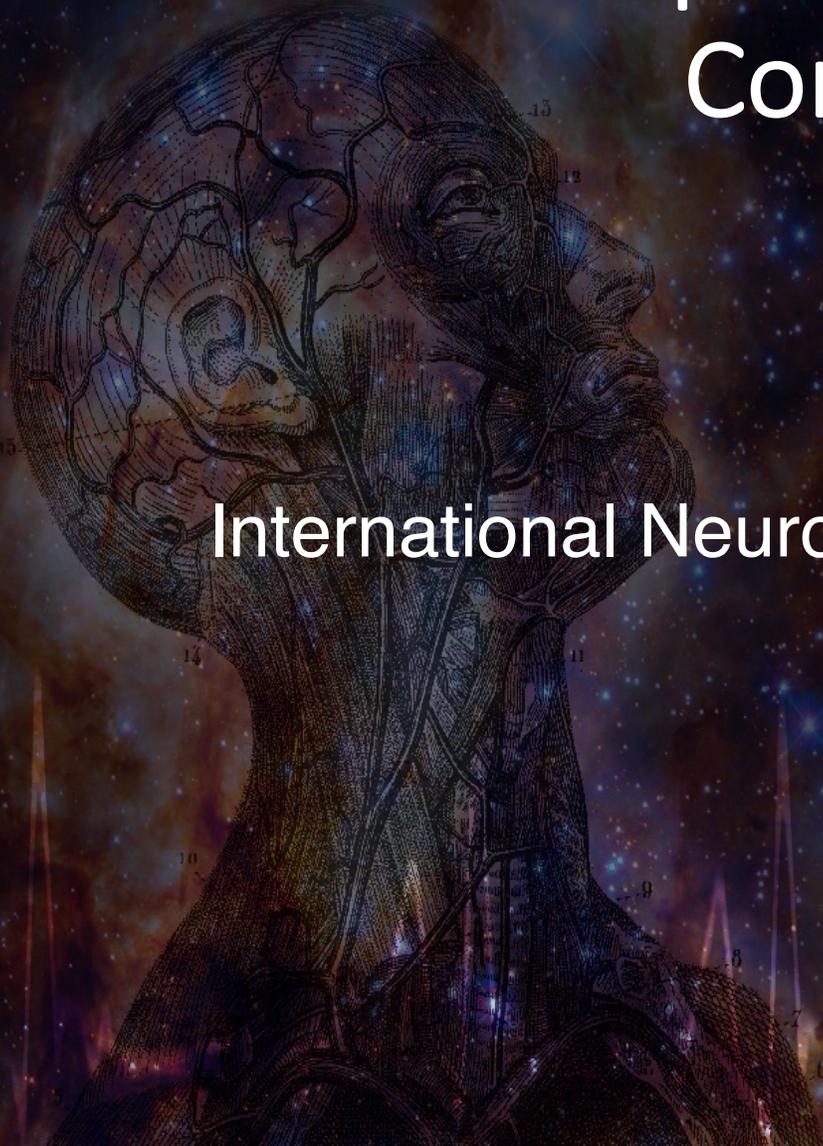




# The Brain in Space: Implications for Human Explorations of Mars and Human Conditions on Earth

International Neuropsychological Society Annual Meeting  
February 5, 2021

Ajitkumar Mulavara, Ph.D.





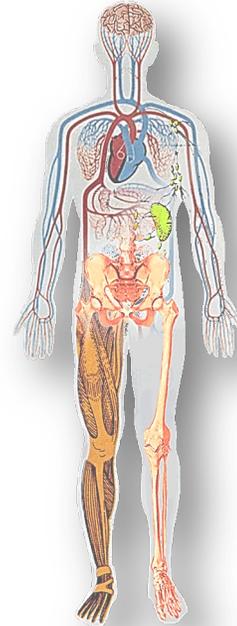
# Introduction



Balance Disorders  
Fluid Shifts  
Cardiovascular  
Deconditioning  
Muscle Atrophy  
Bone Loss



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



## 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



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

Spaceflight hazards **GUIDE** the Risk Management process, help to **PRIORITIZE** research tasks, and **FOCUS** our operational implementation of monitoring tools and countermeasures.

Introduction to CBS



# The CBS “Problem”: Acute Effects on CNS from Radiation Exposure

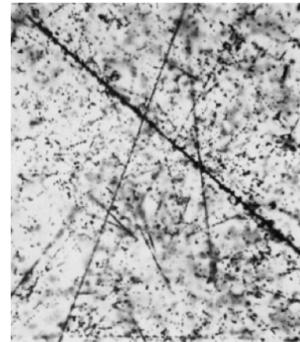


Review of Spaceflight Induced Effects:  
Acute CNS

## Space Radiation Exposure



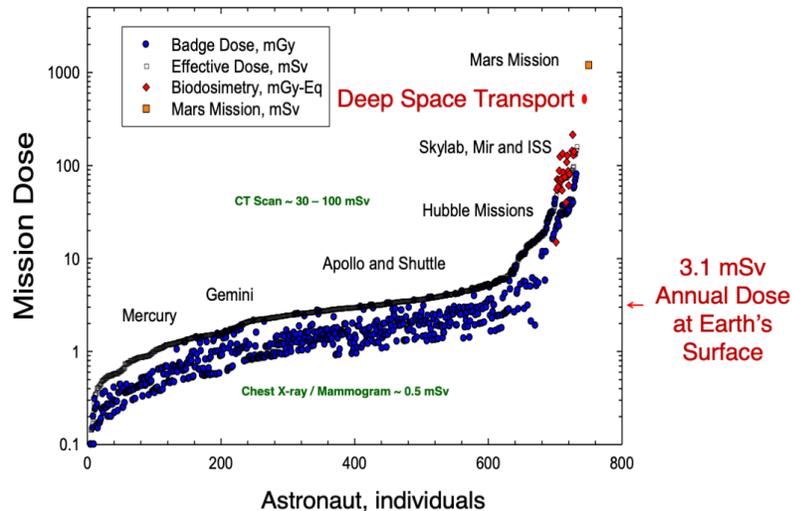
Galactic Cosmic Radiation (GCR)



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

2016 projected exposures as presented to the NASA HSRB, Aug 22, 2019

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



# CNS Radiation Risk Supporting Evidence

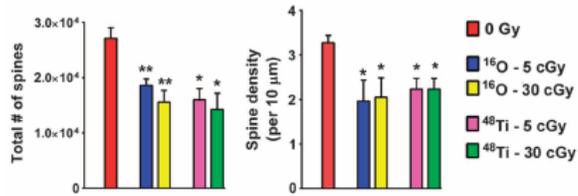
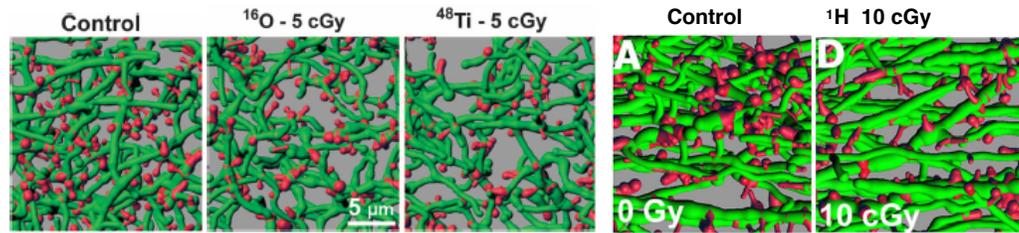
## Neurogenesis, Neuronal Structure, Inflammation



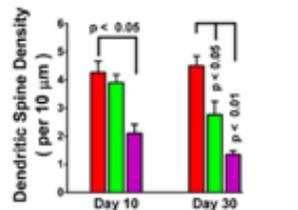
Review of Spaceflight Induced Effects:

Acute CNS

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

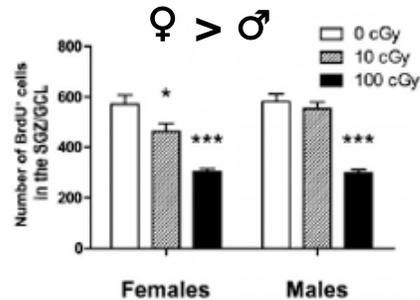
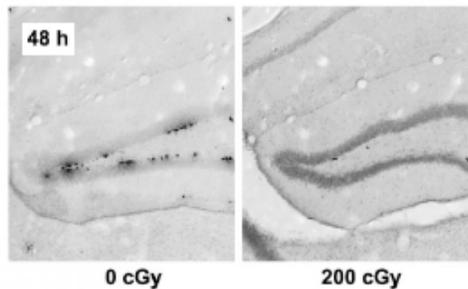


Parihar et al. (2015a)



Parihar et al. (2015b)

