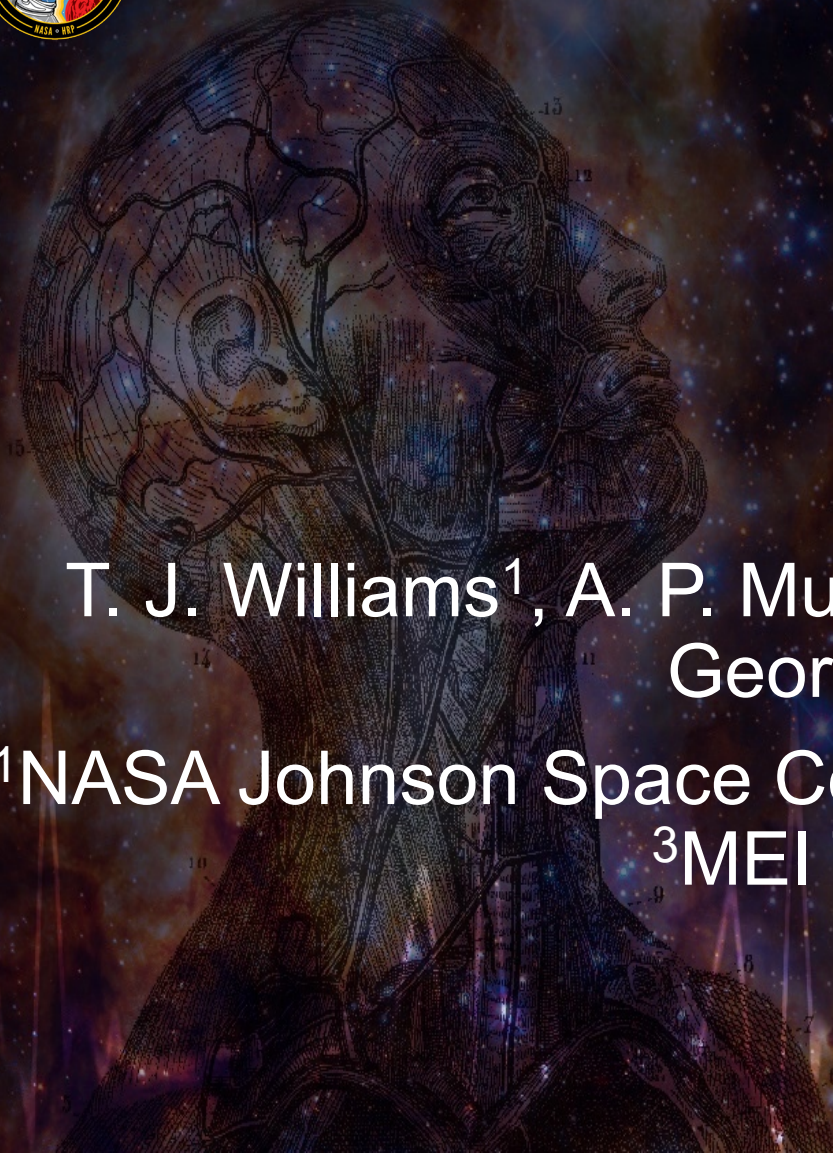




UPDATE TO CBS INTEGRATED RESEARCH PLAN



HRP IWS 2020
January 29, 2020

T. J. Williams¹, A. P. Mulavara², A. Hanson¹, J. Roy Choudhury³, K. George², and A. M. Whitmire¹.

¹NASA Johnson Space Center, Houston, TX, USA; ²KBR, Houston, TX;
³MEI Technology, Houston, TX;



Integrated Risks—Integrated Research Approach

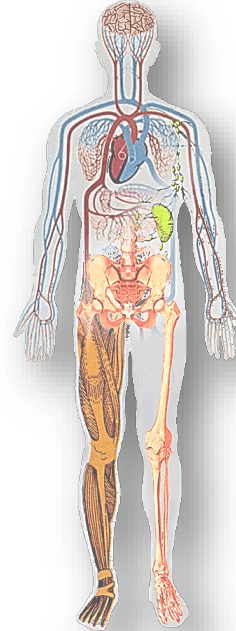


Balance Disorders
Fluid Shifts
Cardiovascular
Deconditioning
Muscle Atrophy
Bone Loss

HAZARD FOUR
Gravity Fields

Acute In-flight effects
Long-term cancer risk
CNS-Cognitive

HAZARD ONE
Space Radiation



CBS Integrated Research Plan

Designed to accelerate discovery (the identification), and mitigation (monitoring and countermeasures development) of the potentially synergistic effects of the 3 spaceflight hazards on operationally relevant tasks, to ensure crew safety and mission success.

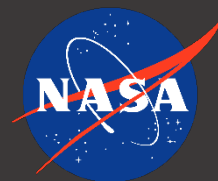
Integrated Research Plan:

- C**NS acute effects of radiation
- B**ehavioral Medicine
- S**ensorimotor

HAZARD TWO
Isolation

Behavioral aspect of isolation
Sensory deprivation
Sleep disorders (circadian dysregulation)

Research Strategy



Synergistic Effects?

1. Each crewmember has a certain capacity to tolerate all three risks
2. Additivity: one risk could be substituted for another (same mechanism of action)
3. Independence: different mechanisms of action, leading to addition of individual responses (i.e., specific-stress response relationships)
4. Challenge:
 - a. Quantitatively predicting the combined effects of the risks
 - b. Characterize & categorize stressors according to domain of action
 - c. Observed combination response & theoretical expectation

Null-hypothesis: Risks are non-interacting and do not disproportionately act on different receptors within crewmembers to impact operationally-relevant performance



SUPPLEMENTS TO THE BULLETIN OF THE HISTORY OF MEDICINE

Founded by HENRY E. SIGERIST

Editor: OWSEI TEMKIN

No. 11

VOLUMEN MEDICINAE
PARAMIRUM

OF

THEOPHRASTUS VON HOHENHEIM
CALLED PARACELSVS

TRANSLATED FROM THE ORIGINAL GERMAN

WITH A PREFACE BY

KURT F. LEIDECKER, M. A., PH. D.

Paracelsus: biological effects of toxicant amplified when individual is weakened by additional, unfavorable factors



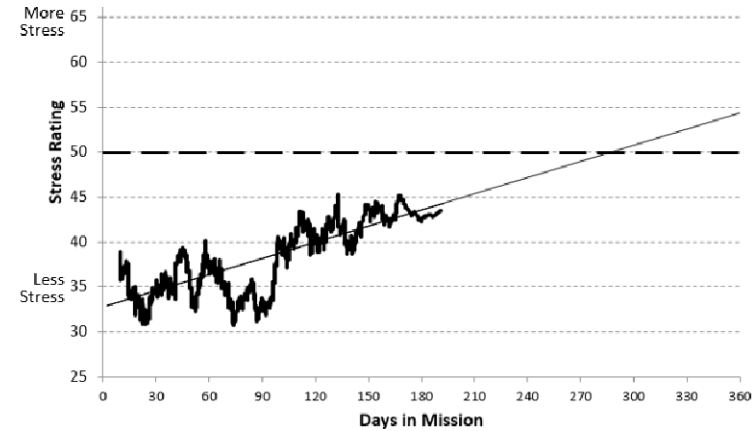
Research Strategy Problem Statement



CBS Problem Statement: There is a risk that the spaceflight hazards of space radiation, altered gravity and isolation & confinement may synergistically interact; with the combined effects resulting in a significantly increased risk to operationally relevant crew health and performance

Dinges et al. (2017)

- Astronauts self-reported that their stress increased progressively during a 6-month International Space Station missions
- Marked individual differences in stress ratings across time in-flight



Operationally-relevant Performance deficits

A. Post-landing Operator Proficiency (*Moore et al, 2019*)

Mission: 6 months aboard the ISS, n=8

Deficits: Manual dexterity, motion perception, dual tasking (cognitive reserve), simulated vehicle operation (complex motor)

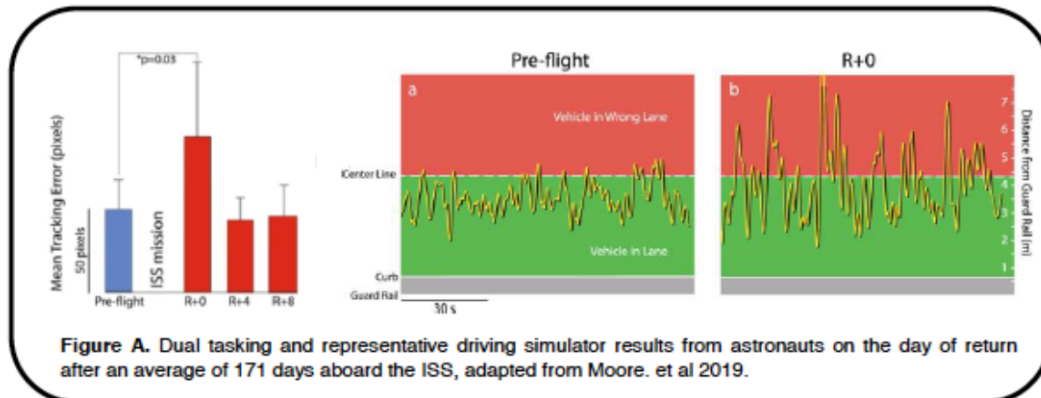


Figure A. Dual tasking and representative driving simulator results from astronauts on the day of return after an average of 171 days aboard the ISS, adapted from Moore. et al 2019.

3. COGNITION & NASA Twins (*Garrett-Bakelman et al. 2019*)

Mission: 340 days aboard the ISS, n = 1

Reduced *Cognition* test battery performance post-flight

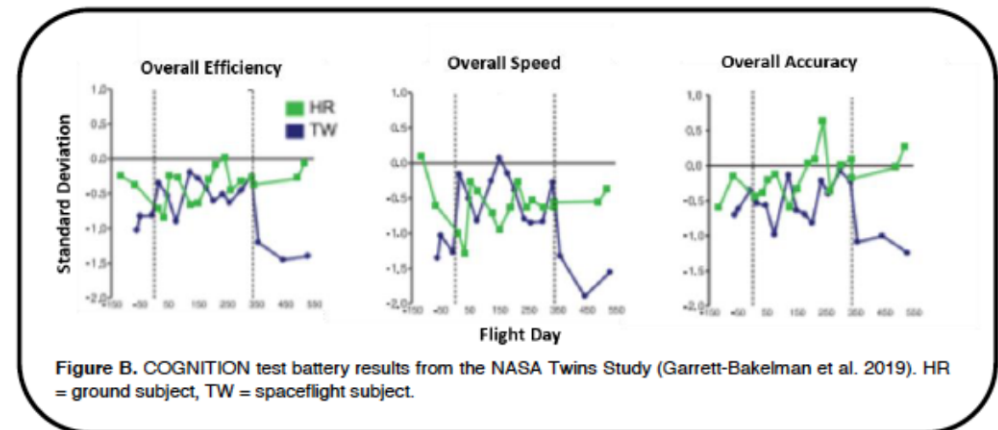
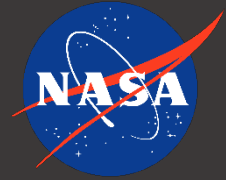


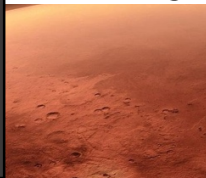
Figure B. COGNITION test battery results from the NASA Twins Study (Garrett-Bakelman et al. 2019). HR = ground subject, TW = spaceflight subject.



