNS-2, CBS-CNS-5, CBS-BMed1, CBS-BMed2, CBS-BMed3, CBS-CNS-4

Task Aims:
1. Assemble a multidisciplinary team into an "integrated" Virtual NASA Specialized Center of Research (VNSCOR): The VNSCOR will address multiple research arms using a standardized radiation exposures and translational conceptualizations that will inform computational models to characterize and predict changes in operationally relevant brain performance pathways. The team will use animals to assess distinct processes of cognitive and behavioral changes to operationally relevant performance, and link neural processes and biomarkers to these constructs to assess combined and order-effects of radiation exposure, isolation and confinement stress, and hindlimb unloading. Standardized handling and behavioral tests will be used to assess brain physiology changes (including blood-brain barrier changes), molecular signaling associated with biomarker changes.

Deliverable Description:
- Computational models that can predict brain performance pathways (with mapping to compensatory pathways) affected by combined exposure to space-like radiation, stress, and altered gravity
- Description of integrative dose-effects, with mapping of compensatory pathways, and adverse outcome pathway heuristic computational modeling and countermeasures
- Heuristic model of performance decrements linked to neural processes and biomarkers
- Proposed model and framework for identifying POLs

Table 6: Seven discreet CBS portfolio tasks under Research Emphasis 6 highlighting the periods of performance, CBS related gaps, and the deliverables for each task (See Figure 2, row six).

Research Emphasis 6

Countermeasures that Maintain Crew Performance Standards during Exploration Class Missions

Task 1: CBS BioNutritional Countermeasures Datamining

Period of Performance: 8/3/2018-1/30/2020

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM26, CBS-SM6.1, CBS-SM7.1 , CBS-SM2.1, SM27, CBS-SM28, CBS-CNS-2, CBS-BMed1, CBS-BMed6, CBS-BMed3, CBS-CNS-4

Task Aims:
1. Review the scientific literature to determine interrelationship of nutrition (and specific nutrients) with CNS effects, and identify potential nutritional countermeasures for spaceflight-induced CNS effects, focusing on how these countermeasures may influence performance outcomes: (a) develop a comprehensive database of relevant research that allows for an assessment of the quality of methods used in the studies; (b) summarize the extent, range, and nature of nutritional countermeasures that could mitigate the CNS effects from individual and combined spaceflight stressors.
2. Summarize relevant research findings to provide a scientifically plausible rationale for an integrated risk mitigation approach using nutritional countermeasures while addressing the implications for these countermeasures in the context of mission related factors (e.g., immune system alterations, food systems) related to crew health and operational performance.
3. Review the scientific literature to determine interrelationship of nutrition (and specific nutrients) with CNS effects, and identify potential nutritional countermeasures for spaceflight-induced CNS effects, focusing on how these countermeasures may influence performance outcomes: (a) develop a comprehensive database of relevant research that allows for an assessment of the quality of methods used in the studies; (b) summarize the extent, range, and nature of nutritional countermeasures that could mitigate the CNS effects from individual and combined spaceflight stressors.

4. Review the scientific literature to determine interrelationship of nutrition (and specific nutrients) with CNS effects, and identify potential nutritional countermeasures for spaceflight-induced CNS effects, focusing on how these countermeasures may influence performance outcomes: (a) develop a comprehensive database of relevant research that allows for an assessment of the quality of methods used in the studies; (b) summarize the extent, range, and nature of nutritional countermeasures that could mitigate the CNS effects from individual and combined spaceflight stressors.
5. Summarize relevant research findings to provide a scientifically plausible rationale for an integrated risk mitigation approach using nutritional countermeasures while addressing the implications for these countermeasures in the context of mission related factors (e.g., immune system alterations, food systems) related to crew health and operational performance.
6. Identify research conducted with animals to identify plausible approaches using animal models to identify and validate nutritional countermeasures for use in the CBS Integrated Research Plan.
7. Identify biomarkers associated with nutrition and nutritional countermeasures and their relevance to (a) structural and functional changes to brain, (b) associated dose-response effects related to physiological changes, and/or (c) real-time performance outcomes.
8. Use results of this literature-based research to identify gaps in knowledge related to (a) potential synergistic effects of deep space travel (e.g., impacts of isolation and confinement and altered gravity, and radiation effects), (b) potential use of nutritional countermeasures to prevent or intervene, and (c) biomarkers that could potentially assess spaceflight changes and inform translational models.

Deliverable Description:

- Report of nutrition research related to CNS effects from combined exposure to radiation, isolation, confinement, and the sensorimotor adaptations to altered gravity
- A report outlining the utility of nutrient (and/or related metabolite) biomarkers in assessing CNS effects from combined exposure to radiation, isolation, confinement, and the sensorimotor adaptations to altered gravity.
- Description of potential benefits of nutrient countermeasures for preventing and/or mitigating spaceflight-induced CNS effects
- List of plausible biochemical pathways that account for the effectiveness of the countermeasures

Task 2: CBS Countermeasure 1 (CM #1) Review & Trade Study

Period of Performance: Planned: 08/01/2020-03/31/2021

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM24, CBS-SM7.1, CBS-SM2.1, CBS-SM28, CBS-CNS-2, CBS-CNS-5, CBS-BMed1, CBS-BMed2, CBS-BMed3, CBS-CNS-4

Task Aims:

1. Conduct the first of two planned CBS Integrated Risk Trade Studies, taking into account feasibility, maturation, cost, etc., using informational framework similar to the National Academy of Science, Engineering and Medicine -style review (i.e., with a focus on level and quality of evidence). This trade study will be a decision-making activity to identify the most technically acceptable, feasible, and scientifically valid countermeasures from transdisciplinary perspective and from among those identified for single and integrated risks.

Deliverable Description:

- Recommendations to inform solicitation for initial development and validation of CBS Integrated Risk consolidated Countermeasures Trade Study results that provide an effective means for recommending countermeasures to mitigate the CNS effects from combined spaceflight stressors that documents the evaluation and decision-making process to ensure traceability and repeatability of the recommendations and to judge the overall satisfaction against a series of identified desirable characteristics of countermeasures (highlighting those characteristics that may conflict with one another or that might be mutually exclusive)

Task 3: CBS Countermeasure 1 (CM1) Development/Validation (Nutrition/Biomarker Signaling)

Period of Performance: Planned: 12/01/2022-12/31/2026

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM24, CBS-SM7.1, CBS-SM2.1, CBS-SM28, CBS-CNS-2, CBS-CNS-5, CBS-BMed1, CBS-BMed2, CBS-BMed3, CBS-CNS-4

Task Aims:

1. Develop and ground-validate measures to counter identified risk from combined CBS stressors using the results of the countermeasure 1 study to identify the most technically acceptable, feasible, and scientifically valid countermeasures from transdisciplinary perspective.

