UPDATE TO CBS INTEGRATED RESEARCH PLAN

HRP IWS 2020

January 29, 2020

T. J. Williams[1], A. P. Mulavara[2], A. Hanson[1], J. Roy Choudhury[3], K. George[2], and A. M. Whitmire[1].

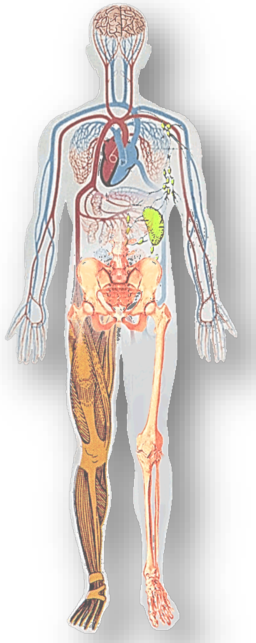
[1]NASA Johnson Space Center, Houston, TX, USA; [2]KBR, Houston, TX; [3]MEI Technology, Houston, TX;

Integrated Risks—Integrated Research Approach

Research Strategy

Balance Disorders
Fluid Shifts
Cardiovascular Deconditioning
Muscle Atrophy
Bone Loss

Acute In-flight effec
Long-term cance risk
CNS-Cognitiv



Integrated Research Plan:

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

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

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.

Synergistic Effects?

Research Strategy

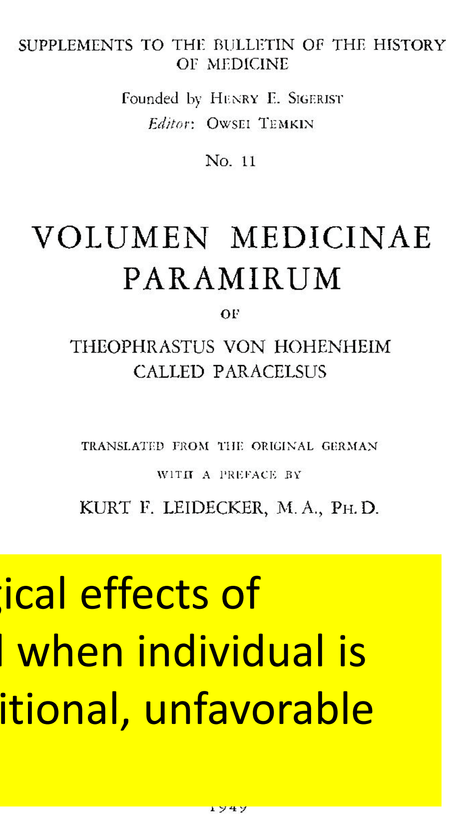
1. Each crewmember has a certain capacity to tolerate all three risks

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

<u>Null-hypothesis</u>: 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 PARACELSUS

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

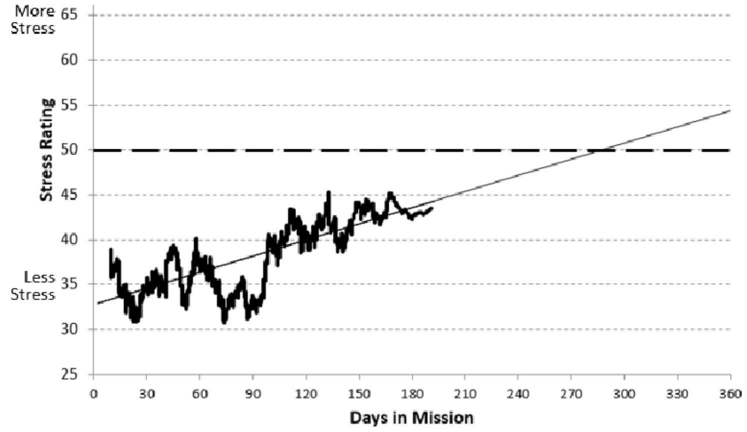
CBS Problem Statement: There is a risk that the spaceflight hazards of space radiation, altered gravity and isolation & confinement may synergistically interact; with the combined effects resulting in a significantly increased risk to operationally relevant crew health and performance

Effects of Spaceflight During and Post-landing

Review of Spaceflight Effects

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)

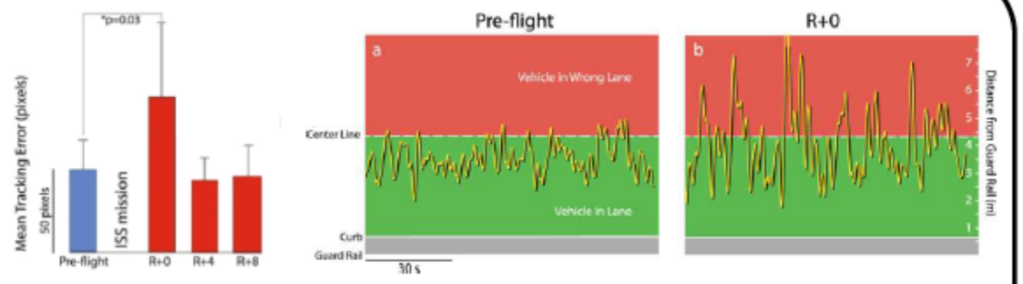


Figure A. Dual tasking and representative driving simulator results from astronauts on the day of return after an average of 171 days aboard the ISS, adapted from Moore. et al 2019.

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

Mission: 340 days aboard the ISS, n = 1

Reduced *Cognition* test battery performance post-flight

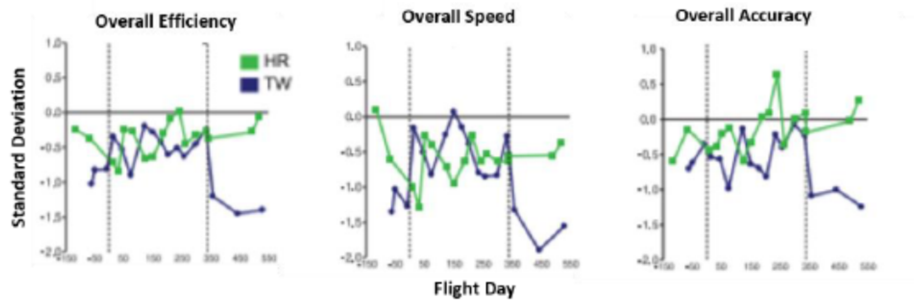


Figure B. COGNITION test battery results from the NASA Twins Study (Garrett-Bakelman et al. 2019). HR = ground subject, TW = spaceflight subject.

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

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

Review Evidence Base/ Data Mining:
What has our research to date demonstrated? Spaceflight Hazards: Space Radiation/Isolation & Confinement/Altered Gravity impacts on CNS/Bmed/SM

Shape Policy

Translational Models to Accelerate Knowledge Base of CBS Combinatorial Effect
Leverage modeling & research outcomes using biomarkers and determine performance/exposure relationships via Brain Performance Pathway: establish first POLs & PELs

Computational Modeling To heuristically determine biological effects that lead to Brain Performance Pathway Changes

Crew Health Standards POLs & PELs
Validate / Implement POLs/PELs & CMs

Countermeasures, Monitoring Tools
Determine individual sensitivities, biomarkers and countermeasures to mitigate risks

Bridge w/animal models & translation

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.