CNS/BMed/SM (CBS) Integrated Research Plan Research Strategy

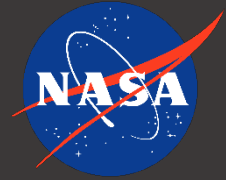


- **Fully integrated research plan** of three risks: Acute CNS, BMed, and Sensorimotor
 - Combines **research efforts across 3 Elements: SR, HFBP, HHC**
 - **Leverages multi-center (JSC/LaRC/GRC/ARC) expertise**
- **Innovative integration of research and modeling capabilities to translate rodent models**, combining past and planned research results, to help inform operationally relevant performance outcome levels in response to stressors and establish crew health standards
 - Determine additive/synergistic dose-rate impacts through fractionated studies of functional, behaviorally relevant outcomes
- **Leverage Interagency Partnerships** for translating animal results to human outcomes





Integrated Research Strategy



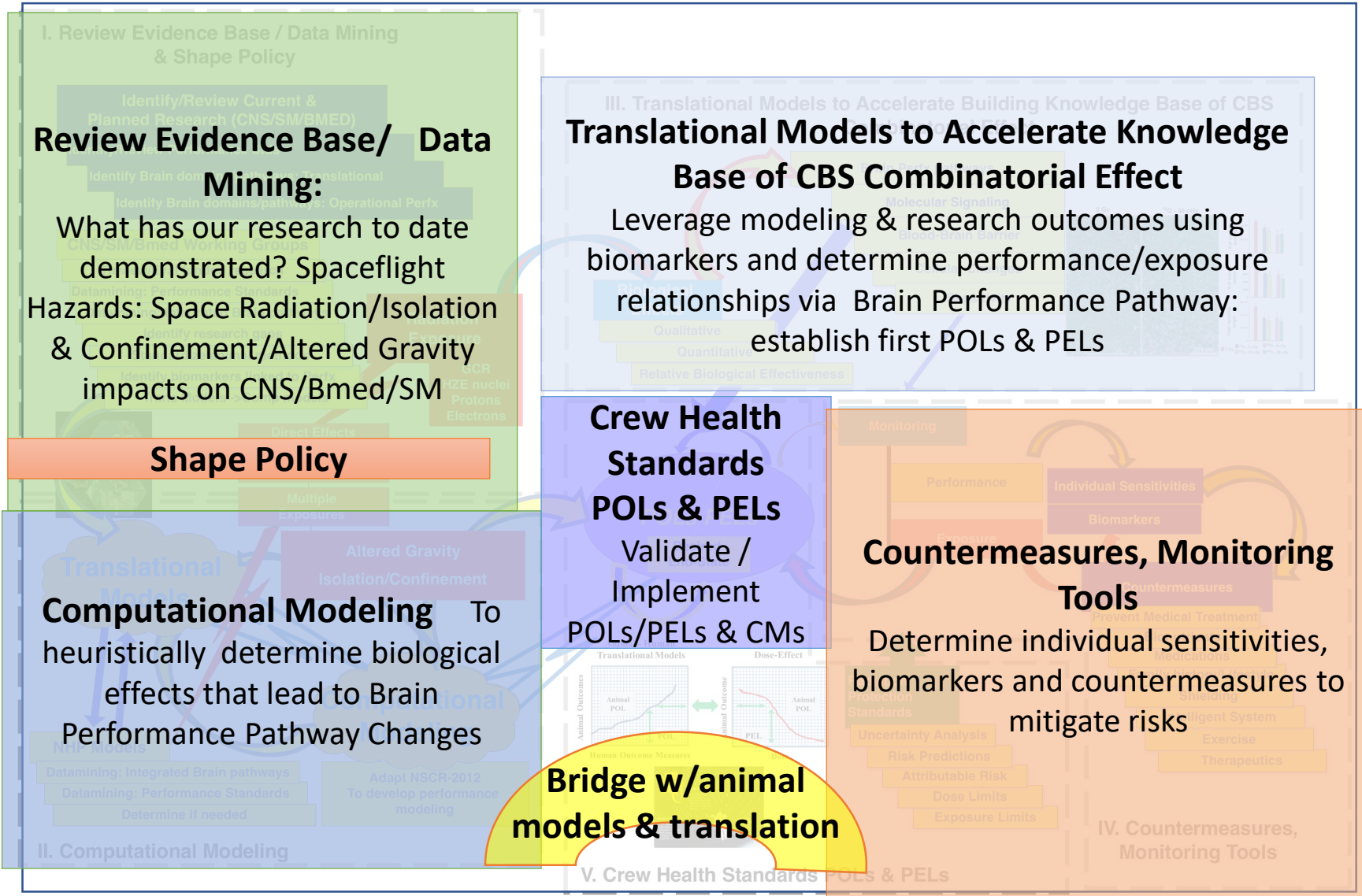
End-state: Identification and validation of monitoring capabilities, countermeasures, and risk mitigation of synergistic impact of CNS/BMed/SM risks posed to operationally relevant performance domains



CBS Integrated Research Plan Strategy



Research Strategy





2019 Standing Review Panel (SRP) Review of CBS Integrated Research Plan (Oct 9-10, 2019)



The Role of the 2019 Standing Review Panel

- In 2016 HRP transitioned to a more integrative and cross disciplinary approach to SRP reviews.
- The 2019 SRP will review the CBS Integrated Research Plan, which focuses on the potential complex interactions of environmental, interpersonal, psychological, and physiological stressors on crew health and performance. This review addressed:

WHY Evidence and rationale for the CBS integrated research plan

WHAT Research strategies and techniques to address issues identified in the rationale, including the intended end state, outcomes or deliverables

WHEN Schedule of knowledge maturity and priority of work



2019 Standing Review Panel (SRP) Review of CBS Integrated Research Plan (Oct 9-10, 2019)



Selected Comments from SRP –

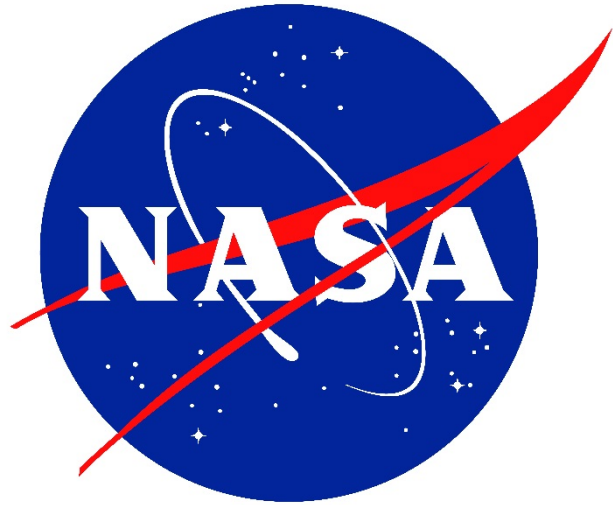
1. The SRP strongly endorses an integrated research approach. It is critical to review progress in the individual disciplines and their integration sufficiently frequently and with sufficient expertise. These need not be overly formal reviews but rather updates to incorporate new findings, methods and interactions, and avoid extending work in areas that end up being less relevant to the integrated solution as research results accrue.
2. Studying the interaction of risks is critical, as recognized in the adaptation of an integrated research plan. For example, social interaction can be tested along with another insult.
3. Single discipline data should be studied further, particularly long-term data available from studies such as non-Human primates (NHP) survivors from other research. This will provide some very long-term (many year) data on radiation effects including effects on cognition and aging.
4. Emerging knowledge of brain development and function, such as the module- and-node models of brain function and the ability to monitor brain functional capacity, to some extent, by functional magnetic resonance imaging (MRI) and electroencephalogram (EEG) provides a significant impact on which to map CBS effects.
5. Defining the specific experiments will require thorough analysis of results obtained, however, clearly defining the research conditions and procedures is critical to be able to combine or compare results from different laboratories.



2019 Standing Review Panel (SRP) Review of CBS Integrated Research Plan (Oct 9-10, 2019)



6. The individual functional assays as have been done by the astronauts in space and on return to Earth and the time course for resolution of functional decline will be useful for assessing POLs.
7. The psychological impacts of space travel and team effects on individual and group outcome as investigated in the human exploration research analog (HERA) will be critical.
8. Recognizing that Central Nervous System (CNS) and sensorimotor (SM) functions are interactive makes it important to have diagnostic tools available during the Mars mission (e.g., EEG or variants, or other imaging tests). These will be among the useful biomarkers that will likely include blood tests (very low volume “chip assays”) and other activity/attitude measures available with monitoring devices.
9. The NASA Space Radiation Laboratory (NSRL) at Brookhaven National Laboratories (BNL) is now operational will allow for improved assessment of cell fate given the likelihood of multiple “hits” to a cell from different particles.
10. Ongoing biomarker and radiation mitigation research for whole body exposure being conducted by National Institute of Allergy and Infectious Diseases (NIAID), Biomedical Advanced Research and Development Authority (BARDA) and Department of Defense (DoD) can help inform NASA, and communication with these agencies is essential.
11. Full review report and the response to the SRP report will be posted on NASA HRP website





BACK UP SLIDES

Snapshot of CBS Funded Tasks and Projects

- VNSCOR on CBS Dose Rates/Mechanism (Davis/Nelson, POP: 4/15/2018-8/31/22)
 - GCRsim effect of operationally relevant performance.
- VNSCOR on CBS Synergistic/Order Effects of Spaceflight Hazards (A. Ronca, S. Rosi, L. Sanford, POP: 10/2019-9/2023).
 - Integration of 3 stressors individually & combinatorial approach.
- Omnibus for CBS Astrocytes Mediator (E. Cekanaviciute, 10/2019-9/2020).
 - Astrocytic regulation of neuronal damage in response to simulated space radiation, using human 3D tissue-on-a-chip (TOC) system.
- Initiated supplemental work from SR as a result of CBS Integration –
 - Tissue Sharing-R. Wyrobek
 - Sex Differences/Resilience Outcomes- R. Britten
 - Sex Differences/CNS- S. Rosi
 - GCRsim + Hindlimb Unloading-J. Raber
- 4 Student Augmentation grants in progress (PoP: 04/2019-03/2020)
 - Targeting DNA Double Strand Breaks as a Countermeasure against Space Radiation-Induced Cognitive Injury (Sydney Boustros, Dr. Raber's Lab,)
 - Development of a Ground-Based, in vitro Model of the Response of Human Microglia to GCR-Irradiated Neural Tissue (Robert Hinshaw, Dr. Lemere's Lab)
 - Does Microglial CR3 Expression Modulate Space Radiation Dependent CNS Damage? (Joshua Hinkle, Dr. O'Banion's Lab)
 - Hadron-Induced Impairment of Executive Function: Role of Perturbed Neurotransmission and the Exacerbating Impact of Sleep Deprivation (Mayumi Machida, Dr. Britten's Lab)

Data Mining Activity

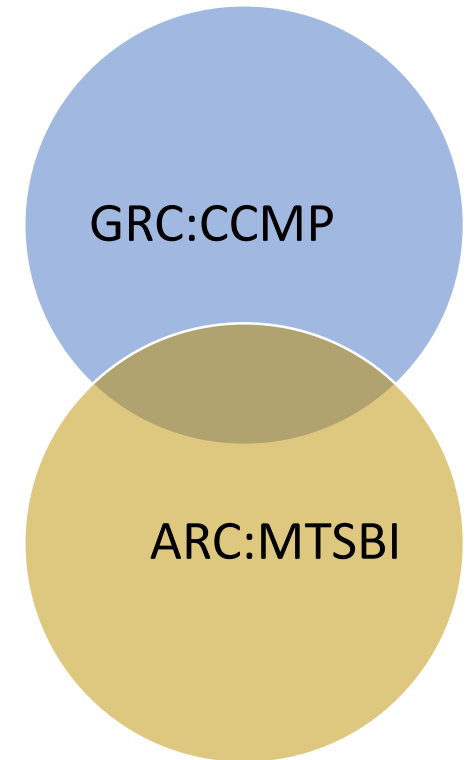
The CBS Data Mining tasks have helped to characterize the overall CBS risk posture and evidence base to date. These tasks help to inform forward funded work, analyze projected risk posture in out years, and help move forward recommendations for POL/PEL updates.

- Data Mining Projects:

- CNS/BMed Data Mining & TIM I (Nelson) (Completed)
- CBS Sensorimotor Data Mining & TIM II (Mulavara) (Completed)
 - TIM I & II Reports to be released as NASA Technical Reports
- NHP Data Mining (Desai) (Completed 5/2019)
- CBS Operational Performance Measures (Roma) (Completed 10/2019)
- Bio-Nutritional Countermeasures for CBS (Smith) (Completed 11/2019)
- Neurobehavioral Biomarkers (Desai) (To Be Completed 4/2020)
- Immune/Micro Inflight Assessment Capability, Biomarker Assessment Protocols (TBD)
- Standardization and Policy Recommendation via a Animal Handling/Facility TIM being planned to evaluate best practices and establishments of a standardization approach to ensure consistent outcomes in animal research.