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

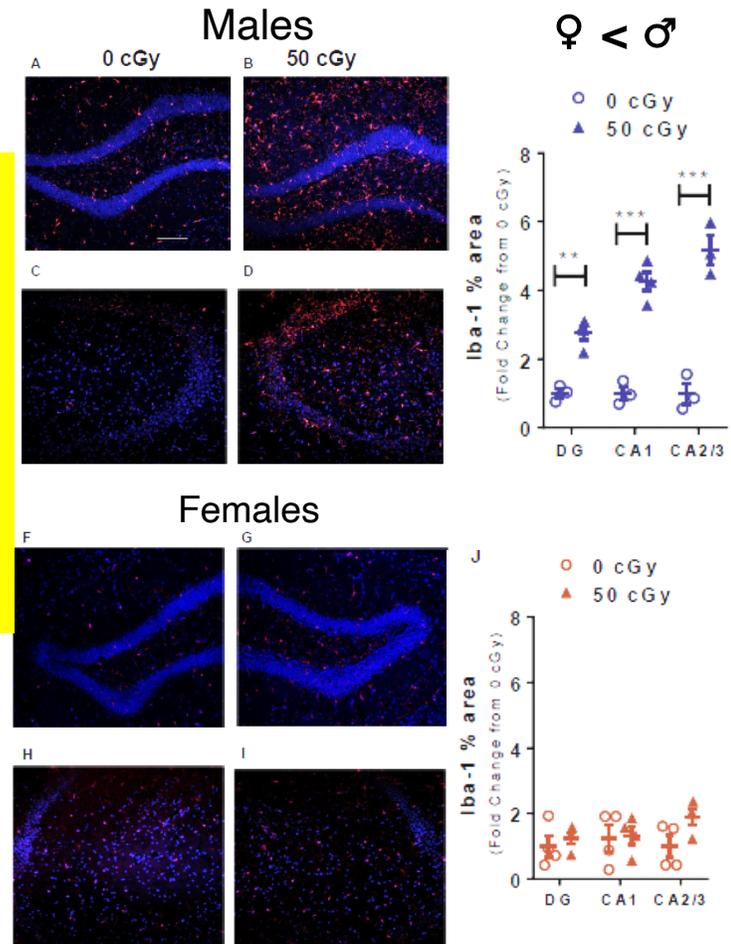


Sweet et al. (2014)

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

Sensitivity of Inflammatory response: ♀ < ♂

Sensitivity of Neurogenesis: ♀ > ♂



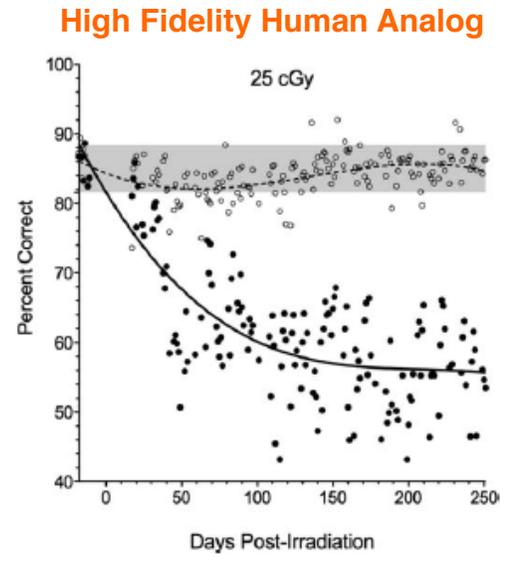
Krukowski et al. (2018)



# Behavior: Executive Function

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

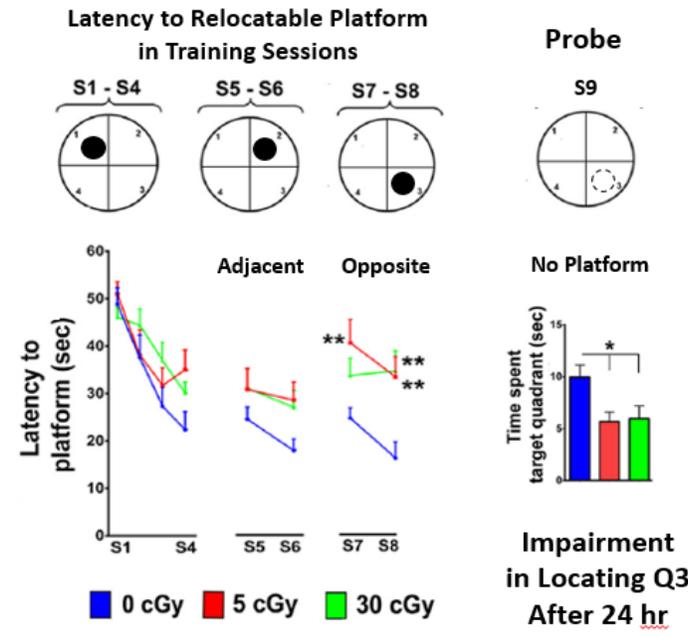
Psychomotor vigilance is impaired in rats after proton irradiation



Psychomotor Vigilance test

Davis et al. (2014)

Cognitive flexibility is impaired in mice 1 year after <sup>4</sup>He ion exposure



Cognitive flexibility

Parihar et al. (2018)

Review of Spaceflight Induced Effects:  
Acute CNS



# Summary of Evidence Supporting CNS Risk



- 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



# 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”



# The CBS "Problem": BMed 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<sup>3</sup>)



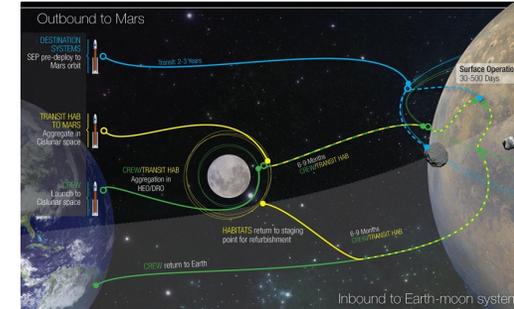
## Exploration Class Missions

### 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<sup>3</sup>



Gateway Habitat  
4415 Ft<sup>3</sup>





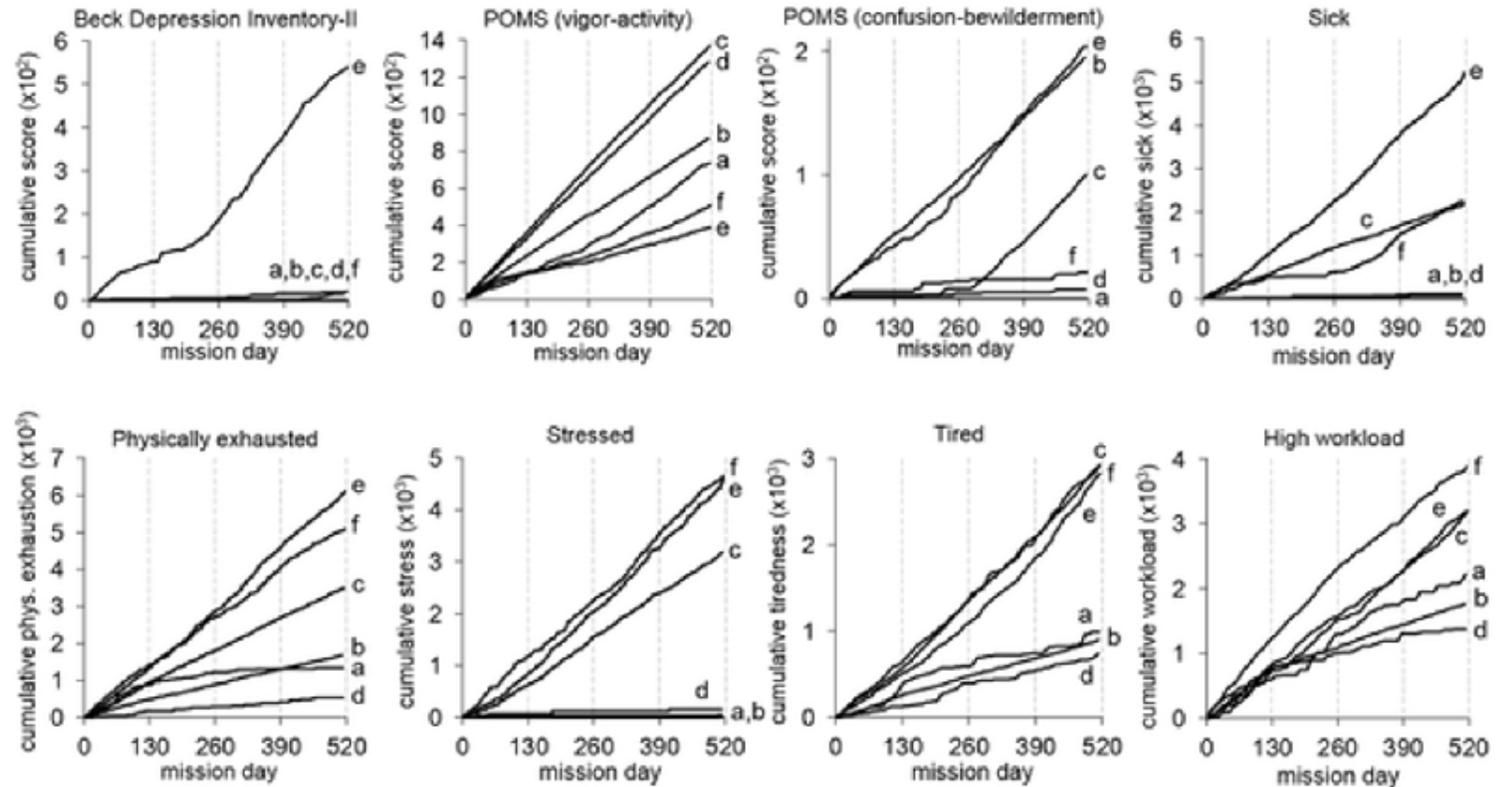
# Simulating Exploration Stressors on Earth: 520 day Confinement in NEK, Russia



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





# Stress During 6 Month Missions



There is also link between elevated stress biomarkers and immune system dysfunction in space flight, such as reactivation of latent viruses, increased production of inflammatory cytokines, and alterations of salivary antimicrobial proteins (Agha et al., 2020; Buchheim et al., 2019; Mehta et al., 2014; Stowe et al., 2001; Stowe et al., 2011).

In a study of n=21 on the ISS, completed visual analog scales twice a day every four days. Stress ratings were highest in the 4th quarter in-flight compared to the 1st ( $p=0.0037$ ) and 2nd quarters in-flight ( $p=0.0038$ ). Analyses within individual astronauts revealed that n=10 (48%) had significant positive correlations between stress ratings and time in-flight (Dinges et al., 2017).