Deliverable Description:

- Ground validated recommendations for pre-, in-, and/or post-flight countermeasures required for CBS Integrated Risk

Task 4: Human Capabilities Assessment for Autonomous Missions (HCAAM) Intelligent System: Monitoring & CMs Performance Pathways

Period of Performance: Planned: 02/01/2022-09/30/2022

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM26, CBS-SM7.1, CBS-SM2.1, SM2.2, SM27, CBS-CNS-2, CBS-CNS-5, CBS-CNS-3, BMed7, CBS-BMed2, CNS-7

Task Aims:

1. Conduct research review focused on how the human system adapts to autonomous systems and habitat to maintain operationally relevant performance by leveraging countermeasures and HCAAM Intelligent System that monitors brain performance pathways and then responds with appropriate countermeasures to mitigate risk and/or compensate for decrements in performance throughout mission.

Deliverable Description:

- Report evaluating potential decrements in human capabilities during an exploration mission, which focuses on how astronauts adapt to autonomous systems and their habitat to maintain their performance
- Recommended countermeasures to mitigate risk and/or compensate for decrements in performance throughout a spaceflight mission

Task 5: CBS Datamining Countermeasures: Family History/Preventive Medicine/Individual Sensitivities/ Exposures/ Monitoring Exposures

Period of Performance: Planned: 04/01/2024-09/30/2024

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM24, CBS-SM7.1, CBS-SM2.1, CBS-SM28, CBS-CNS-2, CBS-CNS-5, CBS-BMed1, CBS-BMed2, CBS-BMed3, CBS-CNS-4

Task Aims:

1. Identify current research that assesses pre-mission risks and vulnerabilities for individuals due to family history, previous spaceflight exposures, preventive medicine, sensitivities, genotype, and phenotype within the context of integrated risk, the risks posed to crew health and safety, and the countermeasures needed should medical conditions arise.

Deliverable Description:
- List of knowledge gaps for countermeasures with respect to potential synergistic impacts of space radiation in isolated and confined environments and altered gravity
- Assessment of individual sensitivities to each risk (space radiation, isolation and confinement, and microgravity) and responsiveness to countermeasures delivered to counter the changes (adaptations) to those risks
- Assessment of differences in SM/BMed brain performance pathways differentially affected by space radiation exposures
- Recommended standardized protocol that encompasses sample collection, storage, processing, and marker measurement to retain the integrity of the test and to keep variation to a minimum
- List of potential SM/BMed countermeasures based on vulnerabilities and sensitivities

Task 6: CBS Countermeasure 2 (CM2) Review & Trade Study

Period of Performance: Planned: 11/01/2025-12/31/2026

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM24, CBS-SM7.1, CBS-SM2.1, CBS-SM28, CBS-CNS-2, CBS-CNS-5, CBS-BMed1, CBS-BMed2, CBS-BMed3, CBS-CNS-4

Task Aims:
1. Further refine development of and ground-validate of measures to counter identified risk from combined CBS stressors using the results of the CBS Integrated Risk CM1 Trade Study and initial Countermeasures 1 research to confirm and finalize the most technically acceptable, feasible and scientifically valid countermeasures from transdisciplinary perspective.

Deliverable Description:
- Recommendations to inform solicitation for Countermeasure 2 update
- Integration of ground validated research and the basis for recommendation for pre-, in-, and/or post-flight countermeasures required for CBS Integrated Risk and Countermeasure 2.

Task 7: CBS Countermeasures 2 (CM2) Human Flight Update/Validation

Period of Performance: Planned: 12/01/2026-09/30/2029

Gaps Addressed: CBS-CNS-1, CBS-CNS-8, CBS-SM24, CBS-SM7.1, CBS-SM2.1, CBS-SM28, CBS-CNS-2, CBS-CNS-5, CBS-BMed1, CBS-BMed2, CBS-BMed3, CBS-CNS-4

Task Aims:
1. Refine and validate countermeasures by integrating data of space radiation exposures in rodents and NHP research that identifies specific brain performance pathway (BPP) regions with targeted countermeasures to reduce vulnerability/risk of decrements in operationally relevant crew health and performance in the sensorimotor, behavioral, and cognitive domain areas linked to mission duration and success.
2. Incorporate flight data to refine CBS research of identified specific brain regions and biomarkers linked with spaceflight hazard induced performance-relevant neural processes and interventions to mitigate those risks.

Deliverable Description:
- Ground- and fight-validated recommendations for updates to pre-, in-, and/or post-flight operationally relevant countermeasures linked to biomarkers that will identify the need for and the consequences of countermeasure intervention

Research Announcement Integration and Supplementation

The CBS portfolio funds tasks through (1) the NASA research announcement (NRA) solicitation process, (2) request for proposals (RFP) that allow for targeted distribution of a research solicitation, and (3) directed tasks initiated by the HRP elements when specific criteria are met. The overall evaluation process for proposals includes a First-Tier Merit Review and a Second-Tier Program Alignment Review. The First-Tier Review will be a merit peer review by a panel of scientific or technical subject matter experts. The Second-Tier Review will evaluate the programmatic balance, feasibility, and cost of proposals. In other words, it is not just merit that drives proposal selection. This ensures compliance with the integrated research approach, and eliminates any duplication of effort.

The CBS portfolio initiated the first CBS "Virtual NASA Specialized Center of Research" through a call for proposals in the NRA NNJ16ZSA001N-SRHHC, (VNSCOR), a joint Space Radiation and Human Health and Countermeasures solicitation. The original aims of two selected proposals that focused on a single research area were slightly re-scoped to ensure the two individual funded studies were complementary in approach and the final deliverables would feed the CBS integrated research strategy. The aims and deliverables of VNSCOR tasks are listed in the table under Research Emphasis 4, Tasks #1 and #2.

The CBS portfolio posted the first CBS-specific call for proposals in NRA 80JSC018N0001-FLAGSHIP, Topic 1: Risk of Synergistic Effects of Radiation, Stress, and Altered Gravity on Spaceflight Behavioral Health and Performance Virtual NASA Specialized Center of Research (VNSCOR). In May, 2019, three VNSCOR proposals were selected that would each contribute to knowledge gaps in CBS Research Emphases 1, 4, 5, and 6. The aims and deliverable for these complementary proposals are listed as Tasks #4, #5 and #6 under Research Emphases 5 in the Table above.

The RFP mechanism is exercised when the requirements are sufficiently defined to specify a product or service. The CBS portfolio has been able to accelerate the delivery of research products by defining specification of desired products and services, and has successfully completed one RFP and a second proposal has been awarded using the RFP process and this second study is in the early period of performance. The aims and deliverables of these two funded tasks are listed under Research Emphasis 2 (Task title: Neurobehavioral Biomarkers Performance/Pathway), and Research Emphasis 4 (Task title: CBS NHP CNS Radiation/Performance Datamining). Both were requests for literature reviews of very specific topics and the deliverables from these tasks are important to help define future research solicitations that will continue to fill knowledge gaps.

The HFBP Element Scientist, serving as the CBS Lead, in consultation with the HHC and SR Element Scientists, recommends to the HRP Chief Scientist the approval of directed tasks in support of the CBS portfolio. Proposals must meet one of two criteria for justifying a directed research task. These two criteria are:

- Insufficient time for solicitation: Sometimes NASA must complete scientific activities in a short turnaround time (e.g., because of the emergence of new opportunities to conduct activities in space). When this is the case, use of a directed task may be the only practical way to respond.