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

NASA

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/Rescilience 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)

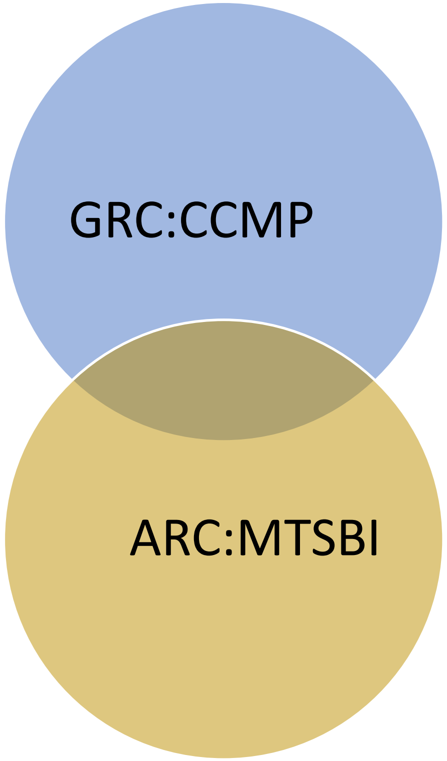
Data Mining Activity

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)

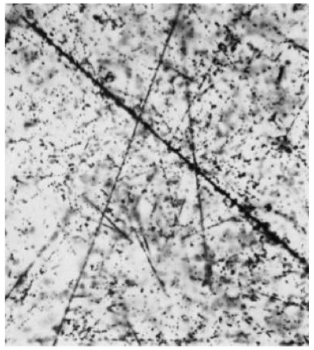
- Intra-agency strategic partnership between NASA and DTRA:
  - Provides SME support with background in neurobehavioral/ radiobiology to provide inputs on operationally relevant cognitive and behavioral performance, and continuity of performance following radiation exposure.
- Participation at 70th International 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 Jennfer 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

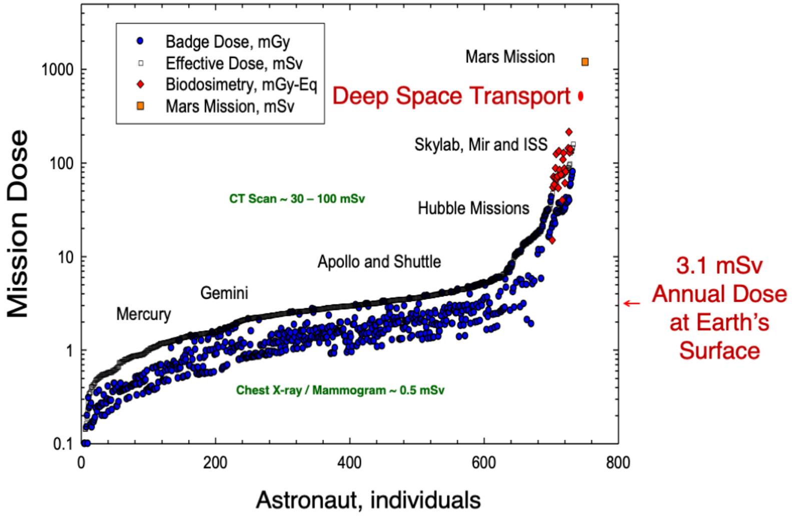
Galactic Cosmic Radiation (GCR)



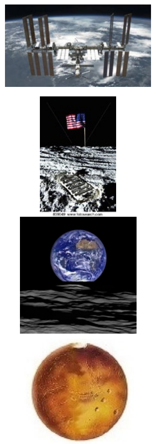
An illustration of the ambient radiation exposure in deep space as *a microscopic field of view of an Ilford G.5 nuclear emulsion* that was worn on the ankle of Neil Armstrong during the Apollo 11 lunar landing mission in July, 1969 (shown to the left).

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

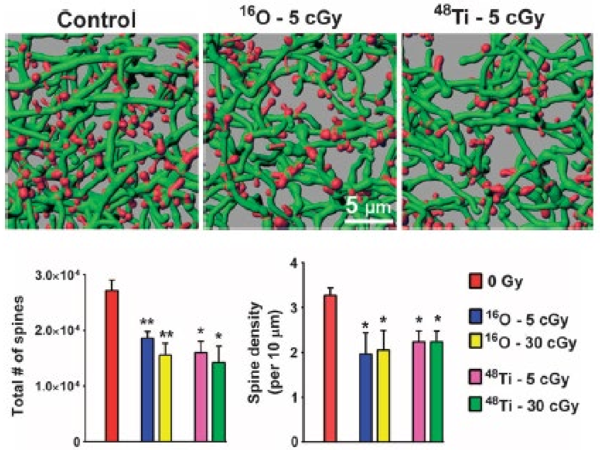
Artemis Lunar Surface, 6 months ~110-120 mGy

CNS Radiation Risk Supporting Evidence
Neurogenesis, Neuronal Structure, Inflammation

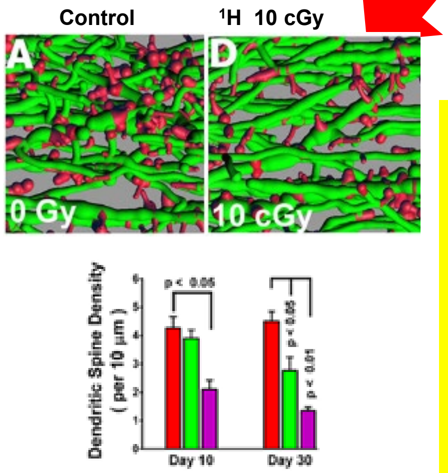
Review of Spaceflight Induced Effects: Acute CNS

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

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



Parihar et al. (2015a)

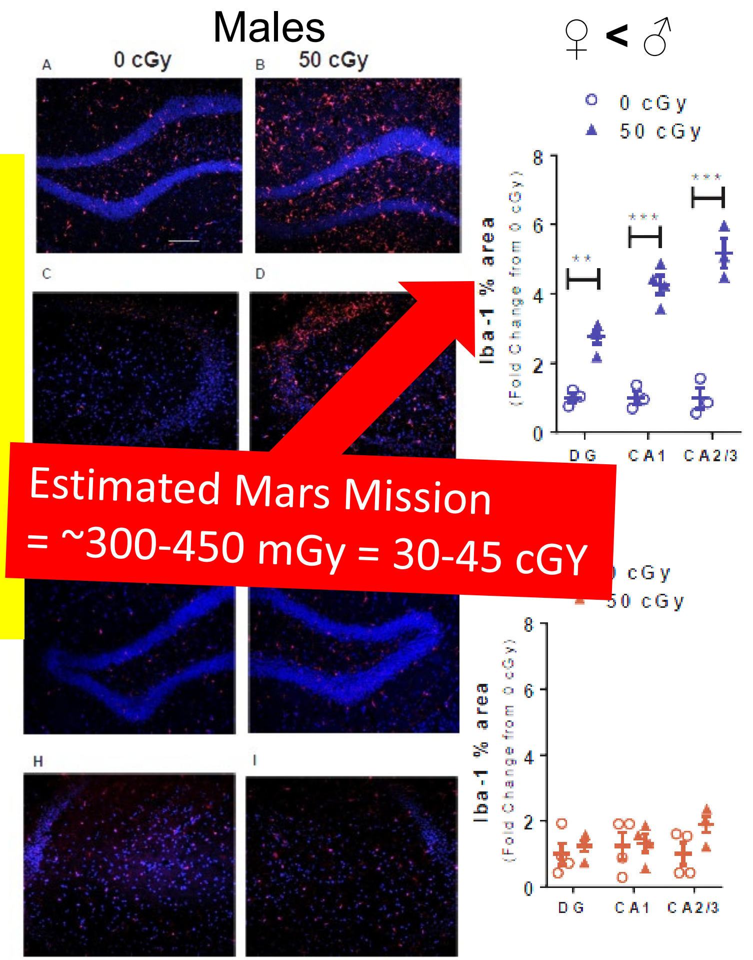


Parihar et al. (2015b)