# Stress Sensitizes the Neuroinflammatory Response in Ventral Mesencephalon



Review of Spaceflight Induced Effects:

BMed

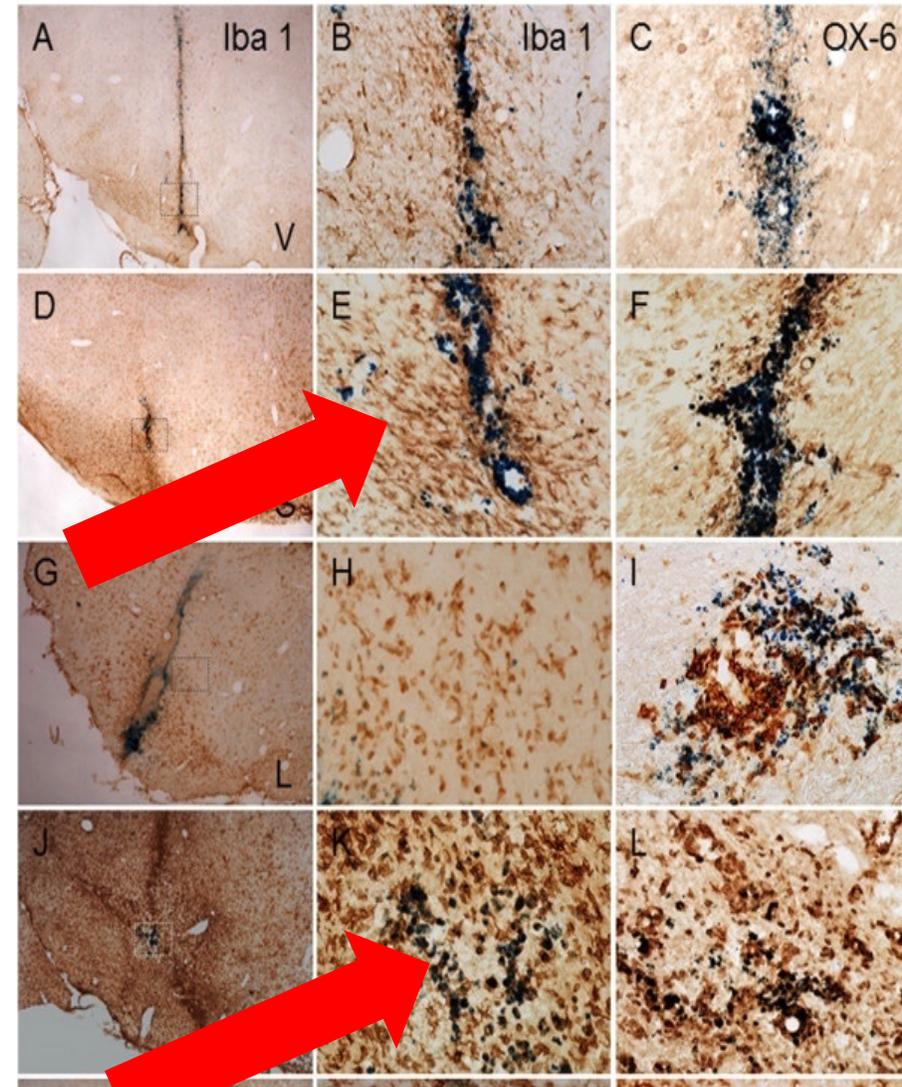
Microglial activation in the ventral mesencephalon of rats

Ventral mesencephalon (midbrain) :  
-efficient motor performance  
-reward signaling

Table 1 Schedule of stressors used during the chronic variate stress treatment<sup>a</sup>

Day	Stressor	Time
1	Forced swimming	10 min
2	Restraint	3 h
3	Water deprivation	24 h
4	Restrain at 4°C	90 min
5	Isolation	24 h
6	Food deprivation	24 h
7	Water deprivation	24 h
8	Restrain at 4°C	2 h
9	Food deprivation	24 h

LPS = lipopolysaccharide (a potent pro-inflammogen)



Non-stressed

stressed

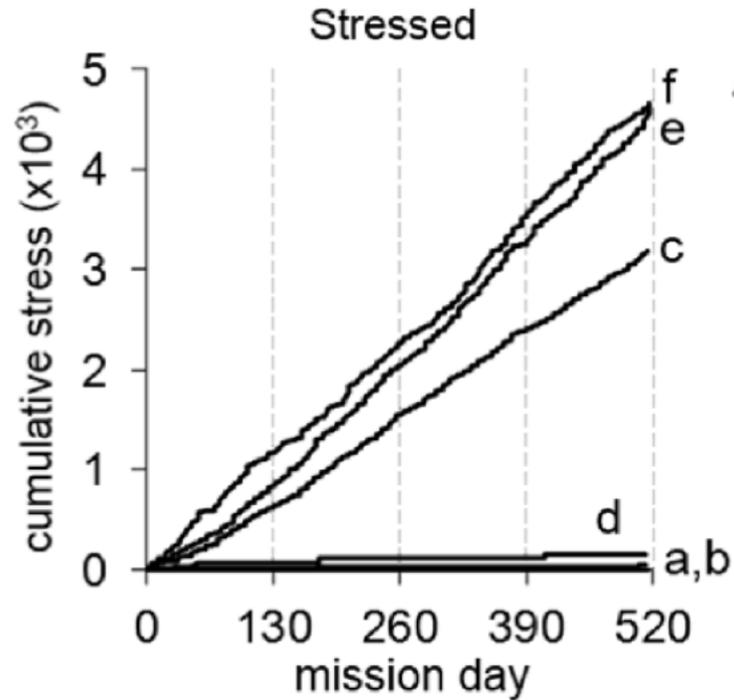
LPS-injected

Stressed  
LPS-injected



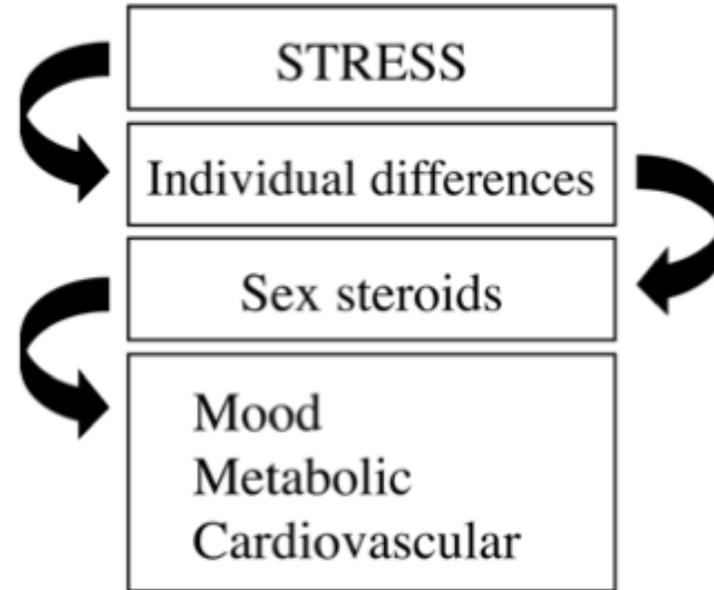
# Individual Differences in Stress Response

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



Basner et al., (2014)

Factors Affecting Individual Differences in Response to Repeated Exposure to Stress



Radley et al., (2015)

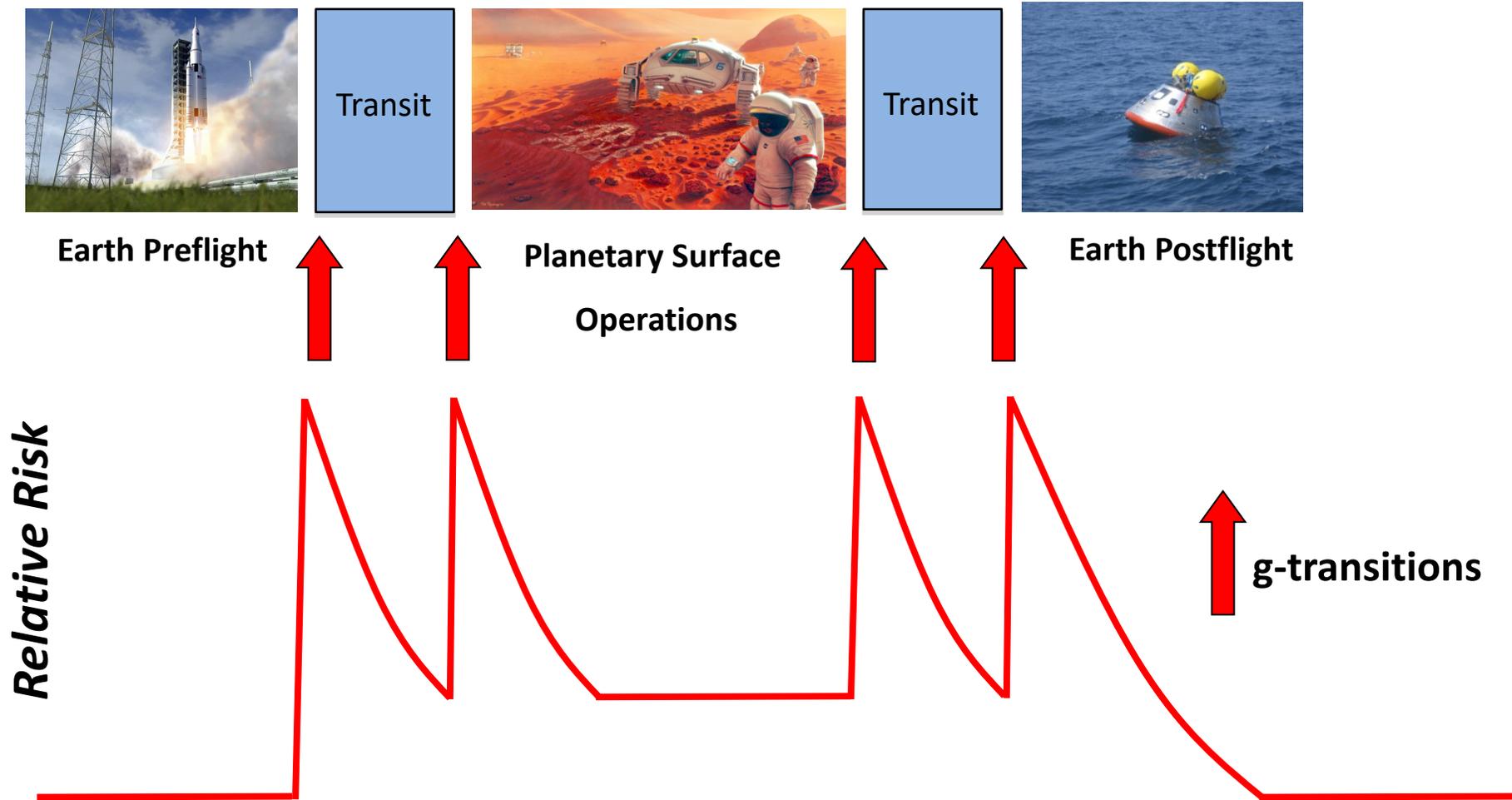
# Summary of Evidence Supporting BMed Risk