- Highly constrained research: The project requires focused and constrained data gathering and analysis that is more appropriately obtained through a non-competitive proposal, and could include a follow-on task to a solicited proposal (e.g. research activity involving operational practices and the associated flight personnel, or research very specific to NASA). This criterion also includes pilot studies and datamining studies.

The CBS portfolio has used the directed task mechanism to authorize several datamining tasks. Final reports from the datamining tasks have provided valuable content to define the foundation of the CBS Integrated Research Plan, identify gaps in knowledge to guide forward work, and help refine descriptions of key deliverables that will be required in future research studies. An emphasis was placed on operationally relevant performance outcomes, brain performance pathways, and biomarkers in each of these datamining tasks. Directed tasks funded to date include the following:

- CBS Sensorimotor Datamining & TIM II (Completed)
- NHP Datamining (Completed)
- CBS Operational Performance Measures (End Date 9/2019)
- Bio-Nutritional Countermeasures for CBS (End Date 12/2019)

The HFBP, HHC, and SR Element Scientists have worked together to review their on-going tasks for studies that can be augmented to accelerate the delivery of integrated CBS Integrated Research Plan objectives. The CBS portfolio supplemented four previously selected tasks sponsored by the SR Element, and awarded student supplementation awards to four investigators to capitalize on existing investment of beam time at the NSRL and to accelerate new methods and techniques for assessing performance outcomes. The HRP announced a grant augmentation competition for students and postdocs to expedite progress in various research areas and to deliver new tools, techniques, or knowledge that could lead to novel breakthroughs addressing one or more of the risks and gaps in the HRP Integrated Research Plan. Four of the seven selected awards augment grants funded by the SR Element. Proactively seeking out ongoing research that can be supplemented to inform research gaps has allowed the CBS Integrated Research Plan team to reduce the time required to evaluate and mitigate risk. The following four aims were added to existing space radiation studies.

- Supplement #1: Add evaluation of sex differences to assessment of the role of oxidative stress and inflammation on synaptic function after exposure to space radiation
- Supplement #2: Add a cohort of hindlimb unloaded rats to a planned GCR sim study
- Supplement #3: Utilize tissue shared from previous radiation-based studies to examine CNS damage indicating biomarkers following exposure to radiation
- Supplement #4: Add evaluation of sex differences to assessment of resilience outcomes study

Recent solicitations for CBS research reflect specific aims of the integrated approach. As an example, NRA 80JSC018N included Topic 2: Individual and Team Problem-Solving Skills Training for Exploration Missions. This topic included the following specific research aim: "*A particular interest exists to present a scientific rationale of how the changes in these problem-solving skills during spaceflight may be at risk due to potential changes in brain domains from exposures to the CNS from radiation, stress, and altered gravity*". Integration of CBS specific aims within future research announcements will encourage subject matter experts to propose integrated solutions and will foster cross-disciplinary collaboration.

Use of Analog Facilities

The CBS Integrated Research Plan proposes using analogs of spaceflight hazards to validate monitoring tools and countermeasures on the ground. The CBS Integrated Research approach uses the NASA Space Radiation Laboratory (NSRL) for translational rodent models. From 2019-2026, 16 of 51 studies planned are CBS tasks. The Human Exploration Research Analog (HERA) located at the Johnson Space Center, Houston, Texas and Russia's IBMP Ground-based Experimental Complex NEK facility located in Moscow, Russia are multi-compartment facilities that are used as ground-based analogs of the isolation, confinement, and remote conditions in exploration missions. New monitoring tools or countermeasures identified or developed by CBS funded work will be validated in combination with planned BMed science objectives of the HERA and NEK studies. Additionally, studies are being conducted in combination with planned studies that will fulfill requirements of the BMed Risk science objectives and will contribute monitoring tools via multiple investigations conducted at the Antarctic stations maintained by the United States Antarctic Program. A number of studies being conducted at the "envihab" facility in Cologne, Germany are also fulfilling requirements of the BMed and Sensorimotor Risk science objective by assessing physiological, neurological, and behavioral outcomes during constant bedrest as a model of microgravity, in combination with elevated carbon dioxide levels and a confined environment. Flight validation of some CBS countermeasures could occur as early as 2022, within the current exploration mission (EM-2) flight plan. The CBS standard measures are projected for validation from 2026 to 2030 using the Gateway outpost as it becomes available.

Outreach and Collaboration

Scientific Meetings and Conferences

Participation in scientific meetings and conferences provides a valuable opportunity to share technical data, and receive feedback on research strategy and outcomes. The CBS team has presented the CBS Integrated Research Plan in a variety of external scientific meetings and conferences, resulting in early peer review of the overall strategy. Feedback from external subject matter experts has been very positive, particularly in regards to efforts for computational modeling of performance outcomes. Between December 2018 and May 2019, components of the CBS Integrated Research Plan were presented at the following scientific meetings and conferences:

- International Society of Gravitational Physiology (May, 2019). The CBS team organized a session titled *Identifying and Reducing Risks to Brain and Behavior during Extended Human Spaceflight*
    - Dr. Whitmire (HFBP Deputy Element Scientist) and Dr. Norsk (HHC Element Scientist) represented the CBS team at the meeting, and presented during the CBS session.

- 16th World Congress of Society of Brain Mapping & Therapeutics (March 2019)
    - Dr. Williams (HFBP Element Scientist) and Dr. Fogarty (HRP Chief Scientist) organized an invited panel, to provide an overview of the CBS Integrated Research Plan. Dr. Mulavara (CBS Portfolio Scientist), Dr. Nelson (Space Radiation and CBS Discipline Scientist), and Dr. Roma (CBS Funded Investigator) presented during the panel.

  - The CBS team connected with 22 neuroscientists, including a computational modeling group at Lawrence Livermore National Laboratory, initiating work with shared outcomes in assessing human performance following exposure to major physiological, neurological, and emotional stressors.

- NASA Human Research Program Investigators' Workshop (Jan 2019)
  - A CBS session was organized to disseminate the CBS Integrated Research Plan and strategy to NASA investigators.

- Russian Space Medicine Conference (Dec 2018)
  - Dr. Williams (HFBP Element Scientist) presented *"NASA's Human Research Program Risk Integration: Is There A Synergistic Risk Of Space Radiation, Isolation & Confinement, And Altered Gravity?", co-authored with* Dr. Norsk (HHC Element Scientist) and Dr. Simonsen (Former SR Element Scientist)

- Invited paper Journal of Neurophysiology
  - Gilles R. Clément, Richard D. Boyle, Kerry A. George, Gregory R. Nelson, Millard F. Reschke, Thomas J. Williams, William H. Paloski. Challenges to the central nervous system during human spaceflight missions to Mars. *In Review*.

In additional to participation in the meetings described above, the CBS team has also organized two separate workshops that included participation of internal and external subject matter experts. The primary focus of these workshops was to establish strategies to translate data from animal studies for use in computational models that will predict human performance outcomes after exposure to the combined CBS risks. Executive summaries for each workshop can be found in Appendix B. A brief synopsis of each workshop is provided below.