Computational Modeling Activity

- Cross-center ITAs and MOUs executed to support CCMP and MTSBI support.
 - Established work-flow for data requests, data packaging, data delivery, and utilization.
 - FY20 MOUs under review to ensure alignment with evolving CBS strategy and schedule.
- MTSBI is developing a database of results from single ion-beam, GCR beam, and flight related exposures to aid in development of proof-of-concept models using a data driven approach.
 - Data delivered from MTSBI to CCMP from Britten Lab.
 - Demonstrations on Naïve-Bayuse and SVM approaches provided to CBS Portfolios.
- IWS presentations from CCMP representing modeling efforts from Britten Data, with focus on dose response and operational performance outcomes.
 - Schepelmann: Probabilistic classifiers can predict radiation exposure in rodents from performance tests
 - Matar: CBS data from literature: findings and limitations
 - Prelich: Predicting single-ion exposure in rodents through performance tests: a data-driven approach using support vector machines
- A Biomarker TIM is being planned by MTSBI (FY20Q3)



Partnerships, Meetings and Presentations (FY20)



- **IAC CBS Presentation, Oct 21-25, 2019:**

- Presented by Dr. Fogarty at IAC

- **Three CBS panels for 2020 IWS:**

- CNS/Space Radiation, Behavioral Medicine, and Sensorimotor: From Rodents to Humans - Translation and Computational Modeling
- CNS/Space Radiation, Behavioral Medicine, and Sensorimotor: Multi-stressor Effect Risk Characterization and Countermeasures
- Integrating CNS/Space Radiation, Behavioral Medicine, and Sensorimotor: Operational Performance and Countermeasures

CBS Abstracts Submitted:

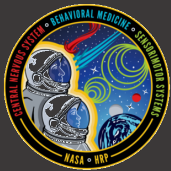
1. T. J. Williams, A. P. Mulavara, A. Hanson, J. Roy Choudhury, K. George, and A. M. Whitmire. Update to CBS Integrated Research Plan
2. A. P. Mulavara, J. Roy Choudhury, A. Hanson, K. George, A. Whitmire, T.J. Williams. Standardizing rodent models to provide the most valid translation to human risks from spaceflight

- **Invited panel session at the 17th World Congress of Society of Brain Mapping & Therapeutics (SBMT) 'Mars Exploration: Impact of Change to CNS on Operational Performance', March 20-22, 2020:**

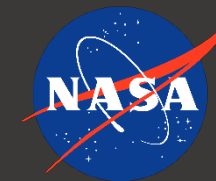
1. CBS Integrated Risk Overview and Problem statement (Mulavara and Williams)
2. Operational Performance: Isolation & Confinement—six months vs one year mission effects on CNS and performance outcomes (Gur R)
3. Operationally-Relevant Performance: Acute & Long-term effects of Galactic Cosmic Radiation on CNS and Behavior (Rosi S)
4. Fractionated delivery effects vs Acute dose effects of Galactic Cosmic Radiation on CNS/ behavior and operational performance outcomes (Davis K)
5. Biomarkers for monitoring Behavioral and Operationally-Relevant Brain Performance Pathways: ISS and ICE Effects on CNS and Crew Behavioral Medicine (Dinges D.)
6. Integrating Performance Impacts: Behavioral Medicine, CNS, and Sensorimotor Effects on operational performance in crew post landing – 6 and 12 months (Wood S)

Partnerships, Meetings and Presentations (FY19)

- **Intra-agency strategic partnership between NASA and DTRA:**
 - Provides SME support with background in neurobehavioral/ radiobiology to provide inputs on operationally relevant cognitive and behavioral performance, and continuity of performance following radiation exposure.
- **Participation at 70th International Astronautical Congress (IAC), Washington D.C., United States, 21-25 October 2019.**
 - Oral Presentation - The Brain in Deep Space: Identifying “Potential” Synergistic Risks to Behavior and Performance from Space Radiation, Isolation and Confinement, and Altered Gravity. Presented by Jenfer Fogarty
- **2019 HRP IWS session devoted to CBS task:**
 - Session enabled dissemination of CBS research plan strategy to NASA investigators. (Available on YouTube, courtesy of TRISH).
- **2019 Russian Space Medicine Conference:**
 - Oral Presentation - Nasa’s Human Research Program Risk Integration: Is There A Synergistic Risk Of Space Radiation, Isolation & Confinement, And Altered Gravity? Authored by Williams, Norsk, & Simonsen.
- **CBS session at ISGP 2019:**
 - Organized symposium at the International Society of Gravitational Physiology (ISGP) on Identifying and Reducing Risks to Brain and Behavior during Extended Human Spaceflight (May 26-31).
- **CBS session at SBMT 2019:**
 - Team organized an invited panel of 5 speakers at the 16th World Congress of Society of Brain Mapping & Therapeutics (SBMT) to provide an overview of the CBS Integrated Risk Research Plan. Connected with 22 neuroscientists, including computational modeling group at LLNL.
- **2019 Review of CBS strategy with NASA Chief Engineer.**

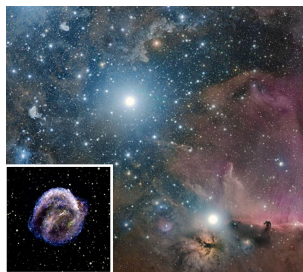


The CBS “Problem”: Acute CNS Risk from Radiation Exposure

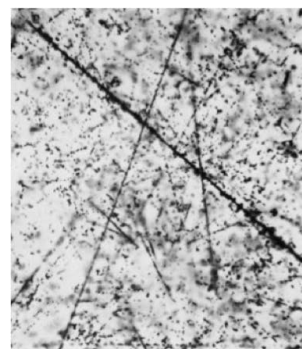


Review of Spaceflight Induced Effects: Acute CNS

Space Radiation Exposure



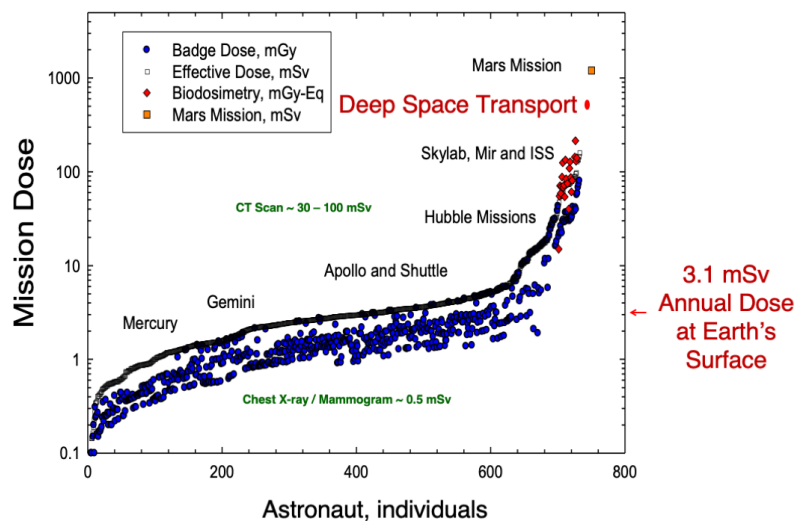
Galactic Cosmic Radiation (GCR)



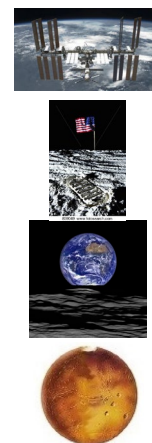
An illustration of the ambient radiation exposure in deep space as a *microscopic field of view of an Ilford G.5 nuclear emulsion* that was worn on the ankle of Neil Armstrong during the Apollo 11 lunar landing mission in July, 1969 (shown to the left).

NASA Estimates each cell in an astronaut’s body being “hit” (traversed) by:

- A proton once every few days
- Helium nucleus once every few weeks
- Heavy ion (Z>2) once every few months



Modified from Cucinotta et al. (2002)



DRM Categories	Mission Type and Duration	Dose mGy
Low Earth Orbit	Short (<30d)	30-60
	Long (30d – 1y)	60-120
Lunar Surface	Short (30d)	15-20
	Long (6 month)	100-120
Lunar Orbital	Short (<30d)	15-20
	Long (1yr)	175-220
Mars	Preparatory (<365d)	175-220
	Planetary (365 – 900d)	300-450

Doses are highly dependent on crew, vehicle, and mission parameters.

Apollo 11, 195 hrs
~1.8 mGy

Apollo 14, 8 days
~11.4 mGy

Artemis Lunar Surface, 6 months
~110-120 mGy



CNS Radiation Risk Supporting Evidence Neurogenesis, Neuronal Structure, Inflammation

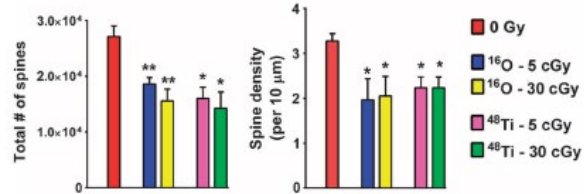
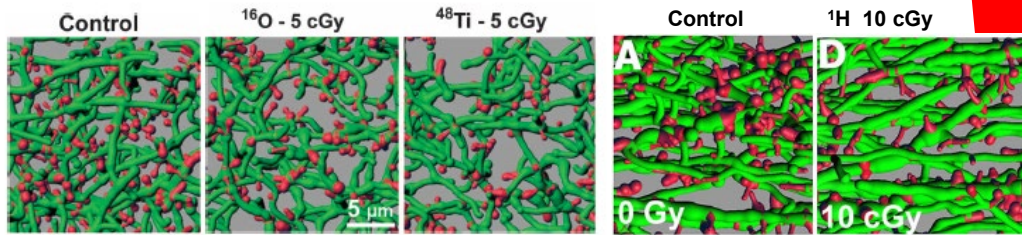


Review of Spaceflight Induced Effects:
Acute CNS

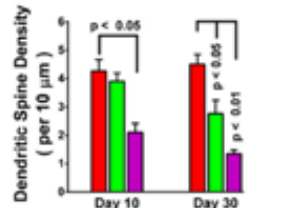
Neuronal Structure in Mice: Reduced Dend and density 8 weeks post ^{16}O or ^{48}Ti ions
Reduced spine density 30 days after ^1H exposure.

Estimated Artemis Mission
= ~110-120 mGy = 10 cGy

Inflammation: Increased microglia activation
100 days after $^1\text{H} + ^2\text{He} + ^{16}\text{O}$ exposure

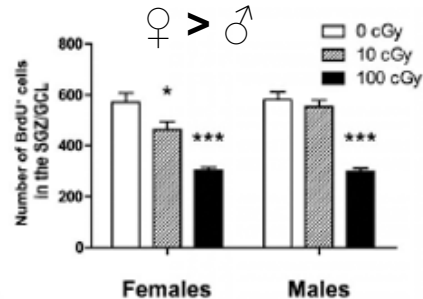
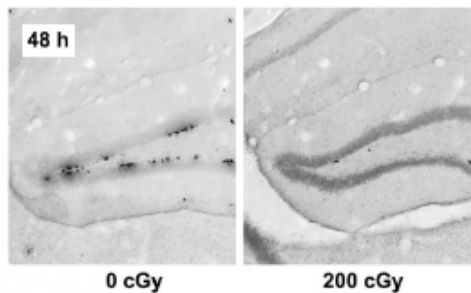


Parihar et al. (2015a)



Parihar et al. (2015b)

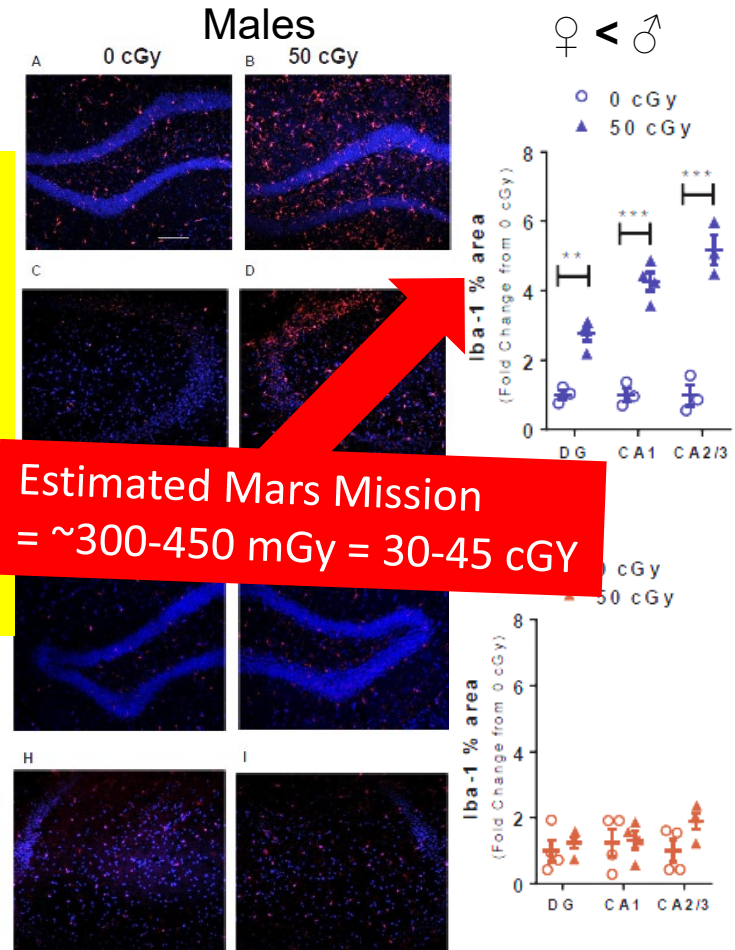
Neurogenesis in mice: Reduction in mouse dividing neuronal precursor cells, 48 hours post ^1H exposure.