- 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



# The CBS "Problem": Sensorimotor Risk

Review of Spaceflight Induced Effects:  
Sensorimotor

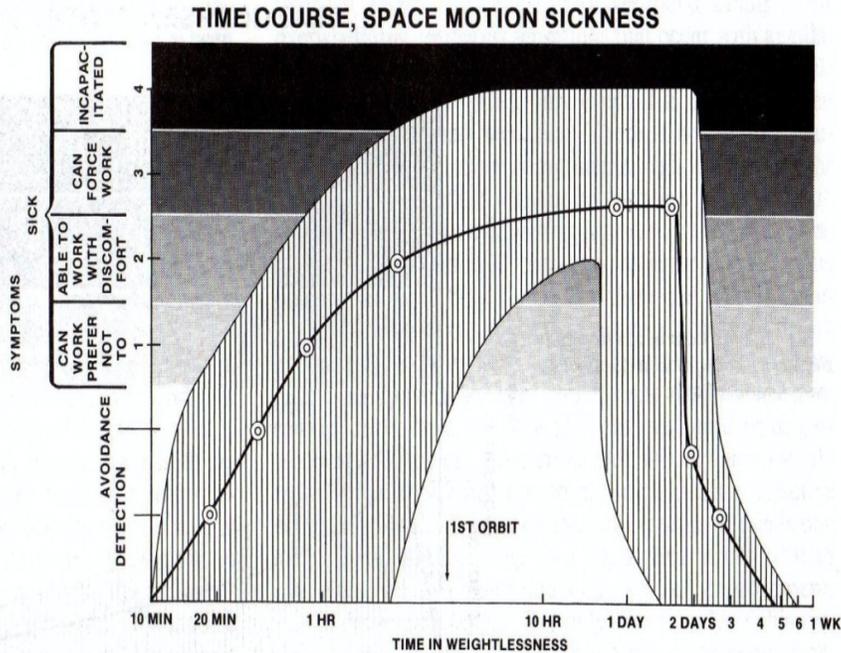




# Prevalence of Space Motion Sickness and Following Return to Earth g



Review of Spaceflight Induced Effects:  
Sensorimotor



Thornton et al. (1987)



Unpublished, J. Locke

## Space Motion Sickness Incidences:

- Mercury/Gemini – 0%
- Apollo/Soyuz – 30%
- Skylab – 56%
- Shuttle – 76%

“Earth Motion Sickness” affects about 30% of individuals after 1-2 week missions, 100% of individuals after long-duration flights.



# Spatial Disorientation



Experiences tied to affective responses and operational performance deficits

Review of Spaceflight Induced Effects:  
Sensorimotor

### Inversion Illusion



Paradoxical sensation of being continuously upside down, even when visually upright in the cabin.

### EVA Height Vertigo



Viewing Earth beneath feet during EVA can trigger sudden sense of height and falling.

### Visual Reorientation Illusion

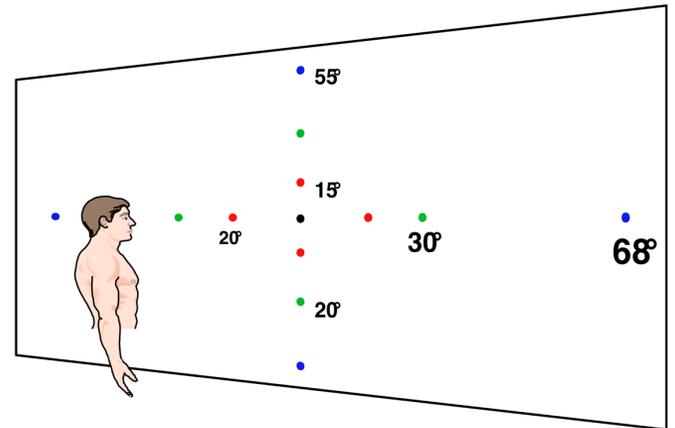


Surface nearest feet seems like a “floor”. Surfaces parallel to body seem like “walls”.

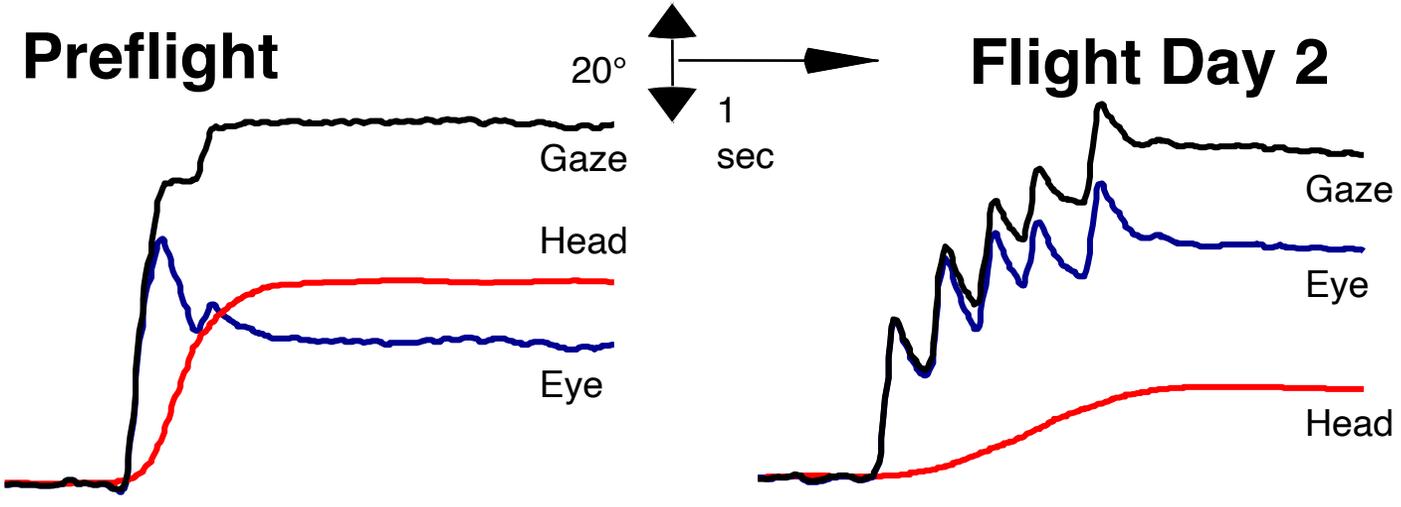
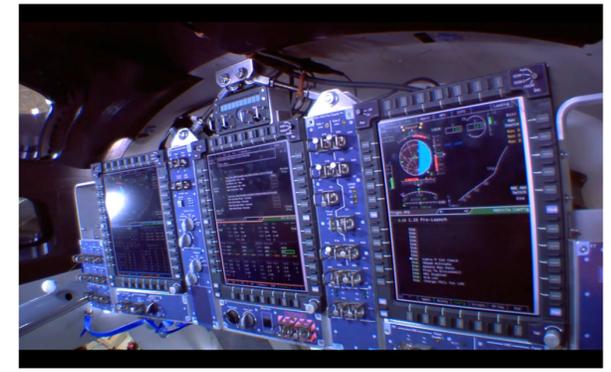


# Visual Target Acquisition

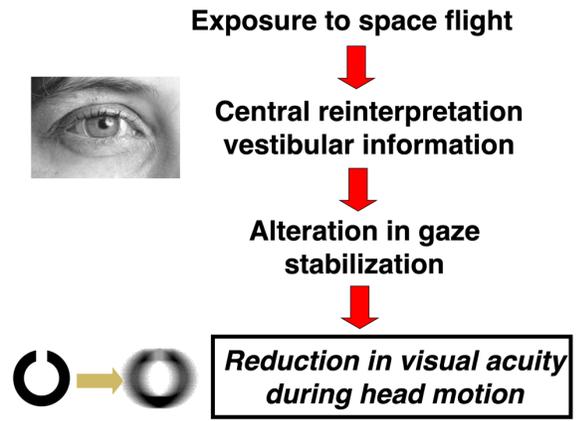
Review of Spaceflight Induced Effects:  
Sensorimotor