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

Sensitivity of Inflammatory response: ♀ < ♂

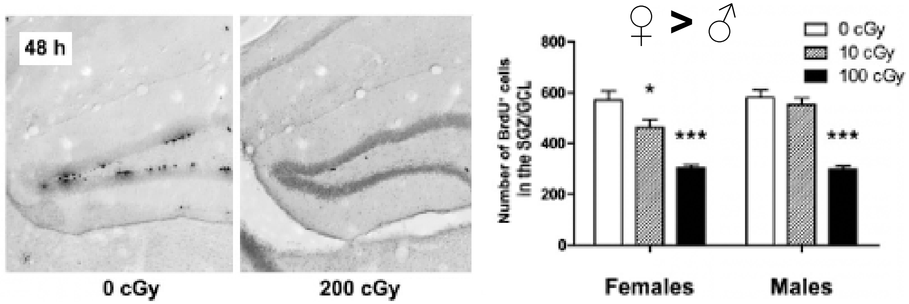
Sensitivity of Neurogenesis: ♀ > ♂



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

Krukowski et al. (2018)

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



Sweet et al. (2014)

The CBS “Problem”: Behavioral Medicine Risk

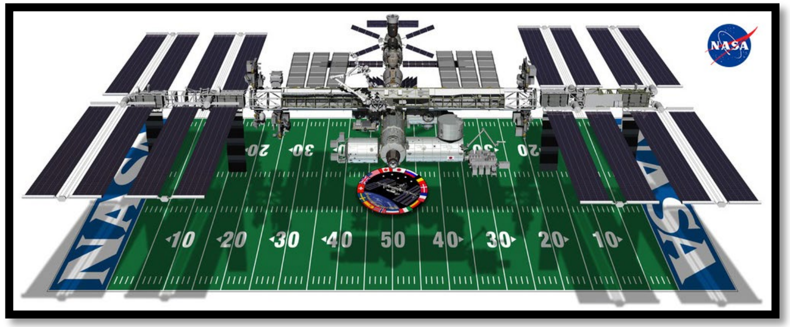
Review of Spaceflight Induced Effects: BMed

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 Ft^3)



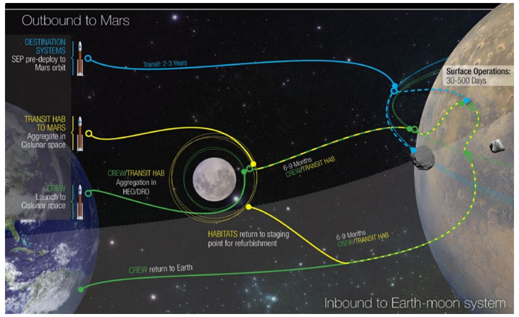
Exploration Class Missions

Deep Space

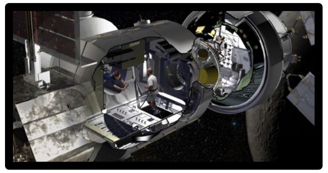
- Unprecedented duration and distance
- Limited volume in confinement and isolation
- Loss and delay of communications with ground
- More autonomous operations
- No re-supply
- No option for evacuation

Major Challenges

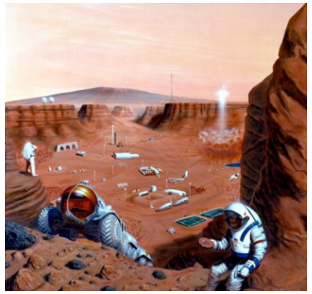
- Stress, conflict, mood & morale
- Sleep, fatigue, workload & circadian
- Selection and crew composition
- Psychosocial adaptation & training
- Meaningful work, motivation
- Growth and resiliency
- Family connectedness and communication
- Net habitable volume, sensory stimulation
- Earth out of view



Orion Capsule 316 Ft^3



Gateway Habitat 4415 Ft^3



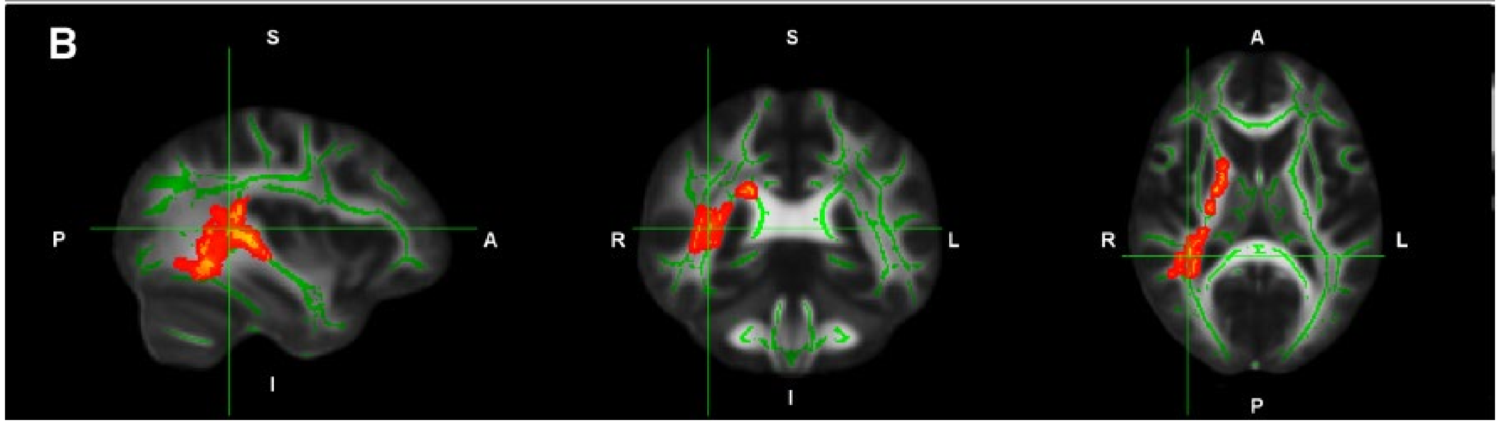
Simulating Exploration Stressors on Earth: 520 day Confinement in NEK, Russia

Isolation & Confinement Analogs

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



Brem et al. (2019)