Sweet et al. (2014)

Sensitivity of Inflammatory response:
♀ < ♂

Sensitivity of Neurogenesis:
♀ > ♂

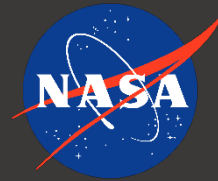


Estimated Mars Mission
= ~300-450 mGy = 30-45 cGy

Krukowski et al. (2018)



The CBS “Problem”: Behavioral Medicine Risk



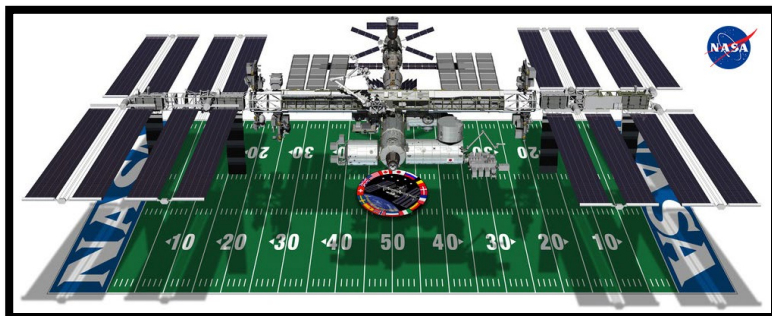
Review of Spaceflight Induced Effects:
BMed

Current Operations

Low Earth Orbit

- Real-time communications (ground operations, family, friends)
- Provision of crew care packages
- Evacuation options
- Cupola and photography
- Exercise 2 hours
- Large volume and private quarters
- Six month duration (to date)
- Long training & preparation period

Astronauts thrive on the ISS
(Habitable Volume: 15,000 Ft³)



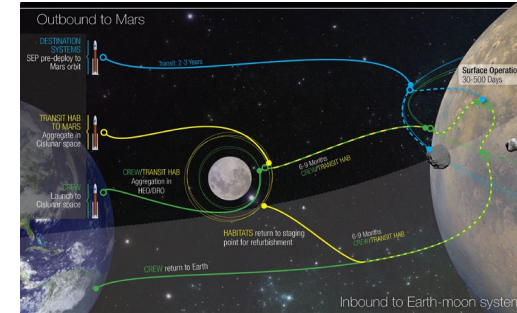
Exploration Class Missions

Deep Space

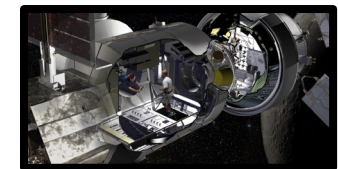
- Unprecedented duration and distance
- Limited volume in confinement and isolation
- Loss and delay of communications with ground
- More autonomous operations
- No re-supply
- No option for evacuation

Major Challenges

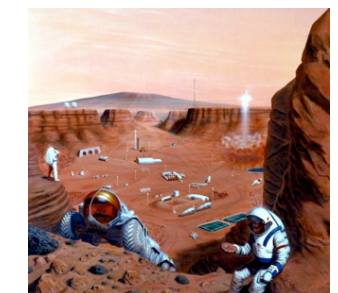
- Stress, conflict, mood & morale
- Sleep, fatigue, workload & circadian
- Selection and crew composition
- Psychosocial adaptation & training
- Meaningful work, motivation
- Growth and resiliency
- Family connectedness and communication
- Net habitable volume, sensory stimulation
- Earth out of view



Orion Capsule
316 Ft³

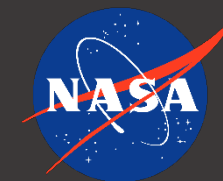


Gateway Habitat
4415 Ft³





Simulating Exploration Stressors on Earth: 520 day Confinement in NEK, Russia



Review of Spaceflight Induced Effects:
BMed

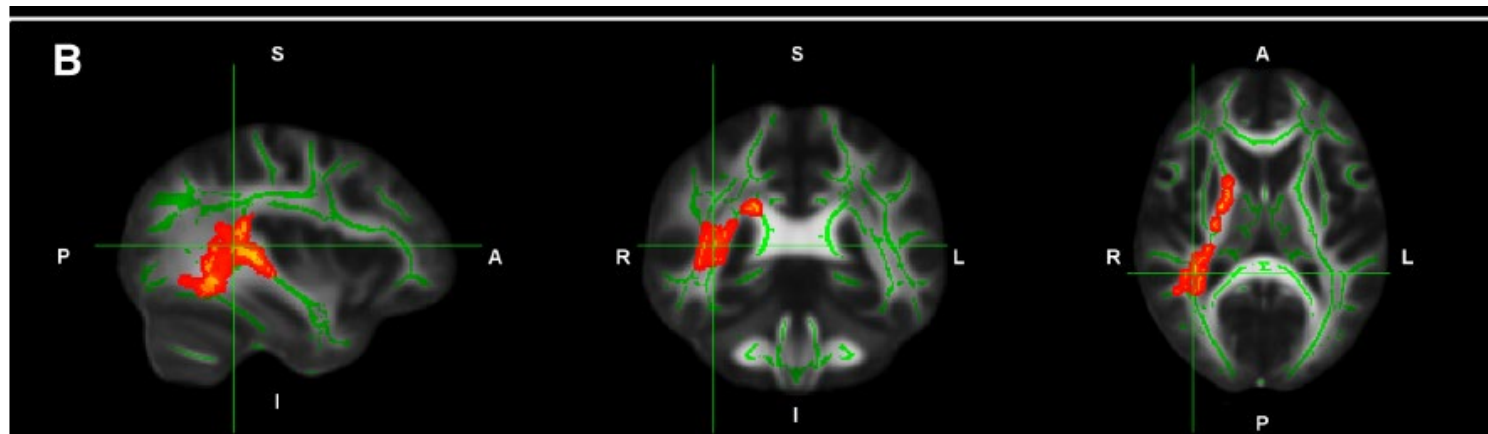
Isolation & Confinement Analog

NEK, Russia



Dysmyelination at the Temporo – parietal – occipital junction in the crew after long term confinement – sensory deprivation, small space available

After ICE exposure, subjects (n=4, 520 day NEK study) showed a **decrease** in Fractional Anisotropy (FA) in the **temporo-parieto-occipital-junction zone (TPJ) of the right hemisphere** – important for **multisensory integration, especially in visuospatial processing, spatial navigation** - FA reduction seen potentially due to plasticity of myelin than to axonal degeneration





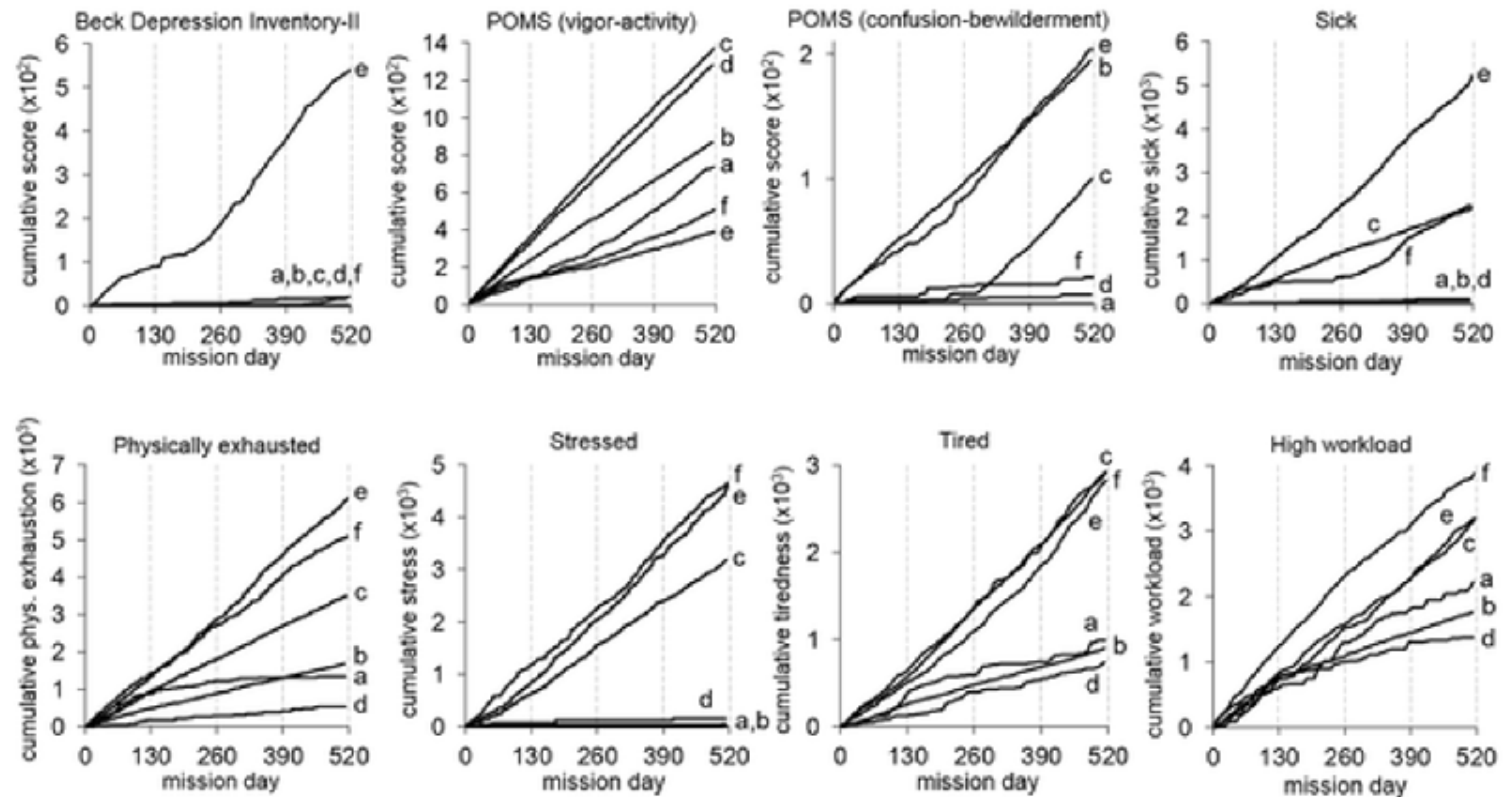
Simulating Exploration Stressors on Earth: 520 day Confinement in NEK, Russia



Review of Spaceflight Induced Effects:
BMed

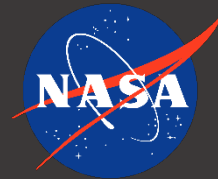
Isolation & Confinement Analog

Psychological and Behavioral cumulative self report scores show differential reactions of crew to long term confinement