Changes in Gaze Control Impacts Ability to See Displays



Clement and Reschke (2008)



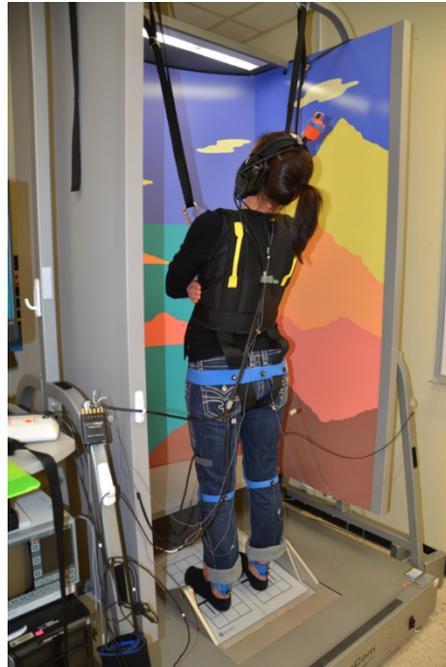


# Recovery of Balance Control after Spaceflight

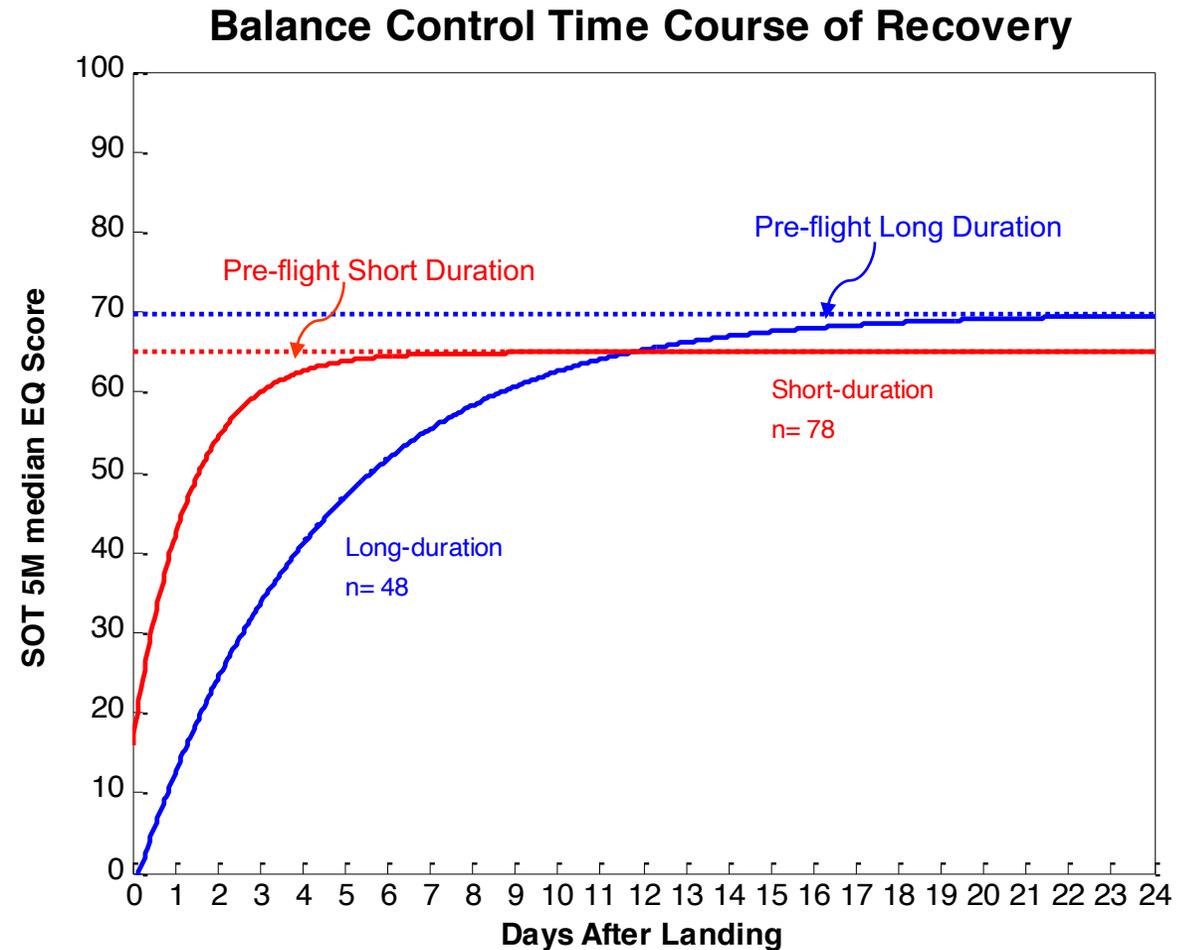


Review of Spaceflight Induced Effects:  
Sensorimotor

Severity increases and recovery is prolonged with increasing exposure time to microgravity.



Balance Control: Sensory Organization Test #5, Head moving condition (SOT 5M)

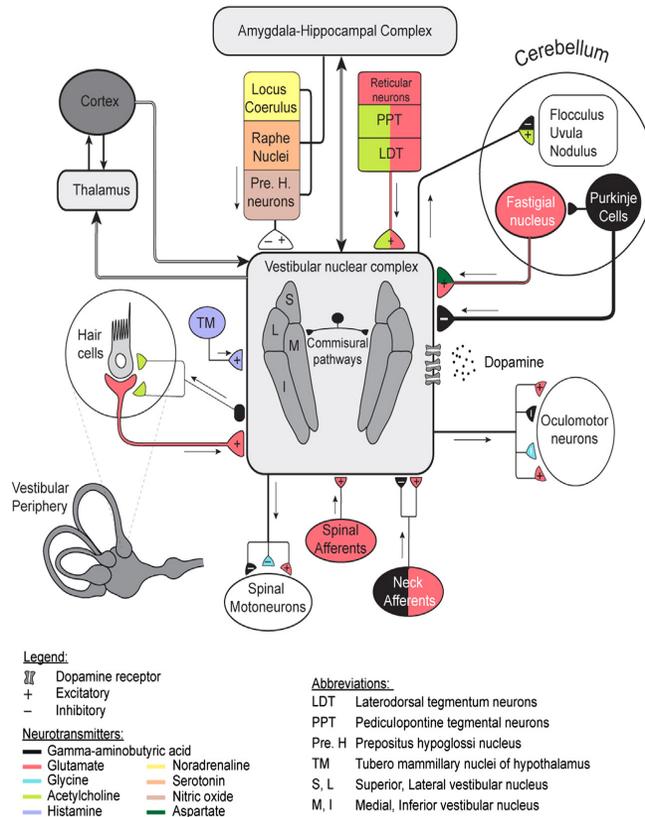




# Emotion is Interrelated to the Vestibular System

Review of Spaceflight Induced Effects:  
Sensorimotor

## A neuroanatomical model of the vestibular system



Gurvicha et al. (2013)

Sensorimotor-affective mechanism - Frontal regions (via motor areas and anterior cingulate gyrus) regulate vestibular areas and attenuate sensory stimulation that can overwhelm cognitive capacities.

Autonomic-affective mechanism - The frontal lobes exert an inhibitory control over the vestibular nuclei in the brainstem.

Consequence - e.g. intense negative stressors (triggered though vestibular dysfunctions, dizziness, disorientation, motion sickness etc.) can lead to difficulties in maintaining sensorimotor coordination in balance and regulating arousal.

Maast et al. (2014)