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

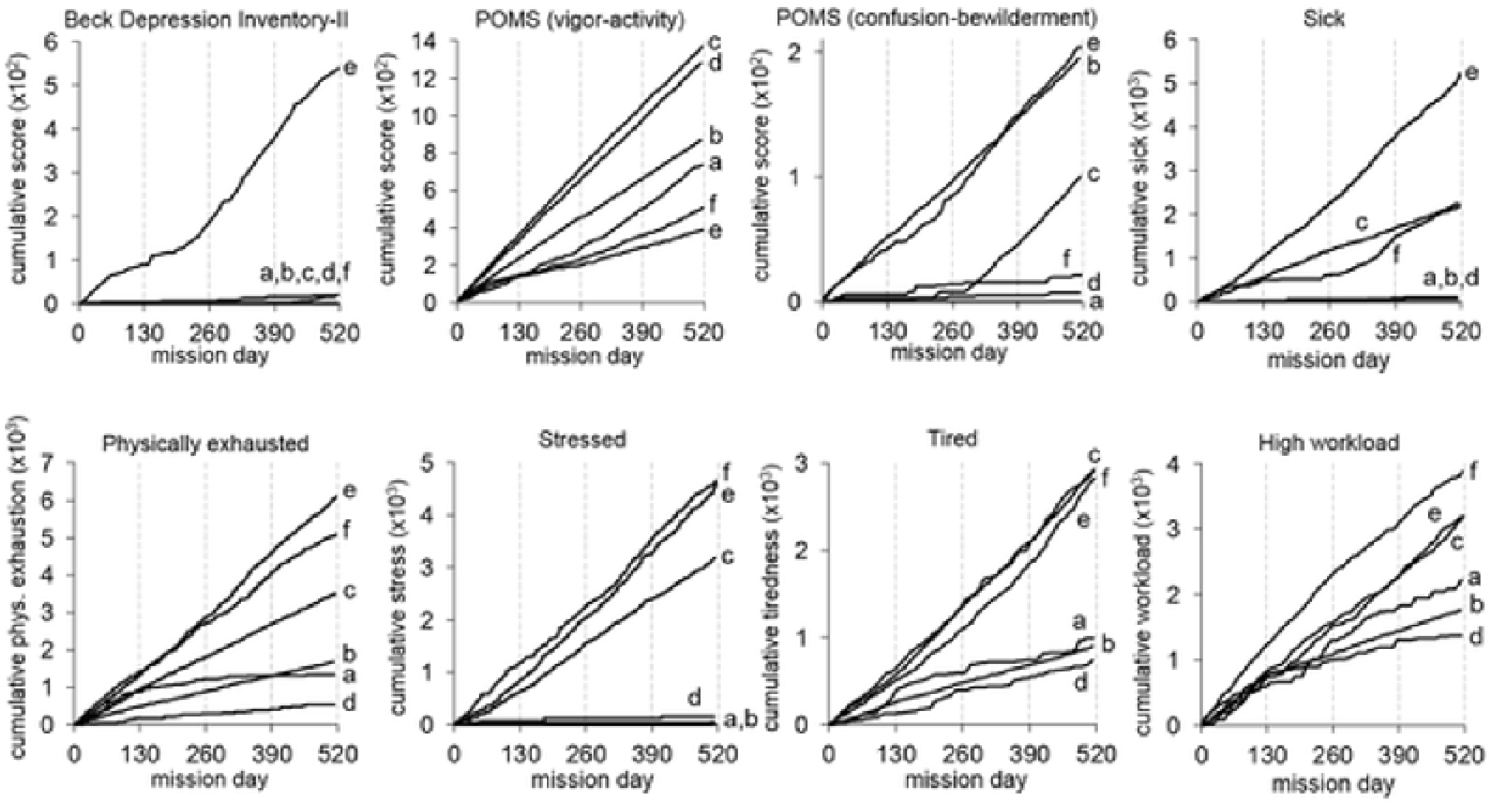
Isolation & Confinement Analogs

NEK, Russia

HERA, NASA JSC

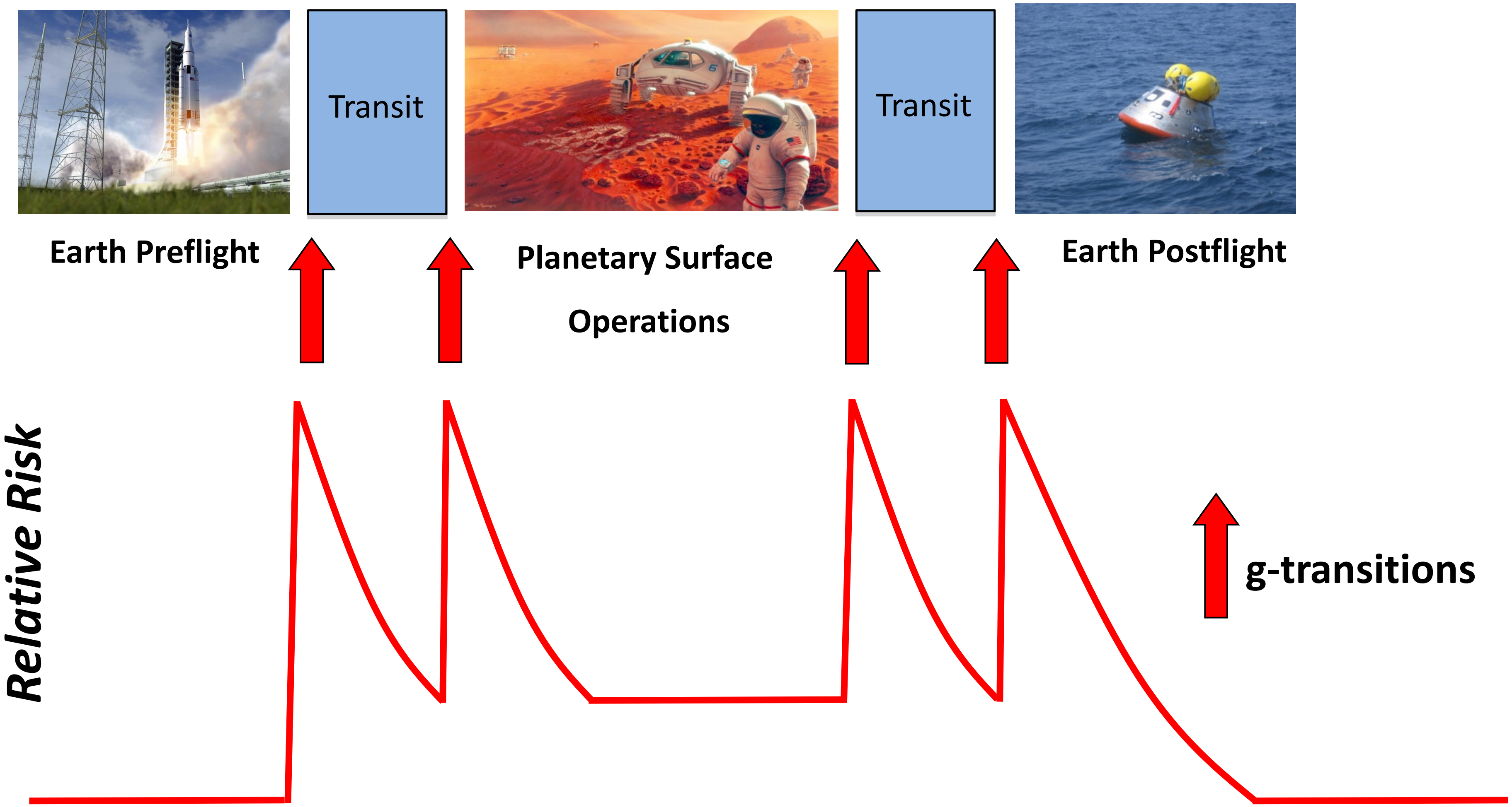
Significant individual variability

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



Basner et al. (2014)

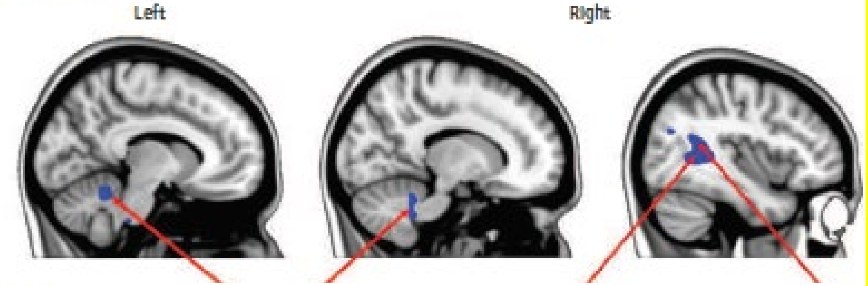
The CBS “Problem”: Sensorimotor Risk



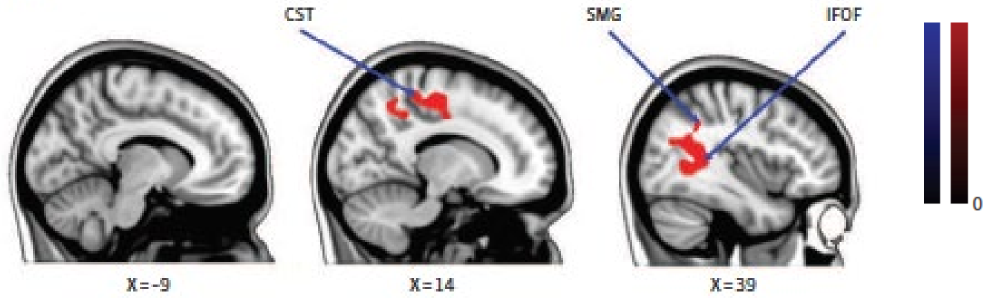
Review of Spaceflight Induced Effects: Brain Structure & Function

Spaceflight Associated Brain White Matter Microstructural Changes

A FA_T Decrease in Fractional Anisotropy (FA)



C RD_T Increase in Radial Diffusivity (RD)