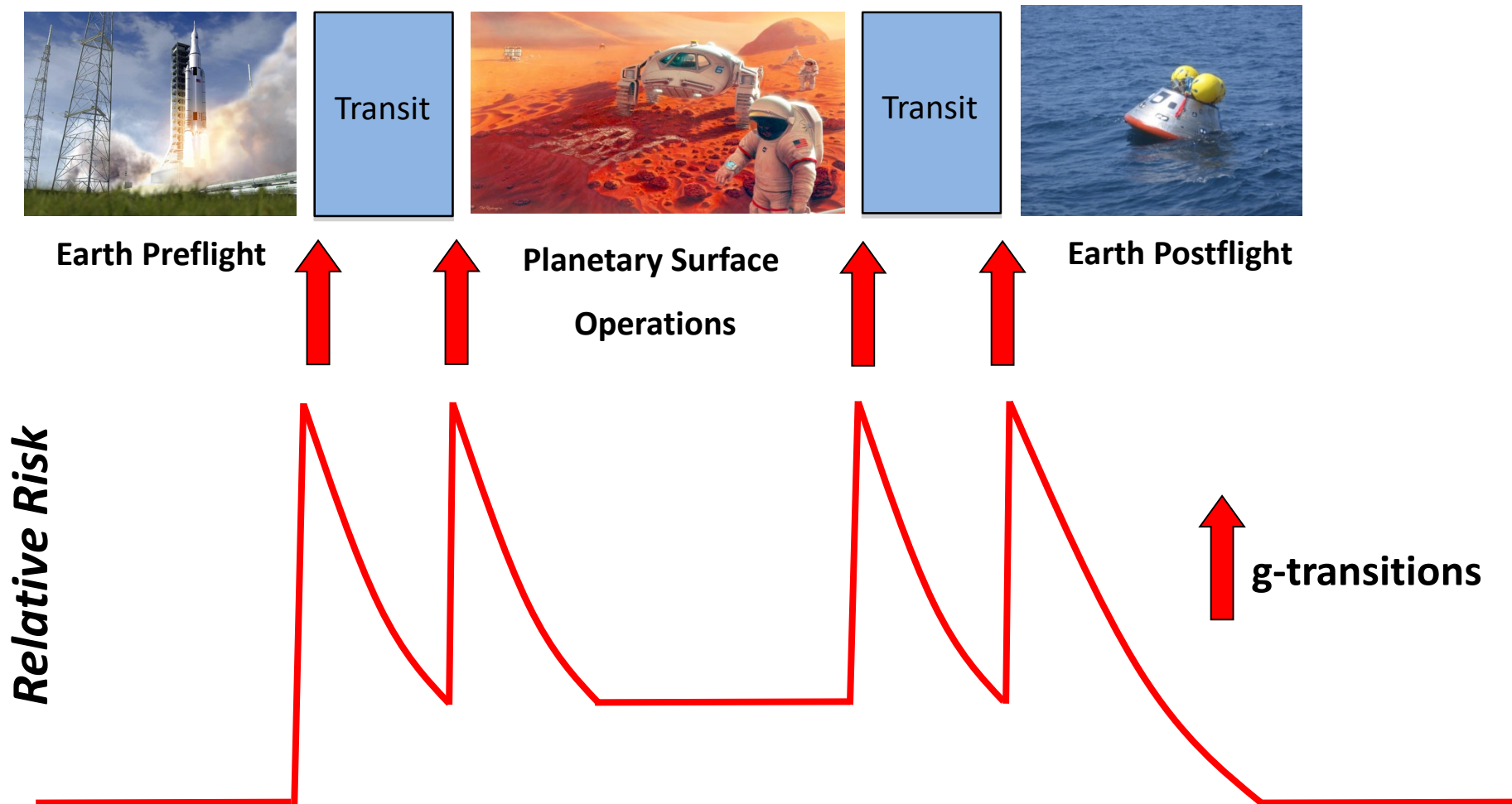




The CBS "Problem": Sensorimotor Risk

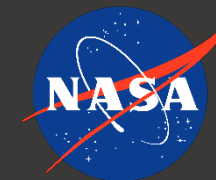


Review of Spaceflight Induced Effects:
Sensorimotor





Spaceflight Associated Brain White Matter Microstructural Changes



Review of Spaceflight Induced Effects:
Brain Structure & Function

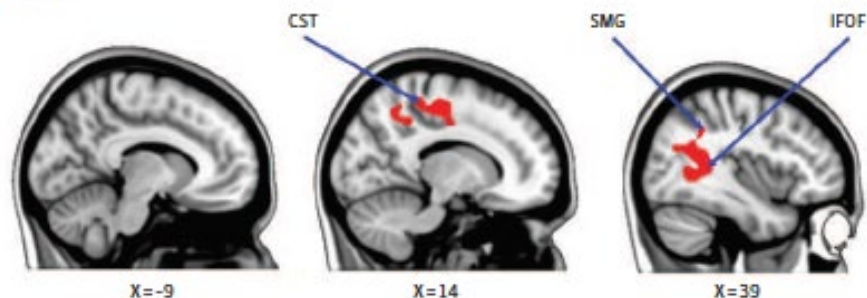
A FA_T Decrease in Fractional Anisotropy (FA)



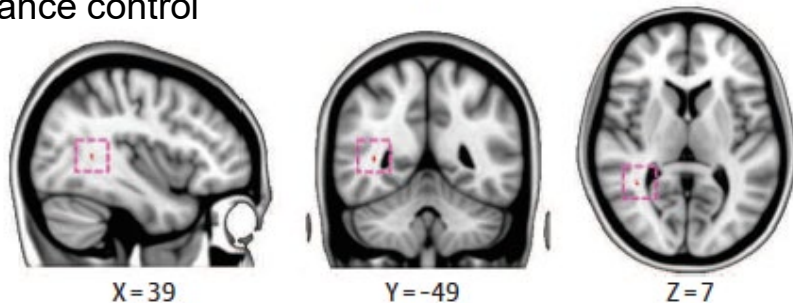
Areas:
visuospatial
processing,
vestibular
function, &
movement
control

- **Fractional anisotropy (FA):** decrease, right superior and the inferior longitudinal fasciculi, inferior fronto-occipital fasciculus, the corticospinal tract, the inferior and middle cerebellar peduncles.

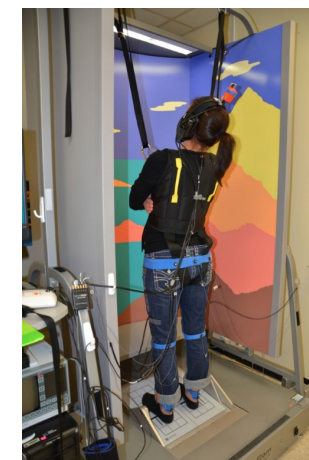
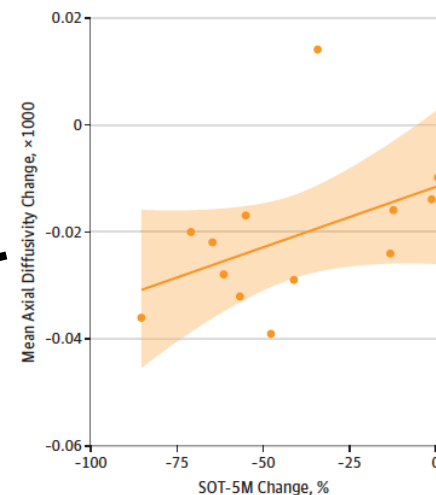
C RD_T Increase in Radial Diffusivity (RD)



Changes of Axial Diffusivity (AD_T) associated with balance control



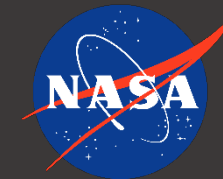
Changes of Axial Diffusivity (AD_T) and Sensory Organization Test (SOT) 5M Balance Score



Lee et al. (2019)



Spaceflight Associated Macrostructural Alterations

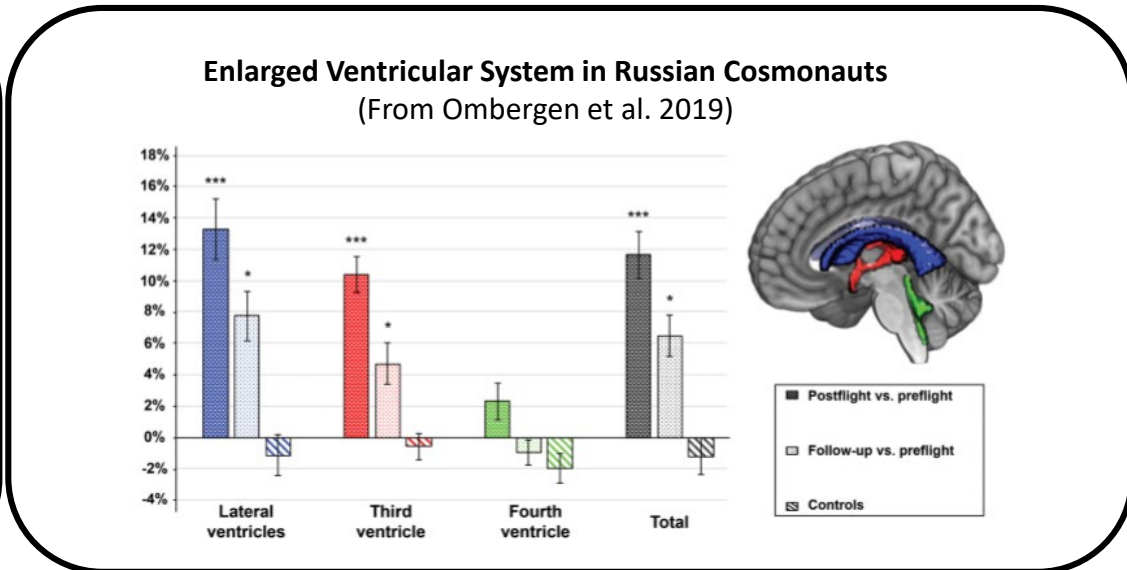
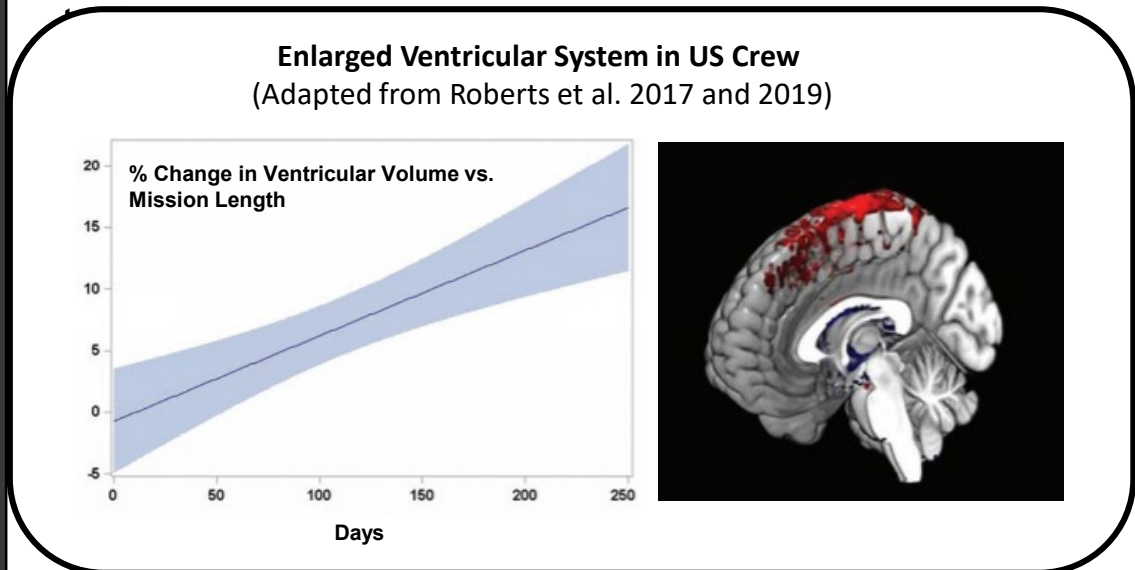


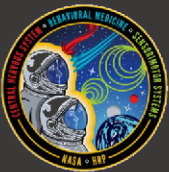
Review of Spaceflight Induced Effects:
Brain Structure & Function

Macrostructural changes in included altered brain position, tissue crowding, CSF distribution, increased ventricular size, periventricular white matter hyperintensities (WMH), reduced gray matter volumes

Duration Effect: Association between longer mission duration, periventricular WMH and greater increases in ventricular volume

Post-Flight: Follow-up scans showed resolution of gray matter volume changes, with persistent ventricular volume increases and WMH. Global loss of white matter was noted from post-flight scan





Effects of Spaceflight During and Post-landing



Review of Spaceflight Induced Effects:

BMed

Dinges et al. (2017)

- Astronauts self-reported that their stress increased progressively during a 6-month International Space Station missions
- Marked individual differences in stress ratings across time in-flight

Operationally-relevant Performance deficits

A. Post-landing Operator Proficiency (Moore et al, 2019)

Mission: 6 months aboard the ISS, n=8

Deficits: Manual dexterity, motion perception, dual tasking (cognitive reserve), simulated vehicle operation (complex motor)

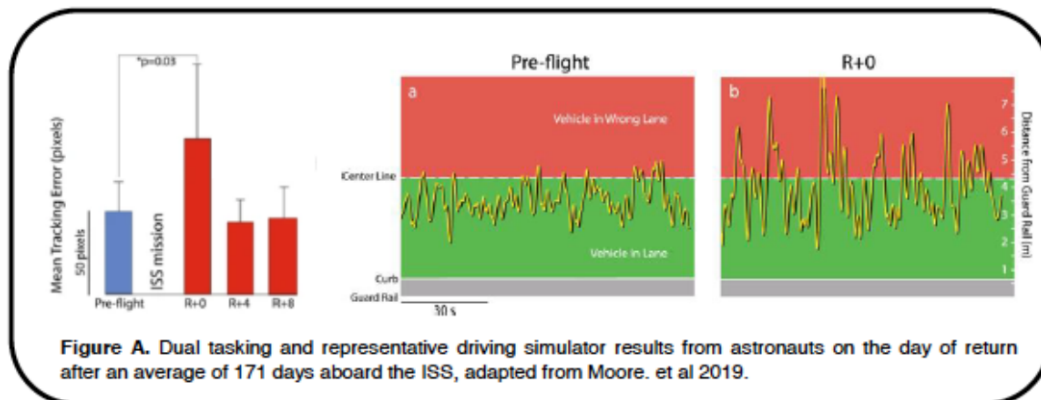


Figure A. Dual tasking and representative driving simulator results from astronauts on the day of return after an average of 171 days aboard the ISS, adapted from Moore. et al 2019.



3. COGNITION & NASA Twins (Garrett-Bakelman et al. 2019)

Mission: 340 days aboard the ISS, n = 1

Reduced *Cognition* test battery performance post-flight

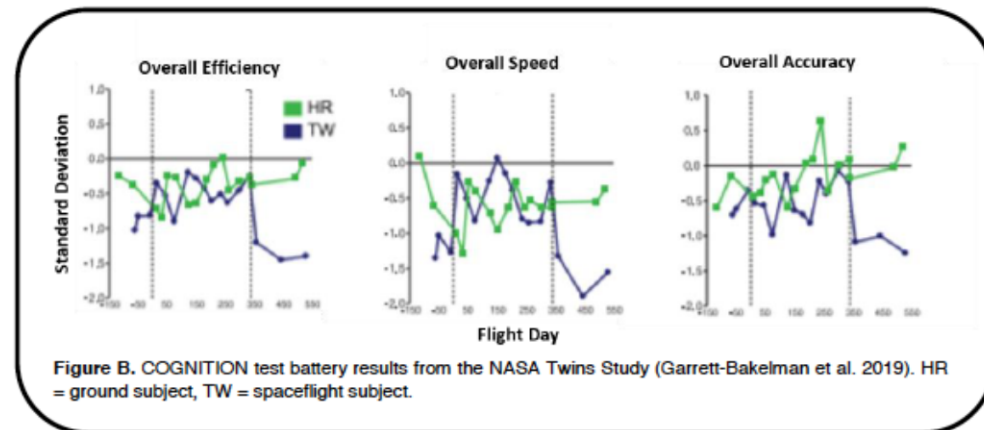


Figure B. COGNITION test battery results from the NASA Twins Study (Garrett-Bakelman et al. 2019). HR = ground subject, TW = spaceflight subject.