# 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)

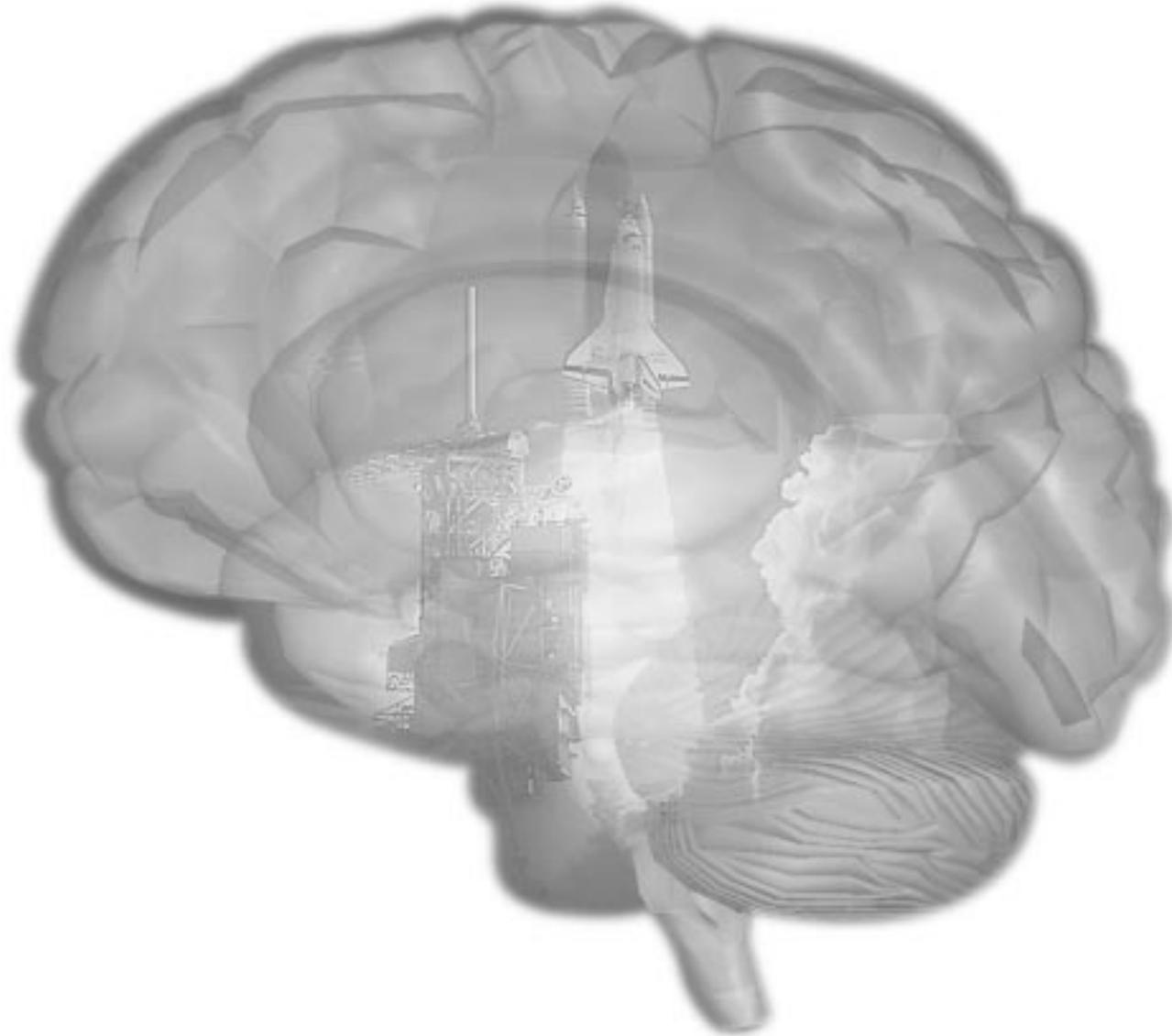
## After return to Earth

- 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



# Effects of Spaceflight on Brain Structure and Function Changes

Review of Spaceflight Induced Effects:  
Brain Structure & Function





# Effect of Exploration Stressors: Isolation and Confinement



Brain Changes in Response to Long Antarctic Expeditions (PI: Stahn) *N Engl J. Med*, 381;23, December 5, 2019 (Impact: 70.67)

Purpose: Evaluate effects of physical and social deprivation on the human brain's plasticity associated with environmental monotony and prolonged physical and social isolation of polar expeditions. Imaging Pre- Post: Changes in volume of subsections of hippocampus & whole-brain gray matter (N=8 of 9). Animal models have shown that exposure to environmental monotony and social isolation have deleterious effects on the brain (esp. neurogenesis).

**BDNF concentration reductions Pre-Post Isolation**  
-Associated with decreases in dentate gyrus volume  
-Reductions in dentate gyrus volume associated with:  
-Lower spatial processing  
-Selective attention

## CBS Translational Biomarker Potential

Human parahippocampal gyrus-orbitofrontal circuit in humans is homologous to the post-rhinal cortex-ventral lateral orbitofrontal cortex circuit in rodents – both are associated with visuospatial malfunction in AD.

> *Brain Res.* 2017 May 15;1663:29-37. doi: 10.1016/j.brainres.2017.02.020. Epub 2017 Mar 8.

## Role of proBDNF and BDNF in Dendritic Spine Plasticity and Depressive-Like Behaviors Induced by an Animal Model of Depression

Hui Qiao<sup>1</sup>, Shu-Cheng An<sup>2, 3</sup>, Chang Xu<sup>1</sup>, Xin-Ming Ma<sup>3</sup>

Review Article

## Dendritic Spines in Depression: What We Learned from Animal Models

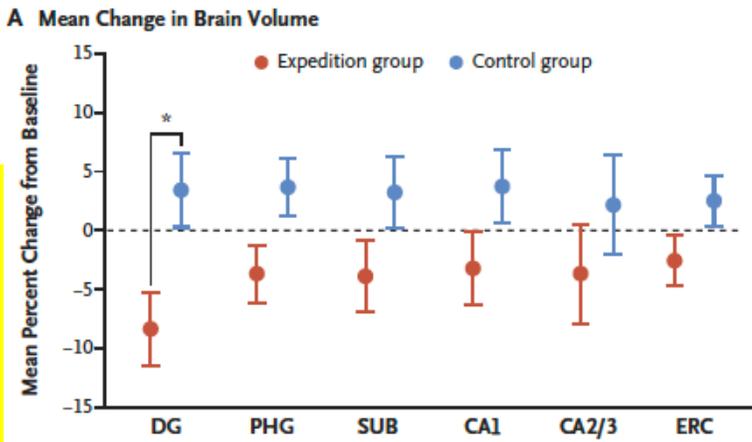
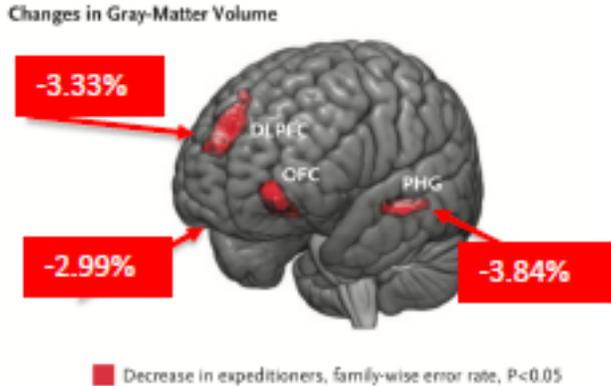
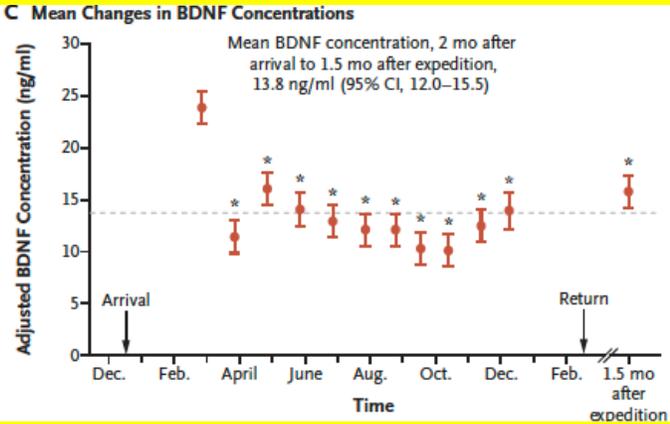
Hui Qiao,<sup>1</sup> Ming-Xing Li,<sup>1</sup> Chang Xu,<sup>1</sup> Hui-Bin Chen,<sup>1</sup> Shu-Cheng An,<sup>1</sup> and Xin-Ming Ma<sup>1,2</sup>

<sup>1</sup>College of Life Science, Shaanxi Normal University, Xi'an, Shaanxi 710062, China  
<sup>2</sup>Department of Neuroscience, University of Connecticut Health Center, Farmington, CT 06030, USA

> *Neural Regen Res.* 2019 Sep;14(9):1530-1535. doi: 10.4103/1673-5374.255974.

## Sodium Butyrate Prevents Radiation-Induced Cognitive Impairment by Restoring pCREB/BDNF Expression

Hae June Lee<sup>1</sup>, Yeonghoon Son<sup>2</sup>, Minyoung Lee<sup>3</sup>, Changjong Moon<sup>4</sup>, Sung Ho Kim<sup>4</sup>, In Sik Shin<sup>4</sup>, Miyoung Yang<sup>5</sup>, Sangwoo Bae<sup>1</sup>, Joong Sun Kim<sup>6</sup>



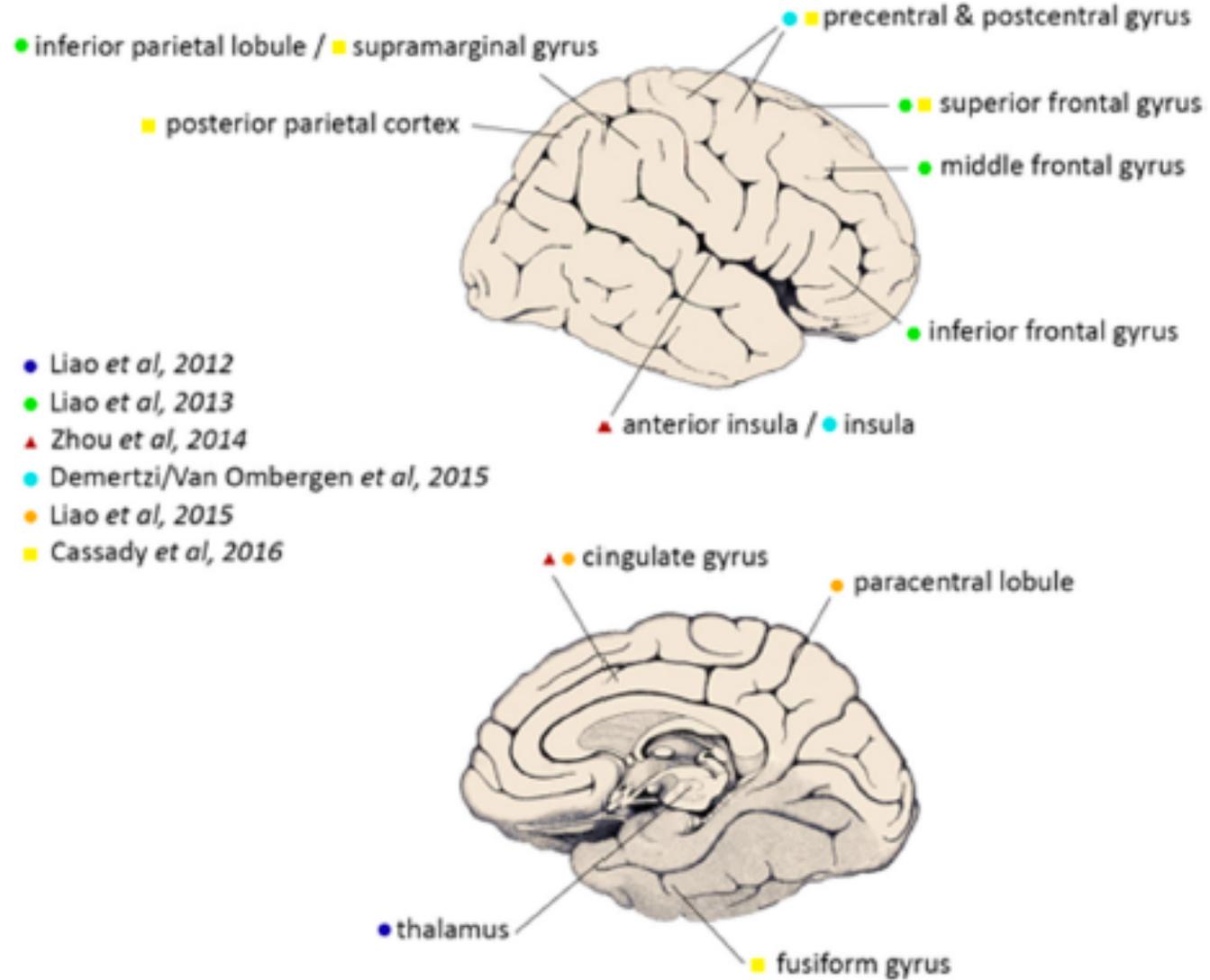
**BDNF powerful influence on dendritic spine growth**  
-Chronic stress impact on BDNF  
-Increases in basal lateral amygdala  
-Decreases in CA3 region of hippocampus  
-Dendritic spine density increases or decreases in line with these changes in BDNF