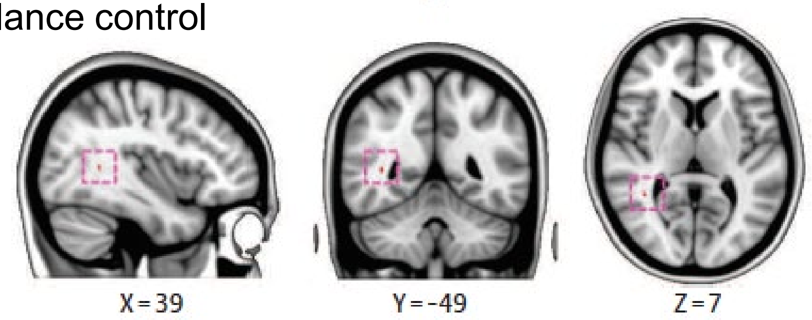


Areas: visuospatial processing, vestibular function, & movement control

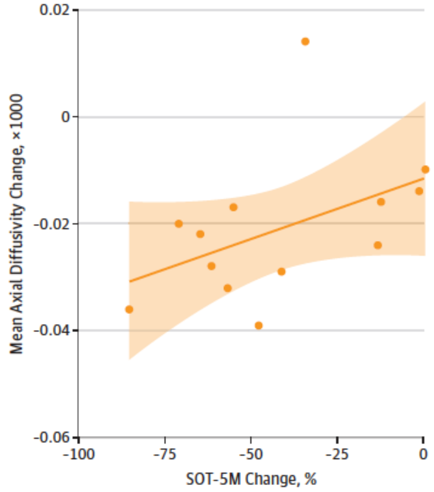
- Fractional anisotropy (FA): decrease, right superior and the inferior longitudinal fasciculi, inferior fronto-occipital faciculus, the corticospinal tract, the inferior and middle cerebellar peduncles.

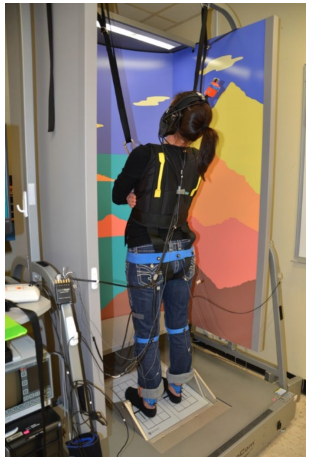
  Radial Diffusivity: increase, white matter structures underlying the precentral and postcentral gyrus, the supra marginal gyrus, and angular gyrus

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

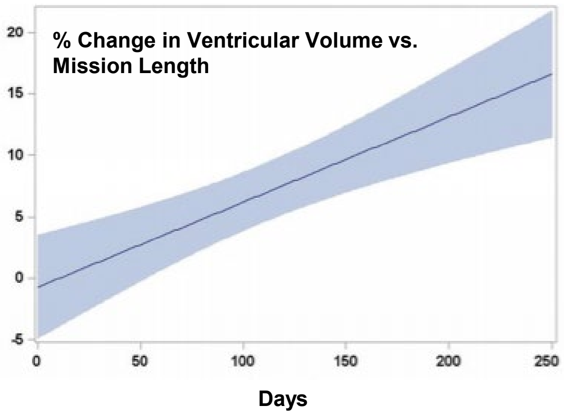
Review of Spaceflight Induced Effects: Brain Structure & Function

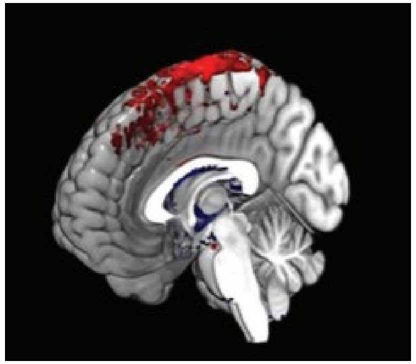
Macrostructural changes in included altered brain position, tissue crowding, CSF distribution, increased ventricular size, periventricular white matter hyperintensities (WMH), reduced gray matter volumes

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

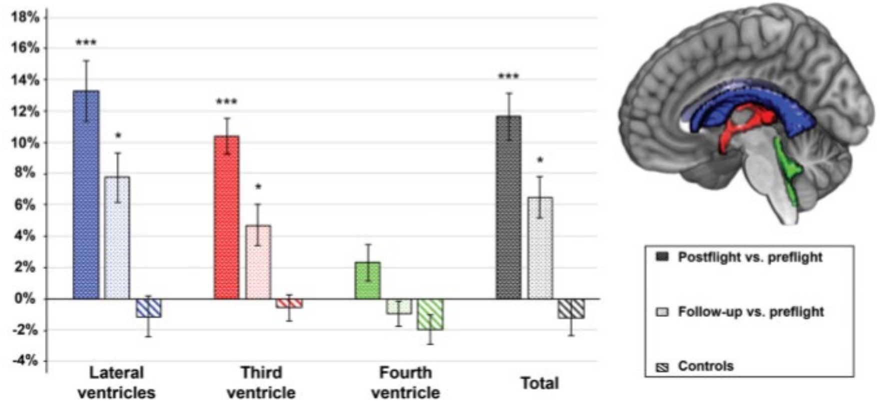
Post-Flight: Follow-up scans showed resolution of gray matter volume changes, with persistent ventricular volume increases and WMH. Global loss of white matter was noted from post-flight scan

Enlarged Ventricular System in US Crew
(Adapted from Roberts et al. 2017 and 2019)





Enlarged Ventricular System in Russian Cosmonauts
(From Ombergen et al. 2019)

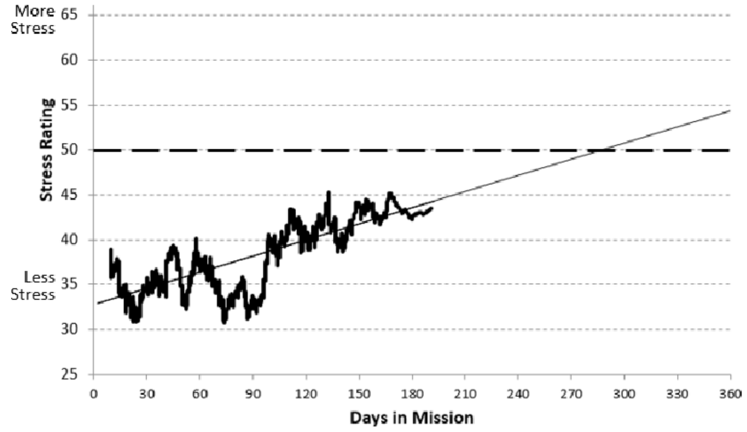


Effects of Spaceflight During and Post-landing

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)

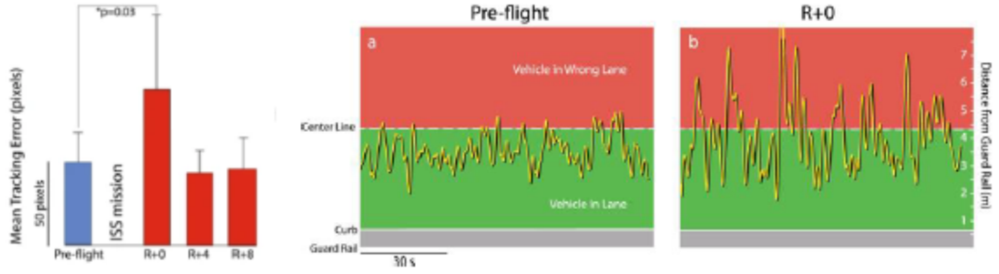


Figure A. Dual tasking and representative driving simulator results from astronauts on the day of return after an average of 171 days aboard the ISS, adapted from Moore. et al 2019.