- Workshop I: *Optimization of Translational Animal Models to Assess Human Spaceflight Performance for Studying the In-Flight Effects of Space Radiation: The Journey to Mars and Back.* South Shore Harbor Resort and Conference Center, League City, TX, June 13 & 14, 2017
  - A panel of NASA funded investigators and external experts convened to evaluate and identify the best approaches for translating animal data to human performance measures that will allow NASA to assess potential performance decrements due to radiation and other spaceflight stressors and to evaluate acceptable countermeasures.
- Workshop II: NASA *Translational Working Group Focused on Synergistic Effects of CNS, BMed, and Sensorimotor Risks.* Gilruth Conference Center, Houston, TX, July 17 & 18, 2018
  - The goal of the workshop was to develop consensus on a battery of cognitive, behavioral, and sensorimotor/neuro-vestibular tests that will allow NASA to assess potential CNS decrements due to radiation, altered gravity, confinement and isolation, and other spaceflight stressors and to evaluate acceptable countermeasures.

Inter- and Intra-Agency and Strategic Partnerships

The CBS portfolio is seeking opportunities to work with other government agencies that focus on public health risks of radiation exposure. A part-time appointment was established with a neuroscientist subject matter expert who supports the Defense Threat Reduction Agency (DTRA):

- Inter-agency strategic partnership between NASA and DTRA
  - Provides subject matter expertise support with background in neurobehavioral science and radiobiology to provide inputs on operationally relevant cognitive and behavioral performance, and continuity of performance following radiation exposure.
- Intra-agency strategic partnership
  - Dr. Williams (HFBP Element Scientist) briefed the JSC Associate Director for Exploration (Dr. Watkins), and subsequently the NASA Chief Engineer on the CBS Integrated Research Plan, providing wider agency awareness of the strategy and potential touch-points to medical and engineering systems in exploration vehicles.

Socialization of the Research Plan

It can be challenging to implement change. The CBS Integrated Research Plan activates a shift from the paradigm of decades of science management within the HRP. Traditionally, research tasks have focused on one effect or one stressor. The HRP Integrated Pathway to Risk Reduction describes the long-range, strategic research plan and schedule. Many risks remain in the high "likelihood and consequence" category until 2026, and no plan exists to evaluate interactions and potential synergistic effects of combined stressors. The CBS Integrated Research Plan proposes an integrated approach to accelerate the process of discovery by directly assessing the effects of combined exposure to three stressors and elucidate potential synergy. To successfully complete the research outlined in the CBS Integrated Research Plan, all stakeholders must be informed and educated, and they must actively engage in the integration approach. Regular socialization and status updates will accomplish this goal. Engaging key stakeholders early in the process will foster trust and result in a common and collective goal to achieve this complex and ambitious plan. The CBS team has presented progress updates to the HRP and programmatic control boards, and has solicited reviews of the strategic plan from a broad audience of stakeholders.

Maintaining and Executing the CBS Integrated Research Plan

The CBS Integrated Research Plan was formed jointly by the HHC, HFBP, and SR Elements, and was given authority to proceed by the HRP Chief Scientist in May, 2018. The HRP assigned Dr. Williams as the technical lead for the CBS Integrated Research Plan. The CBS portfolio is managed within the HFBP Element, under the leadership of Dr. Williams. In November of 2018, the element hired a full time Portfolio Manager, Portfolio Scientist, Science Coordinator and additional science support through civil servant appointments and through the Human Health Performance Contract to manage and implement the CBS Integrated Research Plan. The CBS portfolio team is responsible for implementing the research plan, managing the CBS budgets and schedules, and communicating progress and decisions to all three elements. In turn, the individual HRP Elements are expected to uphold the integrative philosophy and approach in all research planning, and communicate back to the CBS portfolio when relevant content is delivered. The individual HRP Elements will also identify opportunities to accelerate the CBS knowledge base by supplementing existing tasks. To ensure that research products are regularly synchronized and transparent, the CBS Integrated Research Plan includes annual reviews with stakeholders, which will result in updates to the integrated schedules and provide a platform for planning of future research and sharing recommendations to update evidence, risk posture, and crew health standards.

The Chief Health and Medical Office (OCHMO) must review and accept any recommended updates to the POLs and PELs. The master CBS schedule includes three review opportunities to inform the OCHMO of progress, which will provide opportunity to accelerate crew health standard updates.

Summary

This document describes the approach for implementing the CBS Integrated Research Plan, and supplements the white paper titled CBS Integrated Research Plan: Problem Statement. The methods, techniques, approaches and schedule are described, including specific aims and deliverables expected from each planned and funded task that will meet desired goal of the project. Research tasks are organized into six CBS research emphases designed to update crew health standards as required and develop appropriate countermeasures by 2026 to ensure astronaut safety during exploration missions. This integrated transdisciplinary CBS Research Plan fully integrates the three risks of the CBS portfolio and provides strategies to characterize and mitigate those risks using translational research, computational modeling and validated countermeasures.

Appendix A: Examples of External Research Deliverables/Hard Dependencies

Task funded by BMed with CBS Dependency; Supports CBS Research Emphasis 5
Task: Adaptation and Resilience NASA Specialized Center of Research (NSCOR) **Task Aims:** 1. Identify and quantify individual differences in adaptation and resilience using components of the Research Domain Criteria (RDoC) framework to identify and validate molecular, circuitry, and physiological measures that can be used to monitor and select individuals who are highly resilient to decrements in behavioral health and performance during autonomous, long-duration exploration missions. 2. Identify neural circuits and molecular/cellular mechanisms underlying adaptation and resilience in a rodent model using cross-species equivalency. 3. Identify how meaningful work mediates the relationship between factors such as valence, social process domains, operational outcomes, and performance to identify a sensitive, reliable, valid, and feasible set of measures for monitoring meaningfulness of work during spaceflight. **4.** Identify biomarkers and psychological measures associated with the effects of well-being on performance, and determine their contribution to the positive/negative valence systems involved in individual adaptation and resilience. **Deliverables Description:** • Final report summarizing research efforts including: individual risk factors most associated with positive valence, negative valence, and social process domains, and how they relate to performance, adaptation, and resilience • Evidence on how fluctuations in factors such as meaningfulness of work, changes in the physical environment, the degree of sociability, and other external factors such as food, mediate the relationship between risk factors and outcomes • A better understanding of the key threats, indicators, and evolution of the team function throughout its life cycle for autonomous, long-duration exploration missions; psychological measures that can be used to select individuals most likely to maintain team function for autonomous, long-duration exploration missions • Sensitive, reliable, and valid measures that are feasible for assessing spaceflight relevant constructs including adaptability, emotional regulation, sociability, meaningfulness of work, and personal well-being
Task funded by BMed with CBS Dependency; Supports CBS Research Emphasis 6
Task: Effects of transdermal vagal nerve stimulation (tVNS) on cognitive performance under sleep deprivation stress **Task Aims:** Evaluate the efficacy of transdermal vagal nerve stimulation (tVNS) for mitigating the effects of fatigue induced by sleep deprivation on aspects of cognition including attention, arousal, multitasking, and memory in populations of Department of Defense (DoD) subjects. **Deliverables Description:** • Demonstration of a >20% improvement in at least one cognitive skill during sleep deprivation stress when compared to the control population • Assessment of the effects of tVNS (transdermal vagal nerve stimulation) on subjective mood
Task funded by SR with CBS Dependency; Supports CBS Research Emphases 4
Task: Changes in the neuroproteome associated with high charge and energy (HZE)-induced impairment of cognition