VNSCOR Kickoff meetings and standardization

CBS Selects 3 teams for the VNSCOR: Synergistic Order Effects of Spaceflight Hazards

A multidisciplinary team was assembled into a four year VNSCOR project with multiple research arms to assess synergistic and order-effects of radiation exposure, isolation & confinement stress, and sensorimotor disruption (hindlimb unloading), on operationally-relevant brain performance pathways. The team will use standardized handling and behavioral tests, and collectively evaluate brain physiology changes (to include Blood-Brain-Barrier changes), molecular signaling with biomarker changes, and use computational modeling to characterize and predict changes in performance.



- “Probing the synergistic effects of radiation, altered gravity and stress on behavioral cognitive and sensorimotor functions to predict performance decrement in astronauts”, Dr. Susanna Rosi, UCSF – Lead PI for VNSCOR.
- “Oxidative stress and the neuroconsequences of spaceflight environment - Immune dysregulation and antioxidant dietary countermeasure efficacy”, Dr. April Ronca, NASAARC.
- “Impact of inflight stress and sleep disturbances on brain function, neural communication and inflammation”, Dr. Larry Sanford, EVMS.

2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030

CBS POL/PEL Standard Update

CBS Data Integration & POL/PEL Standard Update
Updated POL/PEL Metrics

FY22 OCHMO:
Review of
POL/PEL/Metrics,
Identified CMs

FY26 OCHMO:
Review of
POL/PEL/Metrics,
CM1



Research Biomarkers for POL/PEL & CM Development ID'd

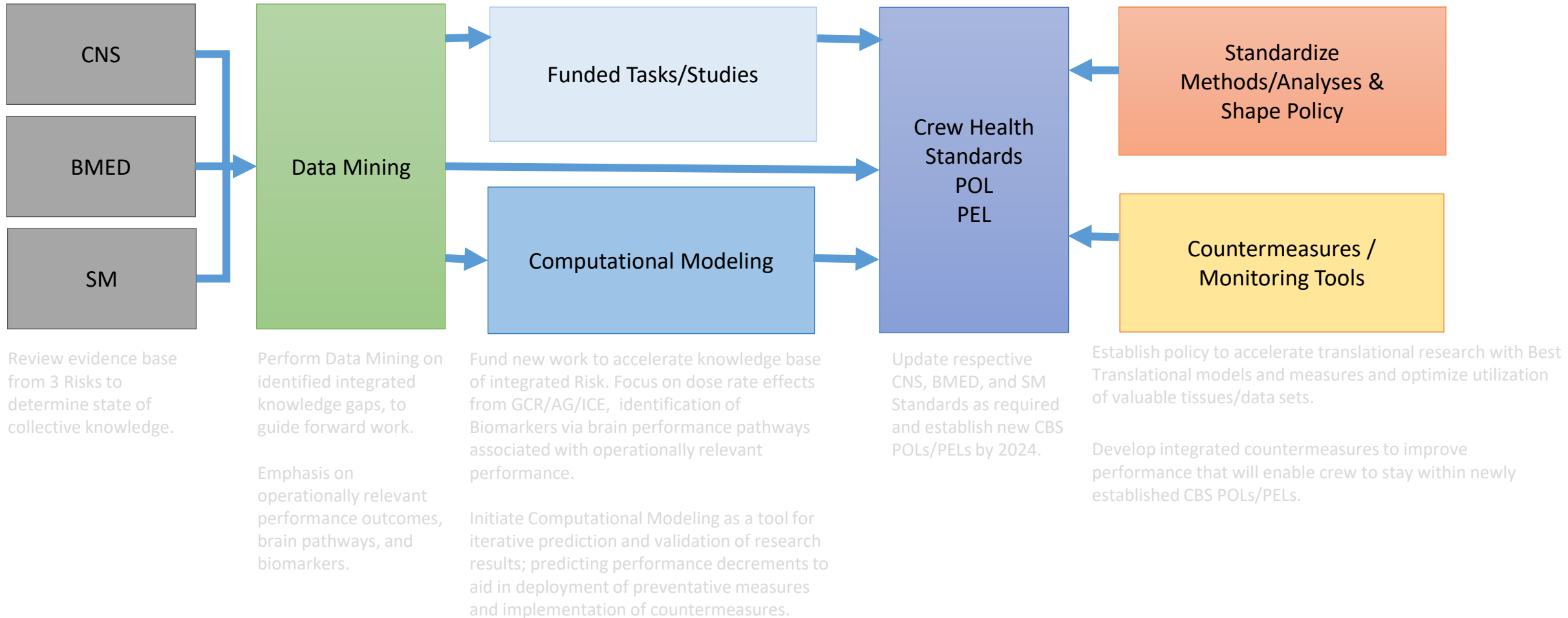
Updated Research Biomarkers for POL/PEL & CM Update

Updated POL/PEL Metrics

Recommended Updated Operational Biomarkers/Monitoring Tool (POL/PEL Metrics)



CBS Strategy Deconstructed



CBS Medical Clerks

- **Meaghan Roy-O'Reilly, Ph.D., MD Candidate;** McGovern Medical School, The University of Texas Health Science Center at Houston Houston, TX
 - **Spaceflight-Associated Structure/Function Alterations in the Brain and Risk to Operational Performance**
 - Literature review for documentation of spaceflight-associated performance decrements and structure/function changes on MRI, which were used to identify brain pathways at greatest risk during long-duration spaceflight and their relevance to mission success. Biomarkers for in-flight monitoring and candidate countermeasures were identified.
 - **Extended rotation period to January 2020**
 - Review paper on findings from clerkship to be submitted for peer review publication.
 - Review of CNS related neurological and BMed evaluations for crew during exploration mission.
 - Presented results of clerkship to HFBP Element, Clinical Director of JSC Clinic, and TREAT Act Lead Clinician 1/6/2020.
- **Michael Wong, MD Candidate,** Washington University in St. Louis
 - **Neurocognitive effects of High LET Cosmic Radiation**
 - reviews the evidence for neurocognitive changes from high LET radiation at mission relevant doses.
 - The underlying mechanisms for these effects are reviewed, with an emphasis on the immunological response and changes to dendrite structure unique to high LET radiation.
 - Finally, in lieu of data for humans exposed to GCR, we review analogs from the medical literature, including traumatic brain injury, Alzheimer's disease, and radiotherapy to elucidate potential effects in astronaut performance and suggest avenues to better understand any decrements from radiation exposure.

Integration within HHC, HFBP and SR

- Monthly CBS Task Force Meeting
 - Held to review deliverables, share activity relevant to the three elements, and socialize upcoming task activities, reports, outcomes and solicitations.
- Briefed the new SR Element Deputy Scientist and Element Deputy Manager on the CBS Integrated Research Plan 12/4.
- Synchronization with revised Element strategy for individual CBS risks:
 - Met with HHC to review POL/PEL integration and update milestones.
 - Meeting with SR to review POL/PEL integration and update milestones 1/9/2020.
- Provided input to the SR Redon Solicitation.
 - Did not go to the ESWG. Comments were sent directly to SR, and CBS will respond to the RFI.
- Suggested IWS panels with content from SR, BMed, and HHC to HFBP Element for feedback to IWS program
- All Elements have access to CBS Share Point documents for all stakeholders.
- Developed workflow for final reports and deliverables review between CBS, HFBP, HHC, and SR.
- Given briefing on CBS IRP to the ESWG, BRESCB, CBS SRP task force.
- Briefed Sensorimotor, Discipline scientists (Drs. Bloomberg and Woods) and SM Risk Custodian (Dr. Reschke).
- Briefing material sent to SRP: The Problem statement, The Implementation Strategy that included the Science plan of Why and the What including all tasks and deliverables included in the CBS PRR document was reviewed by the CBS SRP task force members from all contributing elements.



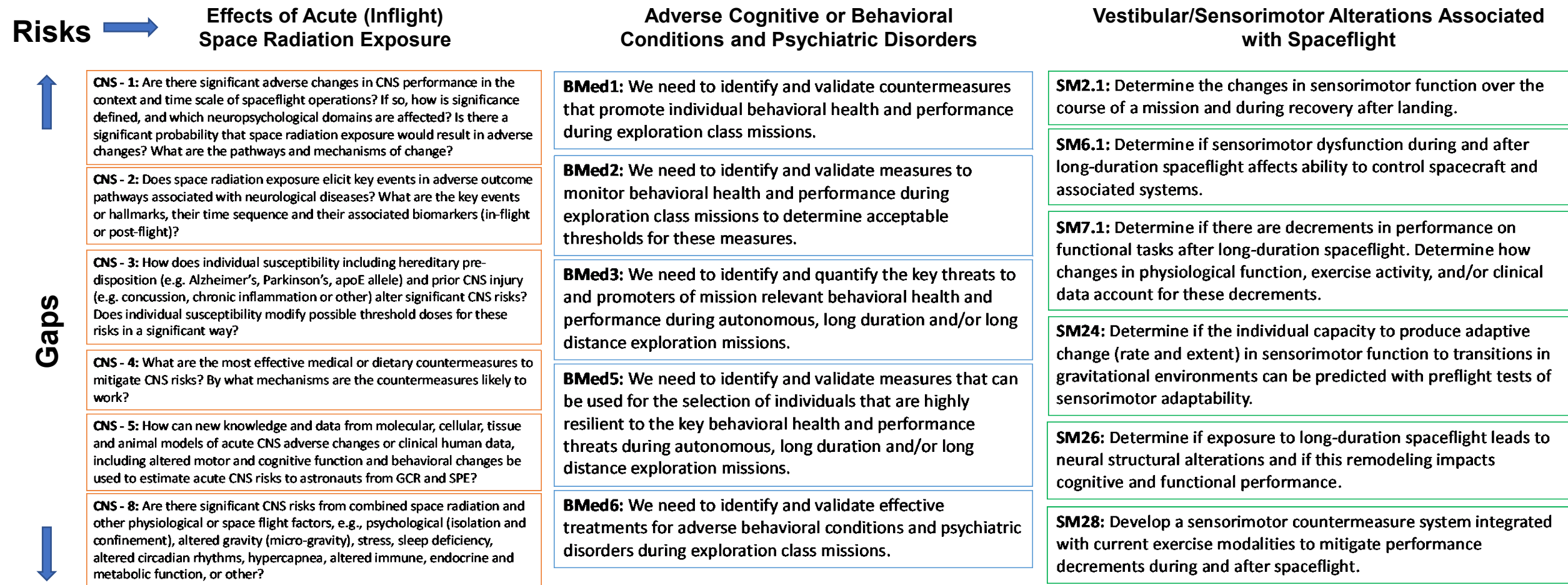
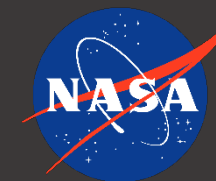
Scientific Goals & Objectives



- **Integrated Research Goal:** Identify and validate operationally-relevant performance outcome pathways and tasks in CNS/BMed/SM risks that are synergistically impacted by space radiation exposures.
- **Objectives:**
 - **Integrated research effort:** Transdisciplinary, Multi-Center
 - **Standardize animal models:** Higher fidelity translational models
 - **Datamining:** Brain performance pathways & biomarkers
 - **Identification of biomarkers and adverse outcome pathways:** CBS exposures
 - **Biomarkers and brain performance pathways** linked to performance
 - Assess **synergistic effect** on multiple operationally-relevant, mission-related outcomes/performance standards
 - Development/validation of **integrated monitoring tools & countermeasures**
 - **Computational Models** (cf., Adverse Outcome Pathways)
 - Systematically assess effects of **radiation type and dose-rates** on operationally-relevant CNS/BMed/SM Brain Performance Pathways & Mechanisms
- **Deliverables:** Validated monitoring tools & countermeasures that are integrated with set of Permissible Outcome Limits (POLs) and Permissible Exposure Limits (PELs)--developed, validated, and recommended to OCHMO.