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

Mission: 340 days aboard the ISS, n = 1

Reduced *Cognition* test battery performance post-flight

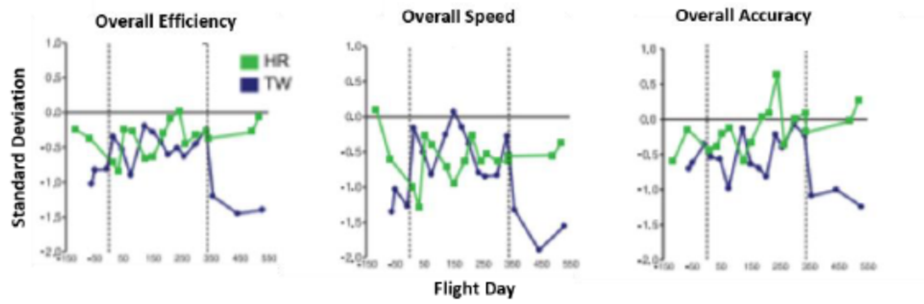


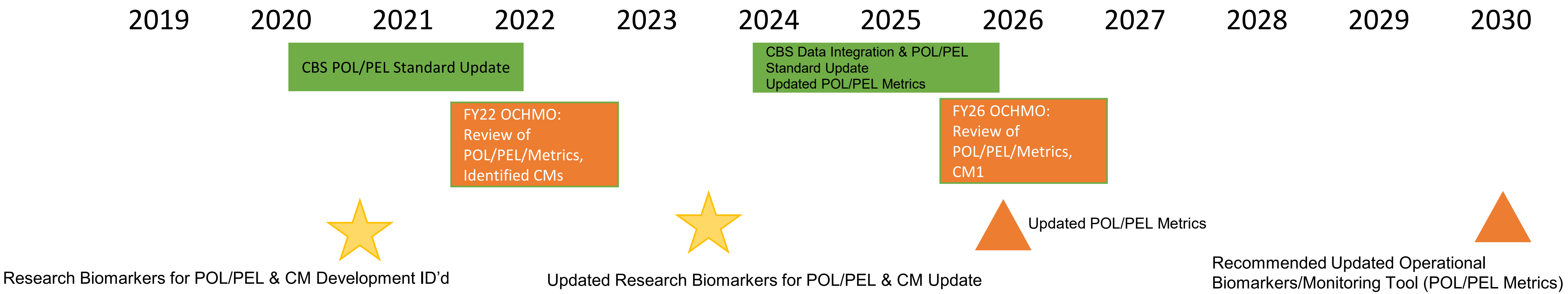
Figure B. COGNITION test battery results from the NASA Twins Study (Garrett-Bakelman et al. 2019). HR = ground subject, TW = spaceflight subject.

VNSCOR Kickoff meetings and standardization

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

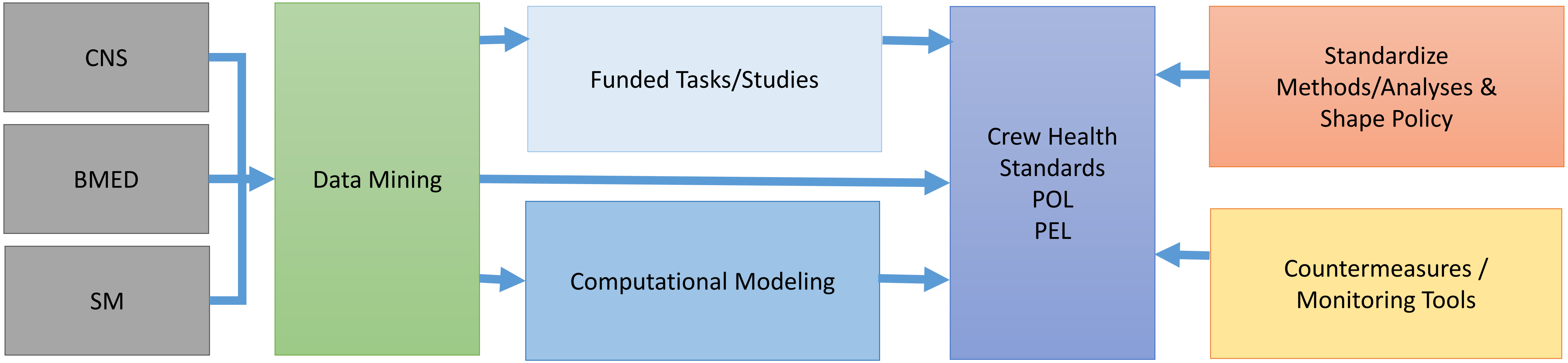
A multidisciplinary team was assembled into a four year VNSCOR project with multiple research arms to assess synergistic and order-effects of radiation exposure, isolation & confinement stress, and sensorimotor disruption (hindlimb unloading), on operationally-relevant brain performance pathways. The 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, NASA ARC.
- "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
FY22 OCHMO: Review of POL/PEL/Metrics, Identified CMs
CBS Data Integration & POL/PEL Standard Update
Updated POL/PEL Metrics
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)


CENTRAL NERVOUS SYSTEM
BEHAVIORAL MEDICINE
SENSORIMOTOR SYSTEMS
NASA
HRP

CBS Strategy Deconstructed



Review evidence base from 3 Risks to determine state of collective knowledge.

Perform Data Mining on identified integrated knowledge gaps, to guide forward work.

Emphasis on operationally relevant performance outcomes, brain pathways, and biomarkers.

Fund new work to accelerate knowledge base of integrated Risk. Focus on dose rate effects from GCR/AG/ICE, identification of Biomarkers via brain performance pathways associated with operationally relevant performance.

Initiate Computational Modeling as a tool for iterative prediction and validation of research results; predicting performance decrements to aid in deployment of preventative measures and implementation of countermeasures.

Update respective CNS, BMED, and SM Standards as required and establish new CBS POLs/PELs by 2024.

Establish policy to accelerate translational research with Best Translational models and measures and optimize utilization of valuable tissues/data sets.

Develop integrated countermeasures to improve performance that will enable crew to stay within newly established CBS POLs/PELs.

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

Risks → / **Gaps**

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

Summary of Evidence - Brain Changes

Review of Spaceflight Induced Effects: Brain Structure & Function

- 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

Review of Spaceflight Induced Effects: BMed

- 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

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

- 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 Fasiculus (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_T decreases in the SLF[32] Predicted: Visuospatial cognitive dysfunction (searching, shifting spatial attention, performing mental rotations, detecting patterns)
Inferior Longitudinal Fasiculus[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 Fasiculus[32]	Connects frontal and occipital/temporal lobes. Hypothesized r… and cognition (non-dominant), goal-oriented behavior, social c…		
R. posterior thalamic radiations[33]	Posterior radiations connect thalamus and occipital cortex, co…		
Calcarine, middle occipital, inferior occipital gyri[33]	Location of the primary visual cortex and secondary visual ass…		
Right fusiform gyrus[33]	Facial and word recognition, within-category identification		
Inferior cerebellar peduncle[32]	Connects the cerebellum to the spinal cord and medulla. Carri… vestibular receptors (afferent and efferent) to help with postu… coordination.		
Middle cerebellar peduncle[32]	Afferent pathway from pons to cerebellum. Controls the initia… timing of volitional motor activity		
Corticospinal Tract[32]	Efferent motor information from the cerebral cortex to the bo…		
White matter underlying primary motor and sensory cortices[32]	Afferent and efferent motor and sensory information, sensory…		
Inferior and posterior parietal lobe[32]	Body spatial representation, central vestibular and propriocep… vertical upright perception		…runk and
Thalamus[33]	Relays information between cortex and subcortical areas.		…l, directed
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