Task Aims:

1. Determine the threshold dose for the induction of HZE-induced spatial memory impairments (HISMI) and HZE-induced attentional set shifting impairments (HIASSI) after exposure to ^{56}Fe, ^{48}Ti and ^{28}Si particles when delivered as a single dose.
2. Determine the threshold dose for the induction of HISMI and HIASSI after exposure to ^{56}Fe or ^{48}Ti particles when delivered in three fractions over a 5-day period.
3. Identify changes in the neuroproteome that are associated with susceptibility or resistance to developing HISMI and HIASSI after exposure to ^{56}Fe particles.
4. Identify whether linear energy transfer level is associated with specific mechanisms of HISMI and HIASSI

Deliverables Description:

• Define the minimum dose of HZE particles that will impair spatial memory and Executive function.
• Model to assess the impact of realistic HZE exposures on a deep space mission.
• Proteomic profiling of brain tissues to identify the mechanism of HICI and will test the validity of a novel hypothesis that HZE-induced changes in the neuroproteome lead to HICI through a perturbation of normal neuronal function and not through neuronal cell death.
• Advanced hardware and work-flows to identify the changes in the neuroproteome; these studies will be the first attempt to establish global changes in the glycoproteome of the prefrontal cortex associated with the induction of HICI.

Task funded by SM with CBS Dependency; Supports CBS Research Emphasis 5

Task: Spaceflight Effects on Neurocognitive Performance: Extent, Longevity, and Neural Bases

Task Aims:

1. Perform structural and functional Magnetic Resonance (MR) brain imaging on crewmembers who participate in a six-month mission on the International Space Station, and investigate relationships between alterations in their neurocognitive function (cognitive, sensory, and motor function) and their neural tissue structure.

Deliverables Description:

• Description of the underlying neural mechanisms of spaceflight-induced changes in behavior and their associated risk to operational performance
• Data to determine if return to normative behavioral function after re-adapting to Earth gravity is associated with a restitution of brain structure and function, or a substitution of compensatory brain processes

Task funded by Cross Cutting Project with CBS Dependency; Supports CBS Research Emphasis 5

: Modeling Cross Cutting Project

Period of Performance: 08/01/2018-08/01/2022

Task Aims:

1. Develop an integrated heuristic, data driven model, from experimental and numerical sources, to establish a means of estimating impacts to operational performance for a spectrum of mission durations and distance.

Deliverable Description:

- An integrated database to manage images, biomarkers, and outcome data to identify brain connectome and related measures relevant to/acquired through the CBS integrated risk research plan
- Develop model to establish a means of estimating impacts to operational performance for a spectrum of mission durations and distance

Appendix B: Executive Summaries for CBS Workshop I & II

Optimization of Translational Animal Models to Assess Human Spaceflight Performance for Studying the In-Flight Effects of Space Radiation: The Journey to Mars and Back

A NASA sponsored workshop held at South Shore Harbour Resort & Conference Center, League City, TX on June 13 and 14, 2017

Executive Summary

A panel of NASA funded investigators and external experts convened to evaluate current paradigms and identify the best approaches for translating animal data to human performance measures to allow NASA to assess potential performance decrements due to radiation and other spaceflight stressors and to evaluate acceptable countermeasures.

The workshop began with overview presentations describing the behavior and cognitive domains that are important to spaceflight, the effects of radiation exposure, and the human-to-animal mapping matrix for high priority domains. The intra- and extramural scientists then delivered brief presentations describing their expertise. The participants then split into four groups for concurrent sessions to facilitate in-depth analysis of four specific areas: cognitive performance, neurobehavioral performance, social systems, and processes and neurocircuitry.

The groups were asked to develop consensus on a standard test battery of cognitive and behavioral tests that:

- support validated translation between animal models and humans
- are conducive to testing impairment due to spaceflight stressors
- are conducive to evaluating mission acceptable countermeasures

The Translational Models of Cognitive Performance and Circadian Dysregulation Session focused on the relevance of successful animal models for evaluating human circadian dysregulation and performance related to cognitive processes including learning and memory.

The Translational Models of Neurobehavioral Performance Session focused on exploring methods for increasing bidirectional translation of research findings between animal models of mood and arousal systems (e.g., depression, anxiety, asthenia, fear, avoidance, etc.).

The Translational Models of Social Systems and Processes Session focused on the underlying neurobiological and psychological mechanisms of stress buffering in social relationships by exploring translational models that have been shown to regulate avoidance, withdrawal, and arousal and may influence a social buffering process.

The Translational Models of Neurocircuitry Session focused on translational models that have demonstrated regulation of neurocircuitry, and relationships between neurobiological and psychological mechanisms. The goal was to identify translational approaches that employ integrative models of neurocircuitry and incorporate multiple levels of analysis (e.g., molecular, cellular, physiological, social processes) to address potential biological control of behavior and performance.

After the breakout discussions, moderators from each group summarized the main points of discussion for all attendees. The moderators later provided a written summary report that captured consensus views and included tables of behavioral tasks linking human and animal constructs.

Major Conclusions and Recommendations from the Participants

1. A number of valuable animal (rodent) behavioral models, including cognitive, affective, and social behaviors, are currently being used to characterize the effects of space-like radiation on the brain. These models have the appropriate sensitivity to detect responses from mission-equivalent radiation doses and many have been validated independently for their ability to predict effects of drugs and pathophysiology of diseases such as schizophrenia, major depressive disorder, and autism, supporting mechanistic similarities and validating translatability to humans.
2. A few additional models may enhance the fidelity and sensitivity of current investigations, especially when used concurrently. Biochemical measures, electrophysiological (e.g. EEG) parameters during task performance, and imaging (especially functional imaging) would complement behavioral measures, validate mechanistic similarities between animals and humans, and provide benchmark biomarkers for inter-species scaling.
3. Models currently in use, in combination with the recommended additional models, could address the effects of non-radiation spaceflight stressors such as altered gravity, sleep deprivation, circadian dysregulation, and isolation and confinement. Priority should be given to adapting current models and organizing them into batteries of tests to evaluate operationally relevant behaviors and the effects of combined stressors.
4. Models currently in use, along with the others identified during the workshop, could assess the effectiveness of countermeasures and mitigation strategies. The participants provided an evaluation of countermeasures.
5. Many experimental parameters should be standardized, whenever practical, to facilitate inter-laboratory comparison of results. These parameters include exposure conditions (radiation and other stressors), animal species, strain, age, sex, post exposure evaluation times, animal husbandry conditions.
6. Spaceflight stressors should be assessed using a battery of well-vetted tests that sample as many neuropsychological domains as practical, and all assessments should be based on the composite score for the battery. An optimal approach would target brain regions and networks (e.g., hippocampus and frontal lobes) and examine broader whole-brain effects. A broader whole-brain approach would identify previously missed targets and assess effects that may be more global or implicate very broad networks.
7. Reference stressors (e.g. blood alcohol levels) to induce spaceflight-like impairment may not be reliable for studying central nervous system (CNS) effects; however, traumatic brain injury is a

diffuse injury model that has pathophysiology properties similar to radiation exposure effects. Manipulating serotonin levels (which can induce human depression) may be a novel method to probe analogous spaceflight outcomes in animals; aging or obesity-related oxidative stress, microlesions in CNS, and social stress measures could be used to establish reference values. However, stress is difficult to standardize across species and humans may anticipate treatments while animals do not, which would differentially affect the reactions to experimental manipulations.