CBS Integrated Research Plan: Individual HRP Risk Areas with associated Gaps





Summary of Evidence - Brain Changes

- Frequent narrowing of the central sulcus, upward shift of the brain, and narrowing of CSF spaces at the vertex, predominantly after long-duration flights
- Volumetric gray matter decreases, including large areas covering the temporal and frontal poles and around the orbits
- For some regions of the brain, effect was greater in International Space Station crewmembers than Space Shuttle crew members
- Bilateral focal gray matter increases within the medial primary somatosensory and motor cortex; i.e., the cerebral areas where the lower limbs are represented
- Changes in white matter affecting connectivity

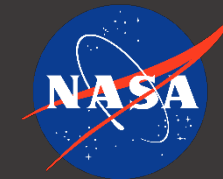


Summary of Evidence Supporting BMed Risk

- Stress increases progressively during mission on board the International Space Station missions and in spaceflight analogs
- Increasing levels of cortisol and number of lymphocytes during in spaceflight analog
- Sleep loss and circadian misalignment occur in space
- Inter-individual differences in responses for crewmembers of spaceflight and analog environments



Summary of Evidence Supporting Sensorimotor Risk



Review of Spaceflight Induced Effects: Sensorimotor

During Spaceflight

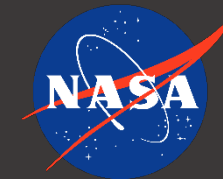
- Space motion sickness
- Spatial disorientation
- Difficulty acquiring and tracking visual targets
- Dynamic vision changes due to alterations in the vestibular ocular reflex
- Modification of vestibular and proprioception interpretations (e.g., pointing, sense of limb position)

After return to Earth

- Earth motion sickness lasting from a few hours to more than a week
- Frequent under- or overshooting when reaching for an object
- Unilateral gaze nystagmus, which is associated with dizziness and vertigo
- Saccadic intrusion during smooth pursuit tracking
- Postural control
- Postural ataxia



Summary of Evidence – Operational Performance



Review of Spaceflight Induced Effects: Operational Performance

- Reduced cognitive reserve may relate to the commonly experienced “space fog” - cognitive and perceptual changes that manifest as attention-lapses, short-term memory problems, spatial disorientation, and confusion when performing tasks; affecting in-flight performance (e.g. manual control)
- Increase in occurrence of sleep pressure markers and related to in-flight performance (e.g. docking tasks)
- Sensorimotor and BMed changes can affect manual control function during and after gravity transitions following short and long duration missions (e.g. landing, driving, docking tasks)
- Sensorimotor changes can affect postural control and mobility function after gravity transitions during short and long duration missions (e.g. egress task)



Summary of Evidence Supporting CNS Risk

Review of Spaceflight Induced Effects: Acute CNS

- Reduction in neuron arborization and synapse number (dendritic spines)
 - Persistent reductions for > 1 year after doses of high- Linear Energy Transfer (LET) nuclei below 5 cGy
- Significantly reduced production of new neurons in brain
- Increased activation of microglia (signaling neuroinflammation)
- Deficits in neurocognitive performance for several mouse and rat behavioral paradigms
 - High-LET nuclei at low doses (<10 cGy, with 1 cGy sensitivity reported in one study)
- Dose threshold for performance deficits following exposure to high-LET nuclei depends on
 - The physical characteristics of the particles, strain, sex, age at exposure, and evaluation time after exposure
 - Male mice appear to be more radiosensitive than female mice in several studies

Microstructural Alterations

Microstructural changes included altered white matter tract organization in the **somatosensory, vestibular, visual, motor** and **cerebellar pathways**.

Reduced connectivity seen between the **vestibular nuclei** and other major brain regions, as well as the **cerebellum** and other major brain regions.

Visual System

Vision: Optic nerve, thalamus, optic radiations, occipital cortex

Cognitive: Visuospatial processing, visual attention, visuomotor control, visual recognition (object, facial, emotional), visually-guided decision making

Somatosensory System

Primary Sensory: Perception of all sensory modalities, including vestibular and proprioceptive

Cognitive: Body spatial representation, sensorimotor integration

Motor System

Primary Motor: Voluntary movement, postural control

Cognitive: Translation of internal/external states into motor commands, planning of goal-directed behavior, sensorimotor integration

Spaceflight-associated alterations in the brain extend to cortical structures known to be involved in **cognition and behavior**

Need to assess potential synergistic impacts on operationally-relevant performance

Brain Pathway Alterations and Predicted Clinical Findings

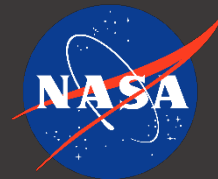
Structure	Function	System	Functional Symptoms
Superior Longitudinal Fasciculus (Right) ³²	Connects the frontal, occipital, parietal and temporal lobes. Visuospatial attention (goal-directed, stimulus driven) and motor control.	Visual, motor, cognitive, behavioral	Observed: Astronauts with largest spaceflight-associated balance disruptions had greater AD ₇ decreases in the SLF ³² Predicted: Visuospatial cognitive dysfunction (searching, shifting spatial attention, performing mental rotations, detecting patterns)
Inferior Longitudinal Fasciculus ³²	Connects temporal and occipital lobes. Visual modality, object/face/place processing, emotional processing, visual memory.	Visual, cognitive, behavioral	Predicted: Visual neglect, visual amnesia, visual hallucinations, prosopagnosia, visual hypo-emotionality
Inferior Occipitofrontal Fasciculus ³²	Connects frontal and occipital/temporal lobes. Hypothesized for role in visual processing and cognition (non-dominant), goal-oriented behavior, social interaction.		
R. posterior thalamic radiations ³³	Posterior radiations connect thalamus and occipital cortex, connect visual information to the occipital cortex.		
Calcarine, middle occipital, inferior occipital gyri ³³	Location of the primary visual cortex and secondary visual association cortex.		
Right fusiform gyrus ³³	Facial and word recognition, within-category identification		
Inferior cerebellar peduncle ³²	Connects the cerebellum to the spinal cord and medulla. Carries vestibular receptors (afferent and efferent) to help with posture and coordination.		
Middle cerebellar peduncle ³²	Afferent pathway from pons to cerebellum. Controls the initial timing of volitional motor activity		
Corticospinal Tract ³²	Efferent motor information from the cerebral cortex to the brainstem and spinal cord.		
White matter underlying primary motor and sensory cortices ³²	Afferent and efferent motor and sensory information, sensory processing.		
Inferior and posterior parietal lobe ³²	Body spatial representation, central vestibular and proprioceptive input, vertical upright perception		
Thalamus ³³	Relays information between cortex and subcortical areas.		
Frontal poles ³⁰	Higher order cognition, emotion, goal directed behavior, task prioritization	Cognitive, behavioral	Predicted: Loss of empathy, perspective-taking, difficulty re-prioritizing tasks
Temporal Poles ³⁰	Semantic naming, facial recognition, integration of emotion with sensory information.	Visual, cognitive, behavioral	Predicted: Social withdrawal, failure to produce appropriate social signals or recognize them, self-centered, loss of empathy, unstable mood states.
Supplementary Motor Region ³⁵	Self-initiated movement, stimulus-cued movement, speech production, temporal triggering. ^{70, 71}	Motor, visual, cognitive, behavioral	Predicted: Akinesia, speech deficits, executive working memory deficits
Premotor Region ³⁵	Integration of visuospatial information for movement planning, both external and internal memory-based ⁷²	Visual, motor, cognitive, behavioral	Predicted: Impaired performance of visually and verbally cued tasks, difficulty initiating memory cued tasks, motor apraxia ⁷³
Primary Sensorimotor Region ³⁵	Integration of sensory and motor skills needed for skilled movement ⁷⁴	Motor, somatosensory	Predicted: Impaired cross motor function and reflexes, impaired fine motor skills, disrupted learning of new motor tasks ⁷⁴
Left Caudate Nucleus ³⁵	Voluntary movement, postural control, cognitive planning of adaptive goal-directed behavior. ⁷⁵	Motor, somatosensory, cognitive	Observed: Decrement in postural control on Recovery from Fall/Stand Test, Dynamic Postural Stability Test. ³⁵ Predicted: Gait disturbances, slowed walking speed. Impaired visual discrimination, alternation behavior, cognitive-driven strategy switching. ⁷⁵⁻⁷⁷
Lower Extremity Primary Motor Area/Mid-Cingulate ³⁵	Motor execution. Processing of internal/external states (emotional states) and translation into motor commands. ⁷⁸	Motor, cognitive, behavioral	Predicted: Impaired movement

Example: Premotor Region

Normal Function: Integration of visuospatial information for movement planning, both external and internal memory based

Pathways Involved: Visual, motor, cognitive, behavioral

Predicted Clinical Findings: Impaired performance of visually cued tasks, difficulty initiating memory cued tasks, apraxia



Contributions

- Human Factors and Behavioral Performance Element

- Thomas Williams, Ph.D., Element Scientist
- Sandra Whitmire, Ph.D., Deputy Element Scientist
- Aaron Allcorn, Element Manager
- Sheik Ahsan, Deputy Element Manager



- CBS Portfolio

- Ajitkumar Mulavara, Ph.D., Portfolio Scientist
- Andrea Hanson, Ph.D., Portfolio Manager
- Jayati Roy Choudhury, Ph.D., Science Coordinator
- Kerry George, Science Support
- Greg Nelson, Ph.D., CBS Discipline Support
- Meaghan O'Reilly, Aerospace Medicine Medical Clerk

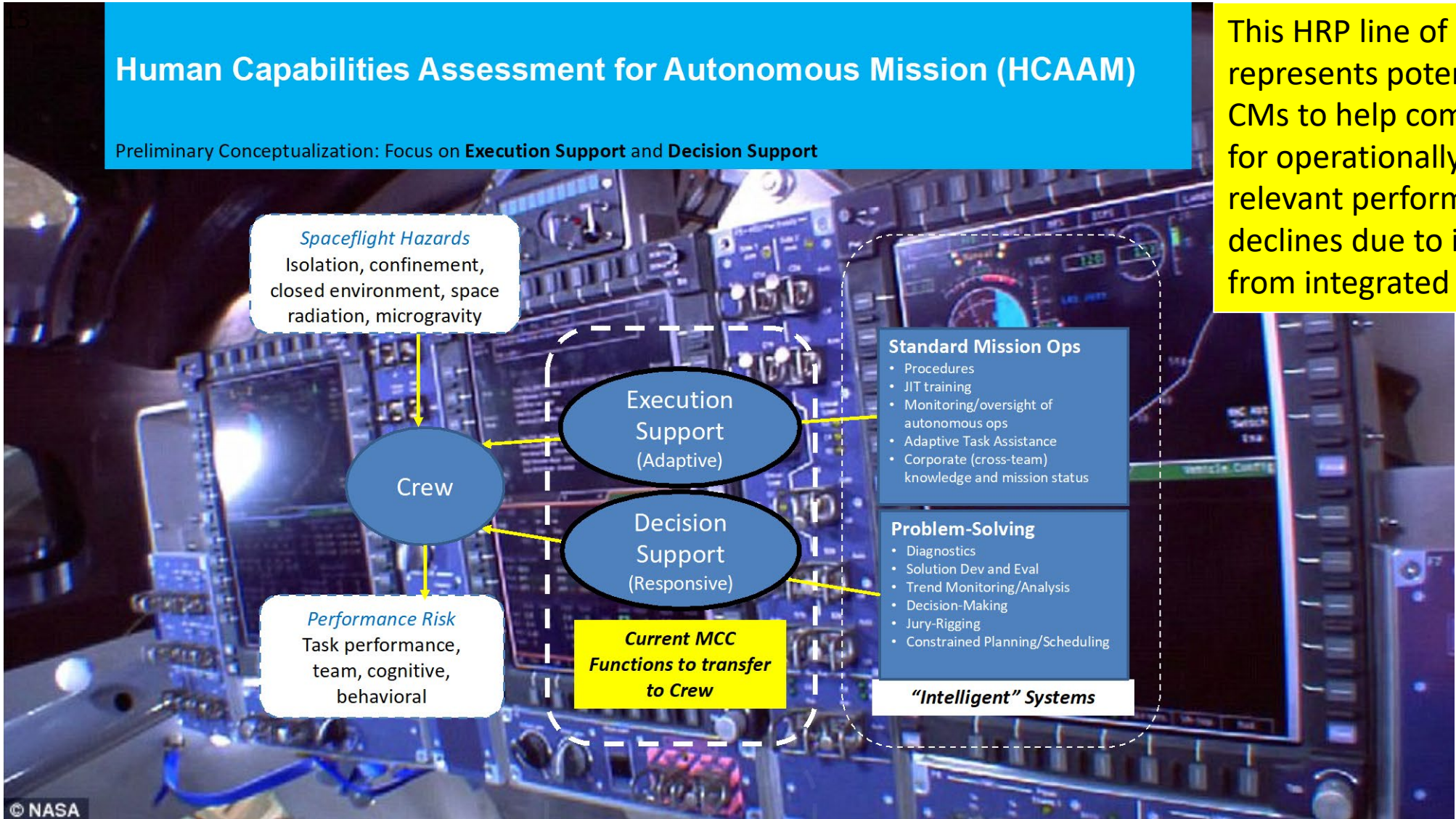




Monitoring Tools & Countermeasures Examples



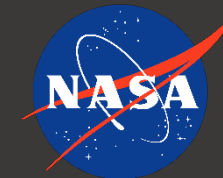
Research emphases: research areas and techniques



This HRP line of research represents potential CMs to help compensate for operationally—relevant performance declines due to impacts from integrated risks....