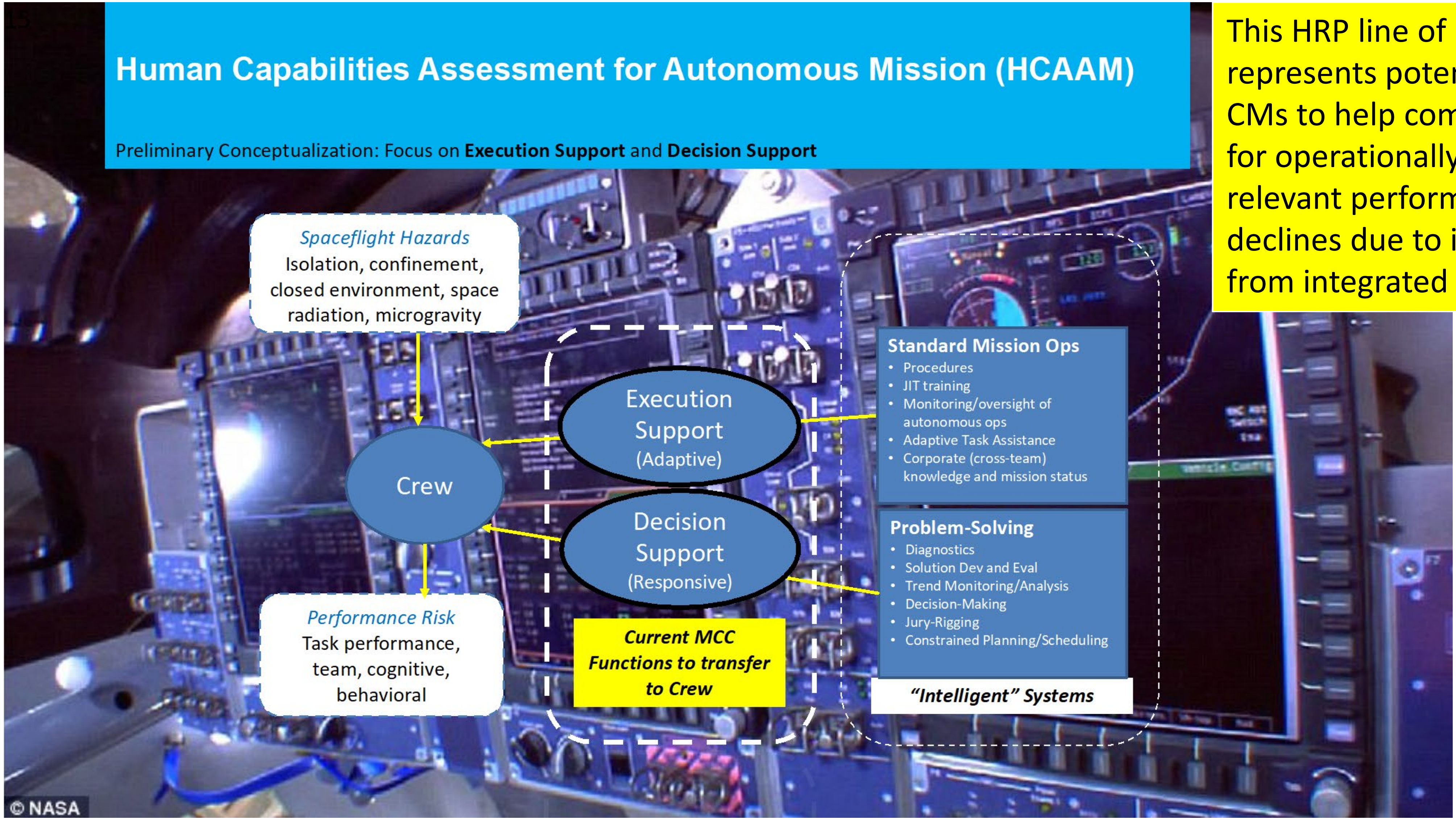
Contributions

- 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

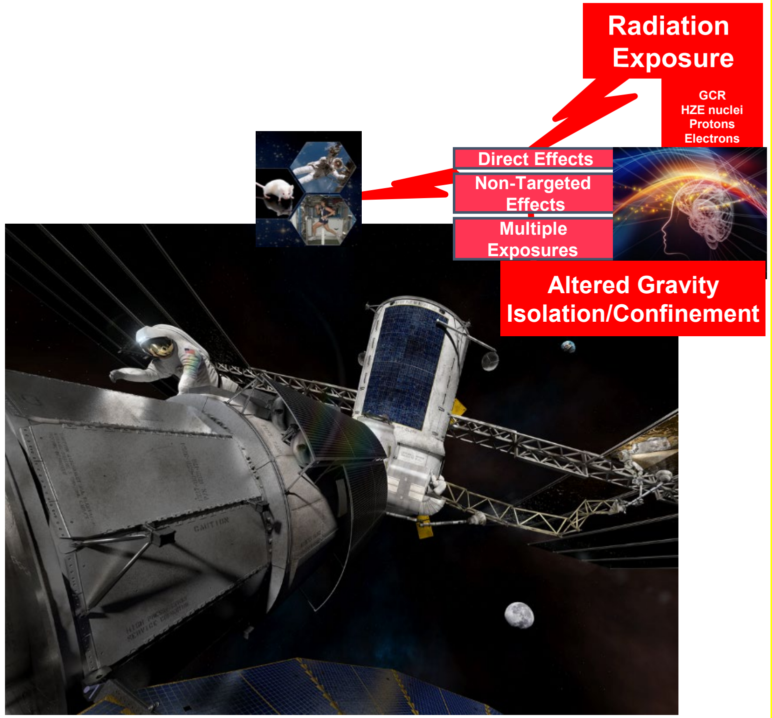
Research emphases: research areas and techniques



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**

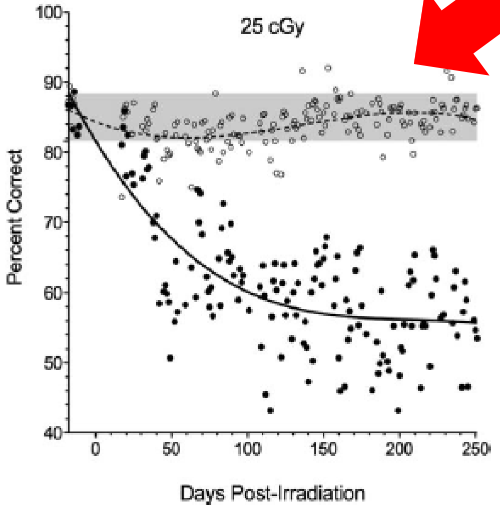
Review of Spaceflight Induced Effects: Acute CNS

Behavior: Executive Function

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

Psychomotor vigilance is impaired in rats after proton irradiation

High Fidelity Human Analog

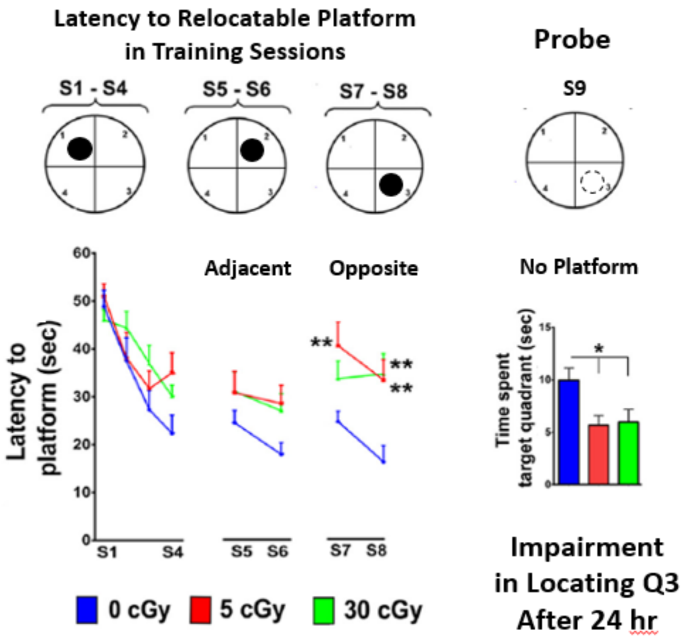


Estimated Mars Preparatory Mission
= ~175-220 mGy
= 17.5-22 cGY

Psychomotor Vigilance test

Davis et al. (2014)