8. Alterations in performance should be evaluated on an individual basis in animals that have been preselected for their suitable or superior baseline performance to better emulate high-performing human populations (astronauts). Deviations from "normal" need to incorporate aspects of what is "normal" for each individual and studies may benefit from evaluation of patterns of behaviors in repeated measure designs. Further refinements in models might include "astronaut like" physically fit animals that have been prescreened for top tier performers in several domains, are age appropriate, and are of both sexes. Such refinements might also include testing during active (awake) phase when practical and including some outbred strains to address inter-individual variability.
9. Individual performance that deviates from cohort averages in test batteries (such as Z-scores or non-parametric equivalents) could be used as quantitative measures to compare the magnitudes of changes in animal and human performance elicited by stressors.
10. No consensus was reached on the use of nonhuman primates. Although, rodent models might not be adequate for evaluation of very complex mental functions such as abstraction and concept formation, rodent models will suffice for most purposes and the use of higher species, if needed, should focus on a small, specific set of questions—not a broad survey.
11. The overall strategy of using assessment tools to link operational requirements for mission relevant tasks to permissible outcome levels in humans, and then to permissible exposure levels in animal analogs of human performance was considered valid.

The following four tables summarize a set of cognitive models, paradigms for non-cognitive behaviors, assessment measures for social behaviors, and examples of models that have been validated for their ability to predict human outcome measures.

Candidate Experimental Measures for Non-Cognitive Behaviors

Measure/Paradigm
Immobilization stress; plasma corticosterone levels (HPA axis) as measure of the stress response. But may not be radiation responsive at low radiation doses.
Light dark box without elevation (measures of anxiety/avoidance)
Acquisition and extinction of learned fear as measured by freezing, operant, or startle behaviors (learned fear, fear inhibition, fear generalization).
Explorative behavior and measures of anxiety in open areas (open field, light dark box) and elevated anxiety provoking areas (elevated zero maze; elevated plus maze).
Sucrose preference test, intracranial self stimulation (reward processing, anhedonia). Does not require ambulation.
Forced swim and tail suspension tests (depressive behaviors).
Cage size modification (chronic stress to model small space environments). Analog to HERA.

A Recommended Set of Cognition Models	
Human Construct	**Recommended Rodent Model**
Fitness for duty Standard (Basner)	Rodent 5-Test (4 cognitive domains, 1 psychosocial)
Vigilant attention	rodent Psychomotor vigilance Test
Psychomotor vigilance (PVT)	5 choice continuous performance test (5C-CPT)
Working memory	Odor Span Test
Fractal 2-back (F2B)	Delayed (non) matched to sample test.
Risk decision-making	Barrus & Winstanley Assay
Balloon analog risk (BART)	Rodent Iowa Gambling Task
Spatial learning and memory	Touchscreen cognitive testing (Bussey et al, 2008), Morris Water Maze, & Barnes Maze (but not necessarily correlated to Visual object learning (VOLT)
Visual object learning (VOLT)	
Perceptual executive functions	Operant set-shifting
Abstraction, concept formation	Rodent Attentional Set Shifting Test (Intra and Extra Dimensional shifting)
Abstract matching (AM)	
Metacognition	Post-decision wagering, etc. Kepecs
Unconstrained Cognitive Flexibility	Unconstrained Cogntive Flexibility Test (Hecht)

Examples of Successful Translation Validation	
Animal Model / Test	**Prediction of behavioral outcome in humans**
Elevated plus maze and elevated zero maze	Anxiolytic effects; for example of benzodiazepines
Forced swim test	Anti-depressive effects; for example of SSRIs and ketamine
Spatial navigation	Spatial navigation - direct analog.
Fear conditioning and extinction	d-cycloserine
	Post-trauma or prior memory testing administration of glucose to activate hippocampus and contextual learning.
Object recognition	Age-related cognitive decline; mild cognitive decline (MCI); neurodegenerative conditions and dementias.
Sleep deprivation manipulation in conjunction with performance test(s)	Sleep deprivation tests.

High Priority Translational Models of Social Systems and Processes (avoidance, withdrawal, etc.)					
Human Construct	Animal Construct	Paradigm Tools (behav. task)	Independent Variables	Outcome Measure	Operational Analog
Social Reinforcement	Social Reinforcement	Place Conditioning	Familiarity (conspecific, cagemate), sex, estrus female, offspring	Latency to approach; time spent; extinction; reinstatement	Proximity; shared social activities; content analysis
		Operant Conditioning	Familiarity (conspecific, cagemate), sex, estrus female, offspring, schedule	Breakpoint, response rate, demand intensity, demand elasticity	Proximity; shared social activities; content analysis
Social Drive or Motivation	Social Drive or Motivation	Social approach	Familiarity (conspecific, cagemate), strain, sex, age, estrus cycle	Latency to approach; time spent	Proximity; shared social activities; content analysis
Defensive Behaviors	Social Avoidance/ Aggression	Resident Intruder (one time)	Familiarity (conspecific, cagemate), strain, sex, age, estrus cycle, length/complexity of residence	Latency to approach; time spent; latency to attack; number of attacks, severity of attack	Response to conflict
		Psychosocial Defeat stress	Strain, sex, age, estrus cycle, length/complexity of residence, sensory contact during adjacent living, number/intensity of defeat bouts	Latency to approach; time spent; latency to attack; number of attacks, severity of attack, social interaction response (approach/avoid)	Response to conflict
Social Discrimination	Social Discrimination: affiliative vs. antagonistic	Olfactory Social Discrimination	Target (Social vs. nonsocial); exploration time	Latency, duration, proportion of sniffing; habituation over time; dishabituation; discrimination index	Social cohesion
	Social Recognition: memory	Olfactory Social Recognition with retention interval	Familiarity (conspecific, cagemate), Target (Social vs. nonsocial)	Latency, duration, proportion of sniffing; habituation over time; dishabituation; discrimination index	Social cohesion
Social Hierarchy	Social Dominance	Tube test (tube of war)	Length of pairing, strain, genetics, life experience, coping biases; barbering of cage mates	Win probability, latency to win.	Conflict, Group Living

HPA= hypothalamic-pituitary-adrenal; HERA=human exploration research analog; SSRI=selective serotonin reuptake inhibitors

Unresolved Questions and Issues

1. The most suitable method for *quantitatively* translating animal and human behavior was not identified. A potential approach could use Z-scores or equivalents based on the results of composite test batteries to compare the magnitudes of deviations from cohort averages. It is not known whether graded exposure levels to stressors (radiation doses, hours of sleep deprivation, etc.) would elicit linear or non-linear responses or how combinations of stressors would interact.
2. The definition of "significance" with respect to impairment in mission performance requirements was not adequately characterized. Some quantitative criteria such as changes in reaction time or error rate in task performance are needed. Furthermore, prioritizing the most important mission tasks and evaluation measures is important for cost-effective management of risks.
3. Although spaceflight stressors induce many changes in performance, whether the changes are considered beneficial or deleterious will depend on the task. For example, reduced distractibility could be interpreted as beneficial for vigilant attention but deleterious in terms of awareness in detecting unexpected anomalies.
4. What compensatory mechanisms does the CNS use to maintain homeostasis during spaceflight? Are the mechanisms the same in animals and humans, or do humans have more options or a greater capacity to adapt than animals (e.g. cognitive reserve), giving them a higher tolerance to stressors?