Research Integration Plan: CNS/Behavioral Medicine/Sensorimotor



Review, evaluate, integrate CBS research results

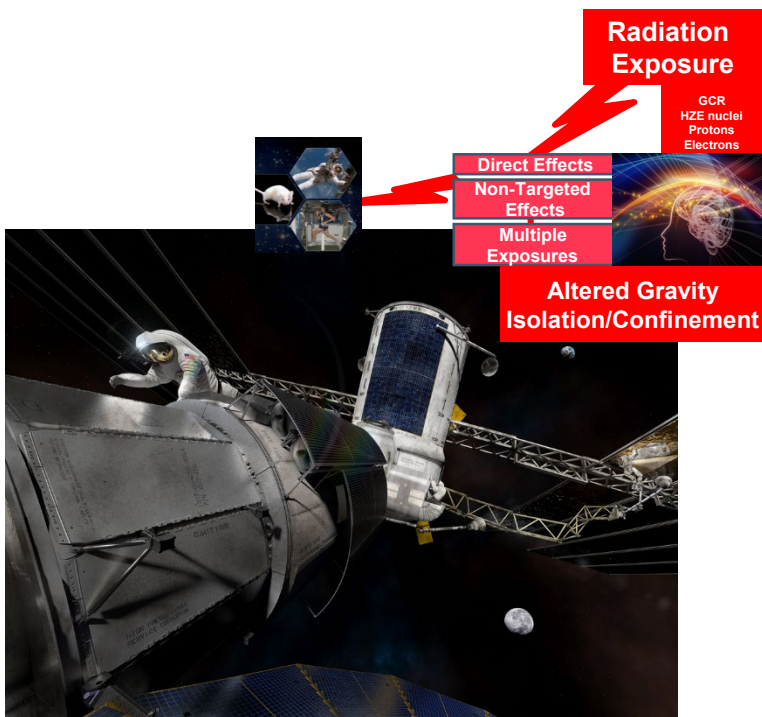
Identify/Review NASA Task Performance Standards

Datamining Efforts:

- Neurobehavioral biomarkers
- Non-human primates (historical findings)
- Brain Performance Pathways
- Biomarkers linked to Operational Performance
- Nutritional countermeasures/biomarker changes
- Translational models
- Standardize animal handling/facilities

Computational Models

- Biomarkers
- Structural/Functional Connectome
- Operationally-Relevant Performance decrements





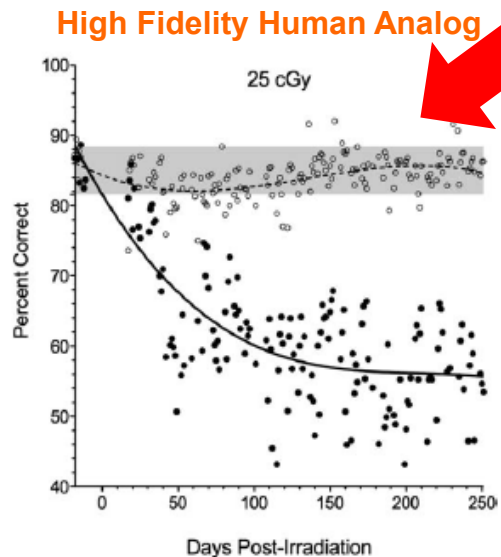
Behavior: Executive Function

Review of Spaceflight Induced Effects:

Acute CNS

Tests performed in Animal Models: Flexibility, Attention, Vigilance, Learning, Memory, Reaction Time

Psychomotor vigilance is impaired in rats after proton irradiation

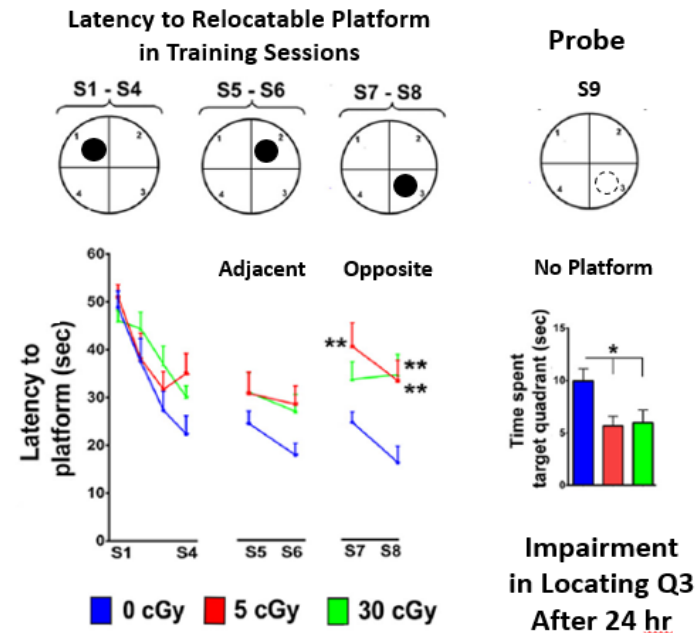


Estimated Mars Preparatory Mission = ~175-220 mGy = 17.5-22 cGy

Psychomotor Vigilance test

Davis et al. (2014)

Cognitive flexibility is impaired in mice 1 year after ⁴He ion exposure



Cognitive flexibility

Parihar et al. (2018)



The CBS “Problem”: BMed Risk

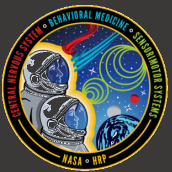


Review of Spaceflight Induced Effects:
BMed



“Every day, I was exposed to ten times the radiation of a person on Earth, which will increase my risk of fatal cancer for the rest of my life. **Not to mention the psychological stress, which is harder to quantify and perhaps just as damaging**” (emphasis added).

From, Scott Kelly’s memoir: “Endurance: My Year In Space and our Journey to Mars”



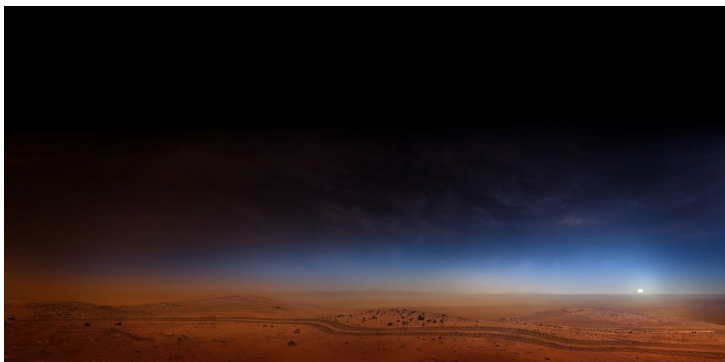
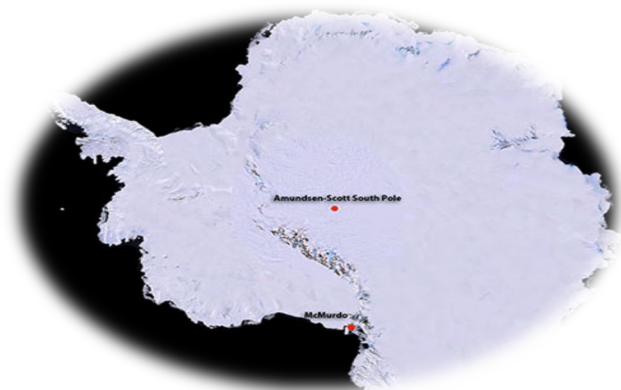
Effect of Exploration Stressors: Isolation and Confinement



Review of Spaceflight Induced Effects:
Brain Structure & Function

Analog Antarctic/South Pole

Hostile Environment



Analog Characteristics

Isolated/remote

- Moderate to High Autonomy
- Dim lighting

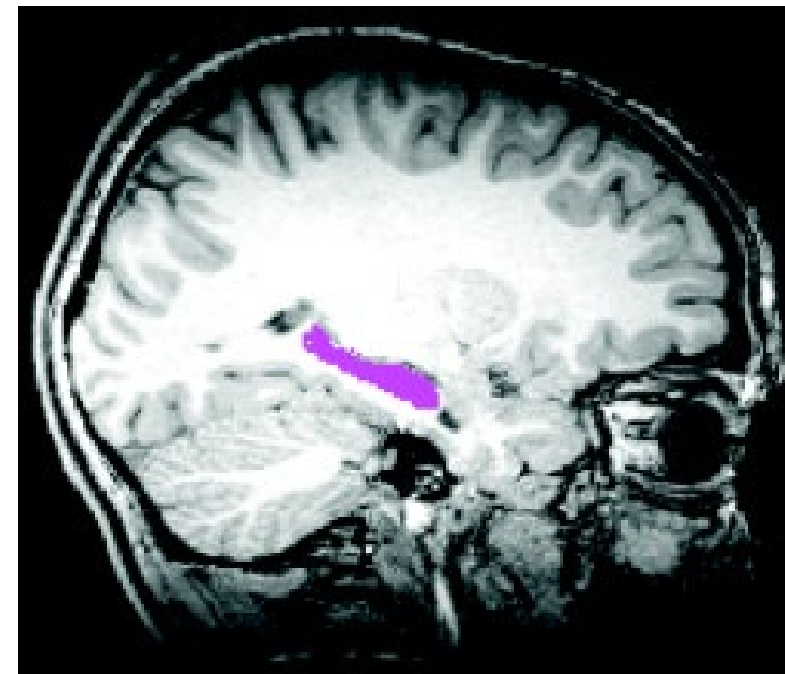
Confined

- Sensory deprivations
- Moderate to Crowding
- Limited personal space
- Team = ~40
- Defined roles

Extreme

- Moderate to Danger
- Sensory conditions
- Limited medevac

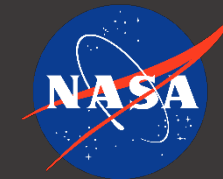
Brain Structure Changes



Neurostructural, Cognitive, and Physiological Changes During a 1-year Antarctic Winter-Over Mission (BMed 3)



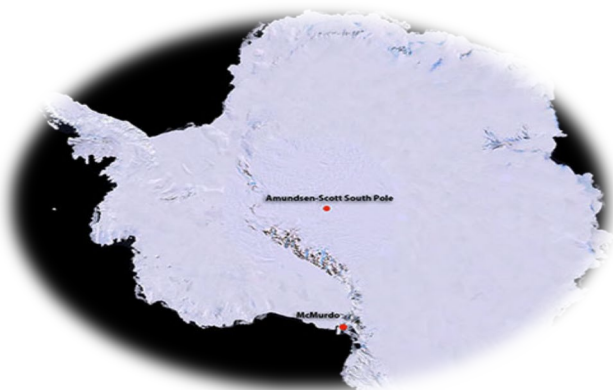
Effect of Exploration Stressors: Isolation and Confinement



Review of Spaceflight Induced Effects:
Brain Structure & Function

Analog Antarctic/South Pole

Hostile Environment



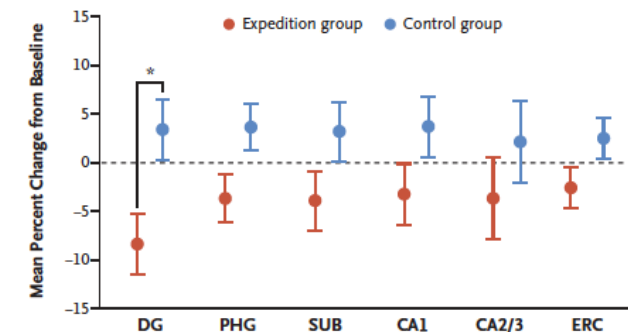
Nine polar expeditioners (five men and four women) who lived in Antarctica for 14 months at the German Neumayer III station.

Reductions in the hippocampal volume of the dentate gyrus (pre vs post expedition) than in the controls (7.2±3% reduction in volume).

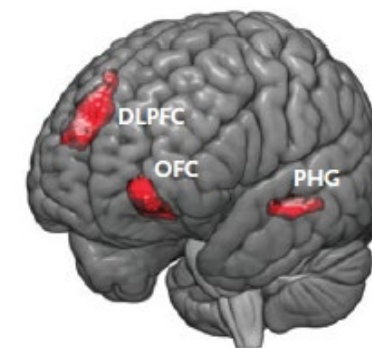
Lower gray-matter volume in the right dorsolateral prefrontal cortex (DLPFC), the left orbitofrontal cortex (OFC), and the left parahippocampal gyrus PHG in the expeditioners than in the controls.

Lower BDNF after first quarter.

A Mean Change in Brain Volume



Changes in Gray-Matter Volume



Decrease in expeditioners, family-wise error rate, P<0.05

Stahn et al. (2019)