# Cortical and Subcortical Brain Areas Most Affected by Spaceflight or Analog Environments



Review of Spaceflight Induced Effects:  
Brain Structure & Function



Van Ombergen *et al*. (2017)  
Koppelmans *et al*. (2016)



# Alterations to the Brain During Spaceflight

## Review of Spaceflight Induced Effects: Brain Structure & Function

Study	Population	Imaging Protocol	Main Findings
Roberts et al. 2019 <sup>19</sup>	n=19, 7 SD and 12 LD Pre- and post flight scans	T1-weighted MRI (3T) - Brain tissue and CSF volumes	<ul style="list-style-type: none"> <li>- Increase in total ventricular volume in LD crew. Significant increase in lateral ventricles and third ventricle, but not in fourth ventricle. Change in ventricular volume associated with increasing flight duration and decreasing crewmember age.</li> <li>- Crowding of parenchyma at the vertex (supplementary motor, premotor, primary sensorimotor regions) and displacement of brain tissue surrounding the ventricles seen in LD crew only.</li> <li>- <u>Clinical Correlate</u>: Change in L caudate associated with poorer postural control, change in R lower extremity primary motor area/midcingulate associated with longer time on seated egress and walk test. Reduced accuracy on WinSCAT code substitution learning subtest, faster reaction times associated with smaller changes in volume of bilateral optic radiations and splenium</li> </ul>
Van Ombergen et al. 2019 <sup>21</sup>	n=11, LD Pre- and post flight scans, 7-month follow-up	T1-weighted MRI (3T) - CSF volumes	<ul style="list-style-type: none"> <li>- Increased lateral ventricle, third ventricle and total ventricular volume after LD spaceflight, with residual baseline increases at 7 months. No significant change in fourth ventricle.</li> <li>- Ventricular volume increases associated with increasing mission duration</li> </ul>
Riascos et al. 2019 <sup>17</sup>	n=19, 10 SD and 9 LD Pre- and post flight scans	T1-weighted MRI (3T) - Brain tissue volume Diffusion-weighted MRI (3T) - WM microstructure, GM diffusivity	<ul style="list-style-type: none"> <li>- Trend for cortical thinning of R occipital lobe; reduced volume of L thalamus; increased lateral ventricular volume.</li> <li>- WM changes in R posterior thalamic radiations, trend towards greater effects in LD crew.</li> </ul>
Pechenkova et al. 2019 <sup>23</sup>	n=11 LD, compared to HC Pre- and post flight scans	fMRI (3T): - Resting state connectivity - Plantar stimulation paradigm	<ul style="list-style-type: none"> <li>- Stimulation-specific increase in connectivity of R posterior supramarginal gyrus with the rest of the brain</li> <li>- Increased connectivity between R and L posterior insula; decreased connectivity between posterior cerebellum and primary visual cortex; decreased connectivity between anterior cerebellum and R parietal cortex</li> <li>- Connectivity modifications at vestibular nuclei, R parietal cortex, anterior cerebellar network, R posterior insula and L posterior insula</li> <li>- <u>Clinical Correlate</u>: Space motion sickness severity associated with connectivity between R posterior supramarginal gyrus and L insular region</li> </ul>
Kramer et al. 2020 <sup>22</sup>	n=11, LD Pre- and post-flight scans 1, 3, 9, 12-month follow-up scans	T1- and T2 weighted MRI (3T) - Brain tissue and CSF volumes - Pituitary evaluation T1-weighted MRI (3T), cine-clips - Quantitative CSF Flow	<ul style="list-style-type: none"> <li>- Expansion of total brain and CSF volumes after LD spaceflight, with persistent elevation 1 year after spaceflight. Largely driven by global WM volume and lateral ventricular volume increases</li> <li>- Increased aqueductal stroke volume and CSF peak-to-peak velocity magnitude</li> <li>- Pituitary depression seen in 6/11 crewmembers</li> </ul>
Hupfield et al. 2020 <sup>24</sup>	n = 12, LD (6-month, n=10, 12-month n=2), compared to HC Pre and post-flight scans 6 month follow-up scans	T1-weighted MRI (3T) - Brain tissue and CSF volumes Diffusion-weighted MRI (3T) - FW shifts	<ul style="list-style-type: none"> <li>- Significantly enlarged ventricular volumes in all 6-month mission astronauts, and 1 of 2 12-month mission astronauts compared to control. Partial resolution of increased volumes seen 6-months post-flight in 50% of subjects</li> <li>- Increased GM volume and cortical thickness in the SMA, pre- and postcentral gyri in the 6-month mission astronauts and 1 of 2 12-month mission astronauts, largely recovered on 6-month follow-up scan</li> </ul>
Jillings et al. 2020 <sup>25</sup>	N=11, LD, compared to HC Pre and post-flight scans 7 month follow-up scans	Diffusion-weighted MRI (3T) - Multi-tissue spherical deconvolution for GM, WM and CSF volumes	<ul style="list-style-type: none"> <li>- GM changes driven by local volume shifts rather than tissue loss, largely reversed at 7-month follow up</li> <li>- WM volume increases in the cerebellum, CST, PMC</li> <li>- GM volume increases in the basal ganglia</li> <li>- Larger visual acuity decreases post-flight associated with greater ventricular expansion</li> </ul>

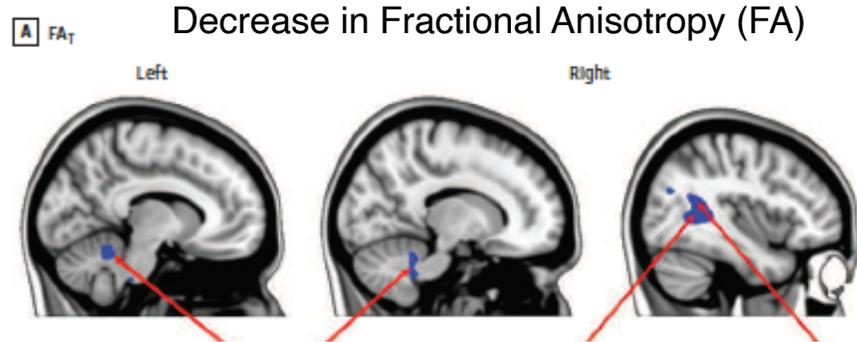
Meaghan Roy O'Reilly, Mulavara AP, Williams Thomas, A Review of Alterations to the Brain During Spaceflight and the Potential Relevance to Crew in Long-Duration Space Exploration npj Microgravity, Accepted, January 2021



# Spaceflight Associated Brain White Matter Microstructural Changes

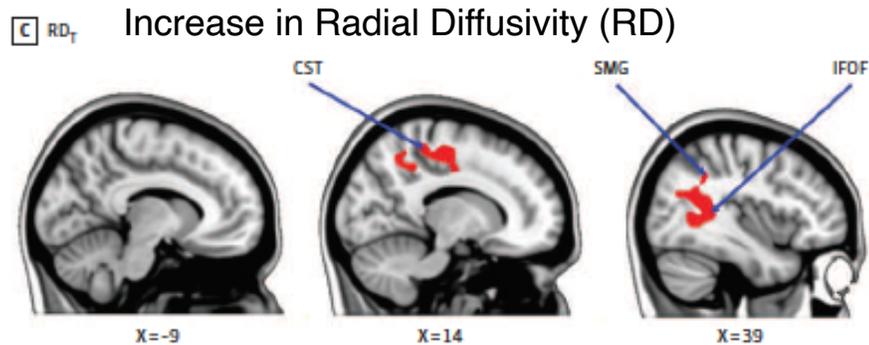


Review of Spaceflight Induced Effects:  
Brain Structure & Function



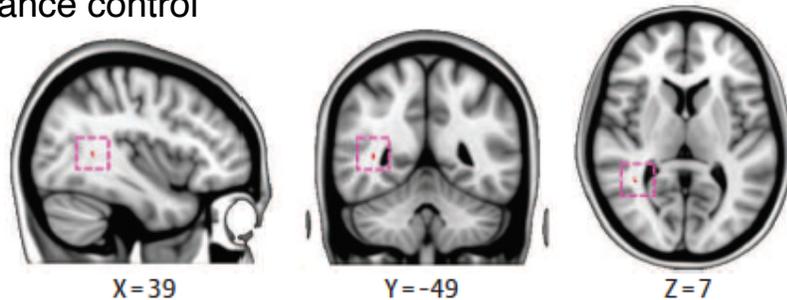
Areas:  
visuospatial processing,  
vestibular function, &  
movement control