5. What are the underlying networks and mechanisms that result in altered behavioral performance, compensation, and adaptation (brain performance pathways)? Are they the same for animals and humans? Can this information be used to design countermeasure strategies?
6. Sensorimotor performance and responses to spaceflight stressors were not evaluated by this workshop panel but were addressed in a subsequent NASA workshop held in 2018.

NASA Translational Working Group Focused on Synergistic Effects of CNS, BMed, and Sensorimotor Risks

A NASA sponsored workshop held at the Gilruth Conference Center in Houston TX on July 17 and 18, 2018

Executive Summary

The workshop brought together 23 extramural investigators, 20 intramural investigators, and personnel from three NASA centers—the Johnson Space Center, the Ames Research Center, and the Glenn Research Center. The goal of the workshop was to develop consensus on a battery of cognitive, behavioral, and sensorimotor/neuro-vestibular tests that will allow NASA to assess potential central nervous system (CNS) decrements due to radiation, microgravity, confinement and isolation, and other spaceflight stressors and to evaluate acceptable countermeasures.

The workshop began with a presentation briefing the attendees on the *CNS, Behavioral Medicine, and Sensorimotor (CBS) Integrated Research Plan*, following by overview presentations describing the behavior and cognitive domains affected by radiation, executive summary and results from the 2017 workshop, sensorimotor domains affected by spaceflight, and a summary of the sensorimotor datamining task. The 18 extramural scientists then delivered brief presentations describing their expertise in animal research. The participants then split into three groups for concurrent sessions to facilitate in-depth analysis of the following specific translational areas.

Session 1: Translational Models of Movement Control focused on postural equilibrium, gait and eye-hand coordination.

Session 2: Translational Models of Vehicle Control, Navigation, Robotics, Extravehicular Activity focused on motion sickness, gaze, spatial orientation and perception.

Session 3: Translational Models of Cognitive Processes focused on learning, attention, working memory and plasticity.

Each breakout group included experts in areas of animal modelling for studying effects of spaceflight factors, human performance changes associated with spaceflight, radiobiology research, and computational modeling. Each of the panels were provided with the results of a previous datamining exercise and references for associated literature that has identified equivalent testing paradigms for human and animal behaviors, biomarkers of behavioral changes, and brain performance pathways that are affected by spaceflight stressors. The groups were asked to review the data provided and develop consensus on a standard test battery of cognitive and behavioral tests that:

- Support the translation of animal models to humans (and “reverse” translate).
- Are conducive to testing CNS decrements due to the integrated effects of space radiation, isolation and confinement, and altered gravity of long-duration spaceflight.
- Are suitable for evaluating mission acceptable countermeasures.

A table of key performance indicators was provided to capture each group's recommendations for analogous human and animals tests for each key indicator. After the breakout discussions, moderators from each group summarized the main points of their discussions for all attendees and shared their completed tables. The moderators later provided a written summary report that captured consensus views.

Major Conclusions and Recommendations from the Participants

1. Most components of the two sensorimotor tests that are currently conducted on astronauts— the computerized dynamic posturography assessment of balance control, and the field test/functional task test assessments of functional performance—could be translated to equivalent animal models, for example, using rotarod, beam walking, treadmills, wire hang tests.
2. Although quadrupedal rodents and bipedal humans differ in movement control, their underlying brain and spinal circuits for balance and motor control are similar, supporting the use of rodents for translatability to humans.
3. In addition to individual tests, the *overall* activity of animals should be monitored because overall activity requires all aspects of balance and motor control, is both an independent and dependent variable, and can be used to evaluate countermeasures.
4. Although participants of session 2 recommended rodent tests to assess motion sickness, gaze, spatial orientation, perception, hearing, vision, and vestibular effects, the participants believed that nonhuman primates (NHP) are better suited for these evaluations. Their rationale for this recommendation included the following:
    - Rodents have low visual acuity and lack binocular vision.
    - Conducting motion sickness research on non-emetic species is unlikely to provide data that is translatable to humans.
    - Gaze holding requires higher neural pathways that will likely be affected by interaction of radiation and microgravity, and it is more likely that any combined stressor effects would be evident in auditory perception tasks, such as language discrimination, which can only be tested in NHP.
    - Although rodent studies are useful for testing spatial orientation, more subtle effects could be probed using NHP models.
    - Rodent assessments of pointing control are weak because pointing is indirectly assessed using gaze control and nose poking. Non-human primates would be better suited for hand-eye coordination studies.
5. Foot sensitivity relates to pain, pressure, and detection of vibration, which provide important feedback for controlling gait. Diabetes might provide an analog of spaceflight effects to the feet because spaceflight induces similar vasculature changes as diabetes. Vibrotactile stimulation of the foot could mitigate foot sensitivity changes because it can improve peripheral control by adding a little sensory noise to increase discrimination—a process called stochastic resonance.
6. Investigators should measure as many physiologic parameters as feasible during experiments to ascertain the etiology of effects of microgravity and radiation. For example, microgravity can disrupt sleep patterns, and sleep deprivation can affect spatial orientation, perception, etc. Thus, if it is determined that microgravity and radiation together have a deleterious effect on spatial orientation, it is essential to determine if this is due to changes in sleep, feeding, hormones, etc.

7. Experiments should be designed to better mimic the time-course of radiation exposure during spaceflight. NASA is focused on the consequences of prolonged, low-dose radiation exposure, but the experiments could be confounded by the short lifespan of many animal models. Effects of aging must be considered in the interpretation of experiments.
8. Anxiety and emotional behaviors have negative impacts on operational performance, and these behaviors should be considered as a separate concern not just included under "attention" problems.
9. Many experimental parameters should be standardized, whenever practical, to facilitate inter-laboratory comparison of results. These parameters include exposure conditions (radiation and other stressors), animal species, strain, age, sex, post exposure evaluation times, animal husbandry conditions.
10. Cognitive reserve could be impacted during periods of gravity transition to a level that could impair cognition; therefore, dual task (sensorimotor + cognitive) investigations are valuable. Cognition can be tested in humans while they "dual task", and an analogous test in rodents could involve treadmill or trackball systems coupled to virtual reality environment used with in vivo electrophysiology and motion capture schemes to detect patterns of brain activity.

The following four tables include the recommended tests from each of the groups that can translate from animals and humans and are conducive to testing CNS decrements due to the combined CBS effects.