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



Cognitive flexibility

Parihar et al. (2018)

The CBS “Problem”: BMed Risk

“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).**

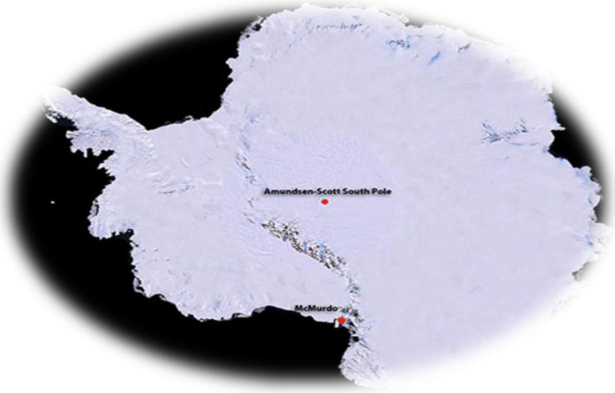
From, Scott Kelly’s memoir: “Endurance: My Year In Space and our Journey to Mars”

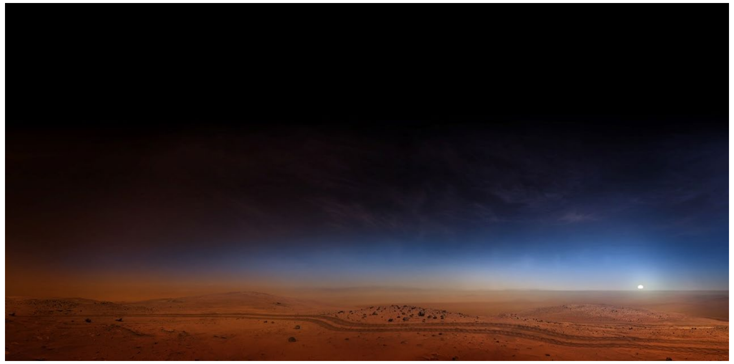
Effect of Exploration Stressors: Isolation and Confinement

Review of Spaceflight Induced Effects:
Brain Structure & Function

Analog Antarctic/South Pole

Hostile Environment





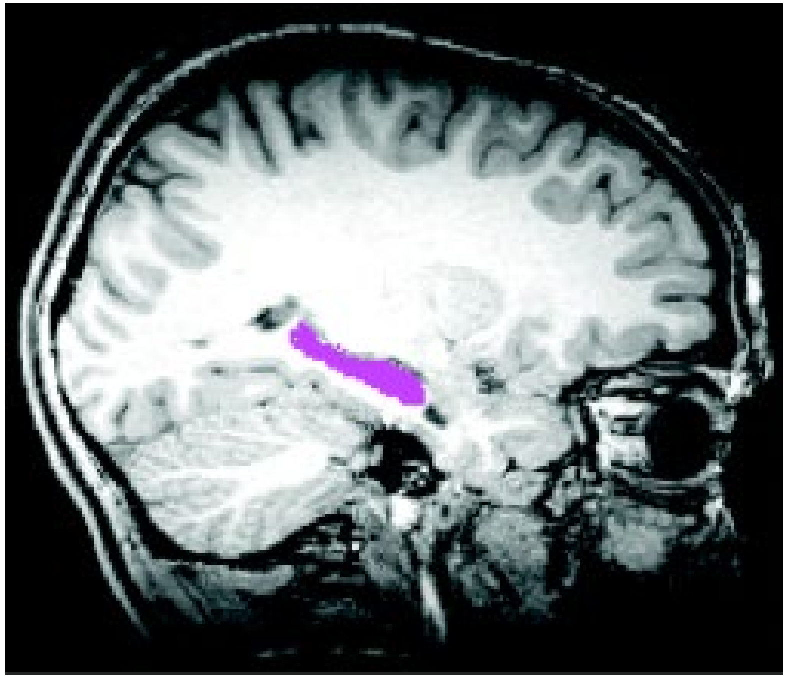
Analog Characteristics

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)

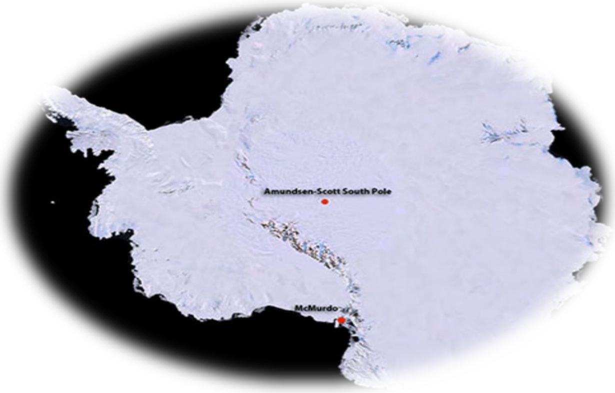
Basner et al. (2016)

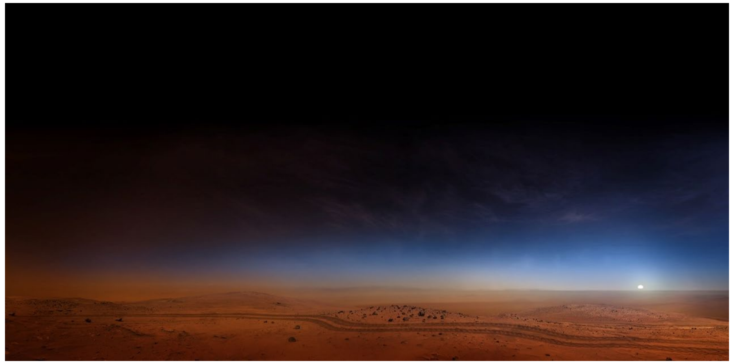
Effect of Exploration Stressors: Isolation and Confinement

Review of Spaceflight Induced Effects:
Brain Structure & Function

Analog Antarctic/South Pole

Hostile Environment



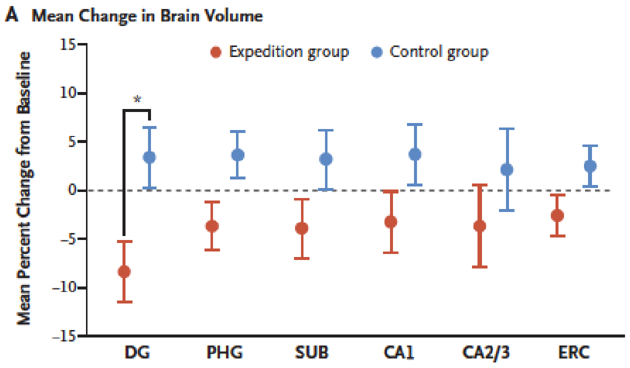


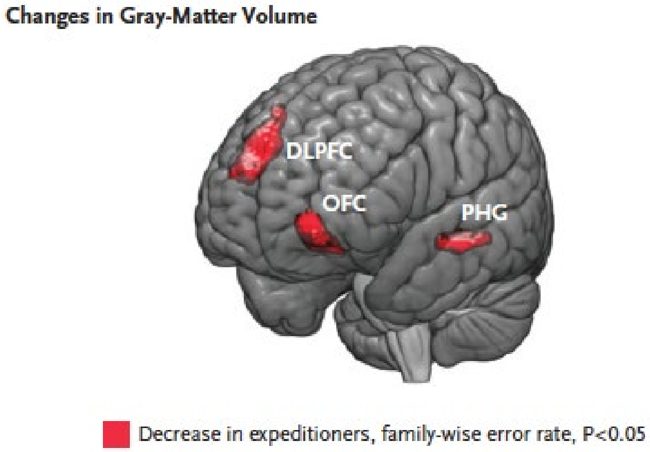
Nine polar expeditioners (five men and four women) who lived in Antarctica for 14 months at the German Neumayer III station.

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.





Stahn et al. (2019)