Key Indicator	Human Performance Test	Animal Model Performance Test	Caveats/Countermeasure/Notes/ Related Functional Performance Tasks
Balance	1. CDP; 2. Get up From Fall Test	1. Rotarod; 2. Zebrafish Active Posturography (ZAP); 3. Floating Platform Tests - Postural sway – measured by Center Of Pressure (COP) Assay (=CDP)	Animal model tests should be developed: a. Floating Platform Test; b. Motion Capture Analysis (exists but advanced version can be developed)
Locomotion	1. Tandem Walking (= Beam Walking in Animal); 2. Perturbation during walking 3. Navigating obstacle course while walking (e.g. Functional Mobility Test) 4. Statistical modeling of Actigraphy data	1. Rotarod; 2. Beam Walking (=tandem walking); 3. Actigraphy in animals; 4. Open field; y-maze, water maze, etc. (=human actigraphy).	Animal model tests should be developed: a. Digigait 2.0 Analysis with Perturbation, belt or surface perturbation (=human perturbation during walking; b. dual task test) [Catwalk]; c. Rodent obstacle course (=FMT)
Proprioception	1. Force and joint position test; 2. Dysmetria (finger to nose) test +/- eyes closed; 3. Foot sensitivity via pressure algometry (provides objective measure) = Von Frey Fibers; 4. Thesiometry, vibration at different frequency ranges for slow or fast adapting sensors	1. Von Frey Fibers; 2. Static force von Frey 3. Two-choice mechanosensory assay 4. Cotton swab assay 5. Tail Clip assay 6. Tape response assay 7. Hargreaves assay 8. Randall–Selitto assay 9. Complete Freund's adjuvant with von Frey 10. Bradykinin with von Frey 11. Two temperature choice assay	Animal model tests should be developed: a. Force and joint position test; b. No identified animal equivalent of dysmetria
Fine Motor Control	1. Peg board 2. Fine motor test (Holden iPad)	1. String pull; 2. Spaghetti eating; 3. Lever manipulation.	Animal model tests should be developed: a. Peg board

Key Indicator	Human Performance Test	Animal Model Performance Test	Caveats/Countermeasure/Notes/ Related Functional Performance Tasks
Learning & Plasticity	1. Sequence/procedural; 2. Eye-Head/Eye-Head-Hand adaptation tasks – a. VOR adaptation test b. Eye Head Hand – visuo motor adaptation task 3. Whole body tasks a. Walking with visuomotor adaptation b. Split Belt Locomotion Test 4. Mismatch negativity	1. Odor sequence learning (non-motor) 2. Eye Head and Eye Head Hand adaptation tasks – a. Nystagmus and compensation following labyrinthectomy b. Rodent VOR test 3. Whole body tasks a. Ladder rung walk test 4. Mismatch negativity (plasticity + perceptual learning, no motor component, EEG measure)	• Adaptability is an important trait that will need to be tested with combined stressors because of the need to adapt rapidly after g transitions
Smell & Taste	1. University of Pennsylvania Smell/Taste Identification Test	1. University of Pennsylvania Smell/Taste Identification Test	• Smell and Taste has been hypothesized to be modified secondary to fluid shifts causing increase in salt and spice intake leading to dysregulation of body salt composition
Pain	1. Back pain 2. Skin sensitivity 3. Pain modulation while modulating vestibular sensitivity	N/A	• Crew after one year long duration mission had significant skin sensitivity for prolonged periods

Key Indicator	Human Performance Test	Animal Model Performance Test	Caveats/Countermeasure/Notes/ Related Functional Performance Tasks
Motion Sickness	1. Graybiel Scale	Not reliable in rodents	Test in higher species: NHP
Gaze	1. Gaze Holding	1. Gaze holding	Test in higher species: NHP
Spatial orientation	1. Path integration – passive and active 2. Virtual maze perspective taking tests	1. Changes in Activity of Head Direction, Grid, Place Cells 2. Morris Water Maze	Test in higher species: NHP
Perception	1. Depth 2. Motion illusions 3. Time	N/A	Test in higher species: NHP
Visual	1. Visual Field Testing	1. Visual Field Testing	N/A
Vestibular	1. Drop Test/Jump down test 2. VEMP 3. OVAR response	1. Righting reflex 2. VEMP 3. OVAR responses 4. Active vs Passive motion on vestibular nucleus neurons	Test in higher species: NHP
Hearing	1. Otoacoustic emissions 2. Auditory evoked potential analysis	1. Otoacoustic emissions 2. Auditory evoked potential analysis	Test in higher species: NHP

Key Indicator	Human Performance Test	Animal Model Performance Test	Caveats/Countermeasure/Notes/ Related Functional Performance Tasks
Attention & Dual Tasking	1. Reaction time – PVT; 2. Dual Task Test: 1. PVT⁺ or PVT 2. Walking with distractors	1. rPVT; 2. Attention set-shifting; 3. 5C-CPT	• used operationally as go/no-go test; operational activities requiring high skill might be most affected; • PVT⁺ should be considered for performance under pressure with distractions
Working Memory	1. Fractal 2 back; 2. Object rotation in space; 3. Spatial WM	1. Radial arm water maze-trials to criterion, latency are common across studies, can be modified for each individual animal, can be modified for test-retest; 2. modified Barnes maze (operant n-back in rodents lacks stable baseline) 3. NHP: touchscreen, saccades	• Docking; Egress procedures and EVA-related; • Crew should stop with plans for completion/performance of task with possible catastrophic consequences if not performed correctly
Memory	1. Mnemonic similarity test (MST) (BPSO) – this test includes Novel Object Recognition (NOR)	1. Object in Place; 2. Social Recognition; 3. Novel Object Recognition 4. Morris Water Maze; 5. Fear Conditioning; 6. Temporal Order 7. Mnemonic similarity test (MST) (BPSO)	• Needed for recall of training, what you did minutes, hours, days, ago

CDP=computerized dynamic posturography; FMT=functional mobility test; VOR=vestibular ocular reflex; VEMP=vestibular evoked myogenic potential; OVAR=off-vertical axis rotational, rPVT=rodent psychomotor vigilance test; EVA=extravehicular activity; 5C-CPT=continuous performance test; EEG= electroencephalogram, PVT^+=psychomotor vigilance test with distraction

Unresolved Questions and Issues

1. More information is needed on changes in taste and smell perception during spaceflight before appropriate animal tests can be recommended. Radiation does not seem to affect rodents' abilities to taste or smell, and there is no overt change in the reinforcing value of food after irradiation. If changes in taste and smell cause astronauts to alter their food choices, an analogous study could be designed for rodents.
2. There are numerous pain assays for rodents, but a greater understanding of the pain-associated issues facing astronauts is required before an appropriate animal model can be designed. However, stimulus-evoked assays in rodents appear to have limited clinical translatability.
3. How does one separate locomotion levels from locomotion activity in rodents? For example, when rats are recovering from vestibular changes, they do not move much. Activity level may be a biomarker of their recovery.
4. Because the neural pathways that generate nausea and vomiting are not well understood, additional basic studies are needed to map these pathways.