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

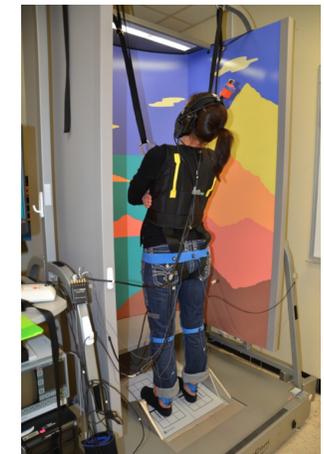
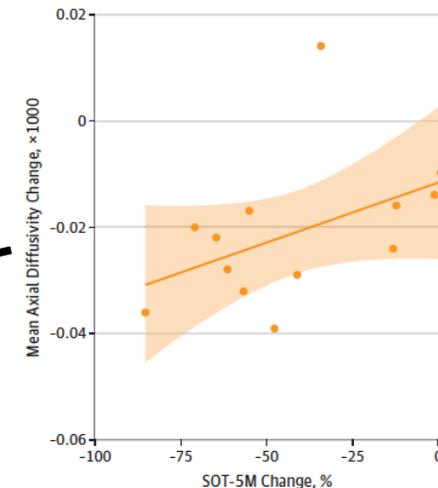


Radial Diffusivity: increase, white matter structures underlying the precentral and postcentral gyrus, the supra marginal gyrus, and angular gyrus

Changes of Axial Diffusivity ( $AD_T$ ) associated with balance control

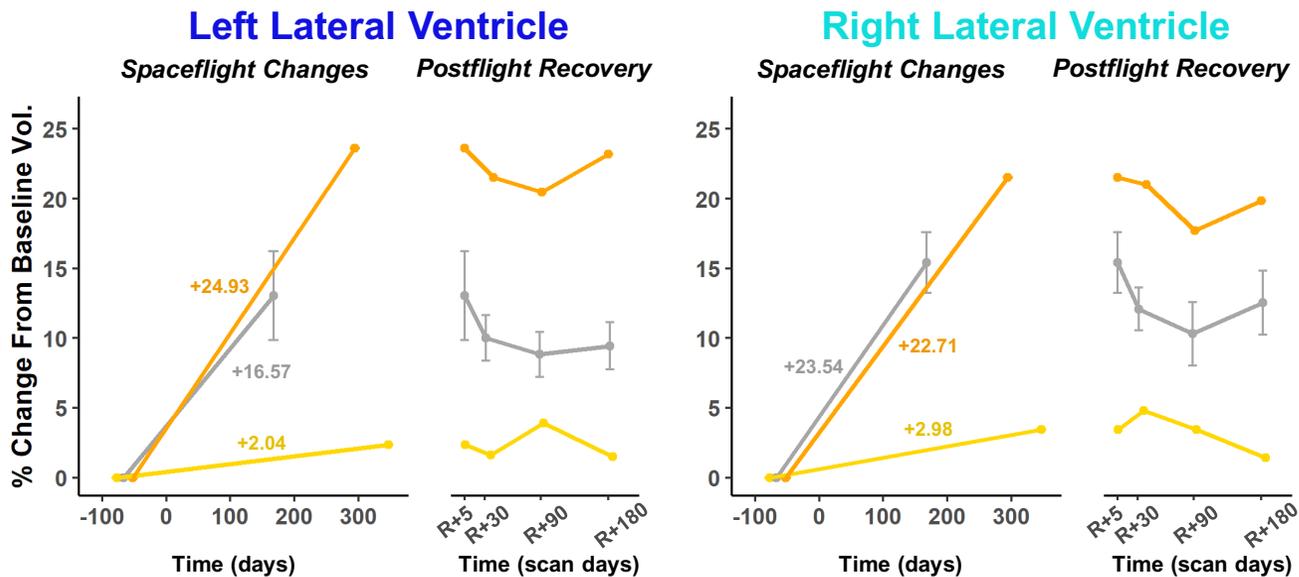


Changes of Axial Diffusivity ( $AD_T$ ) and Sensory Organization Test (SOT) 5M Balance Score

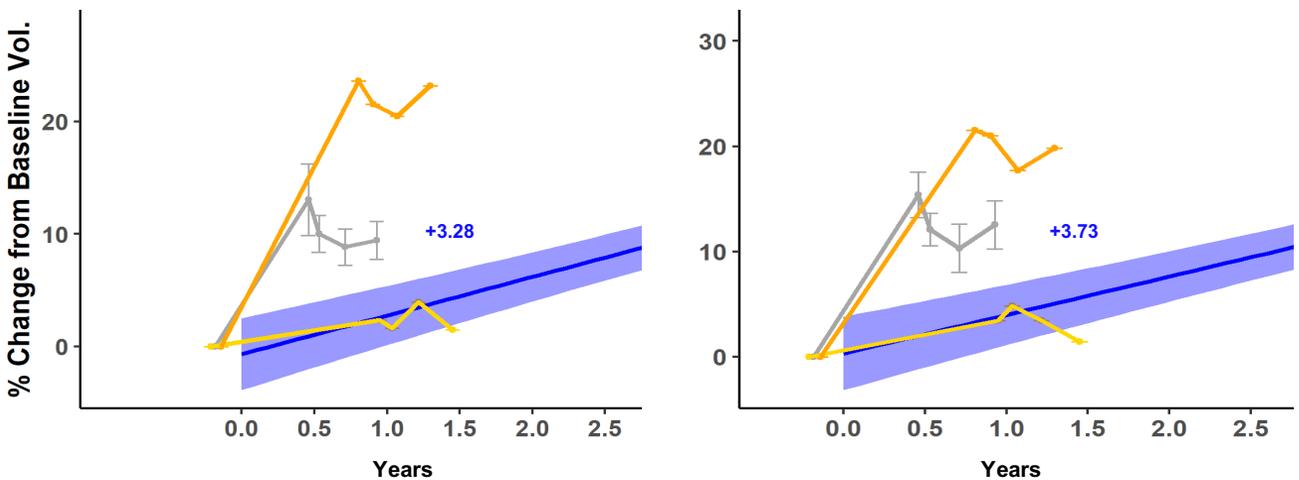


Lee et al. (2019)

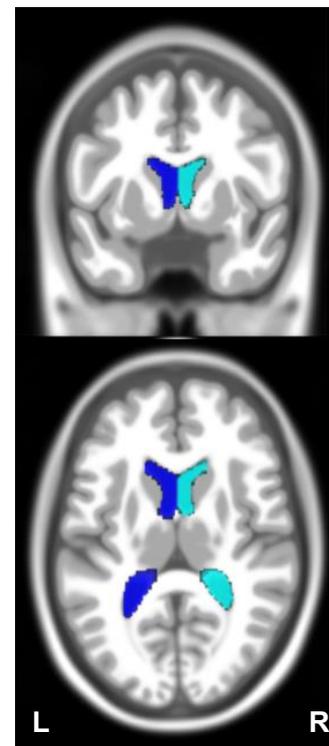
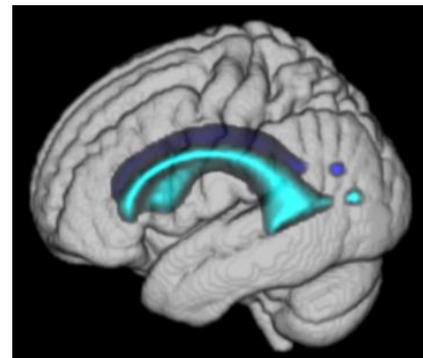
# Ventricular expansion with 6-12 month missions



TM<sub>1</sub> TM<sub>2</sub> = 12-month astronauts; ■ = 6-month astronauts; Day 0 = Start of flight; R = Return



TM<sub>1</sub> TM<sub>2</sub> = 12-month astronauts; ■ = 6-month astronauts; ■ = Control Group



Ventricular expansion with flight; little recovery by 6 months postflight



# Summary of Evidence - Brain Changes



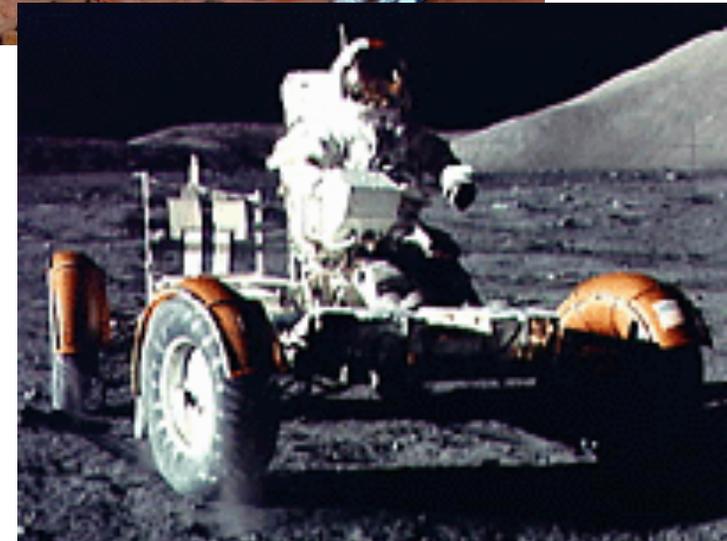
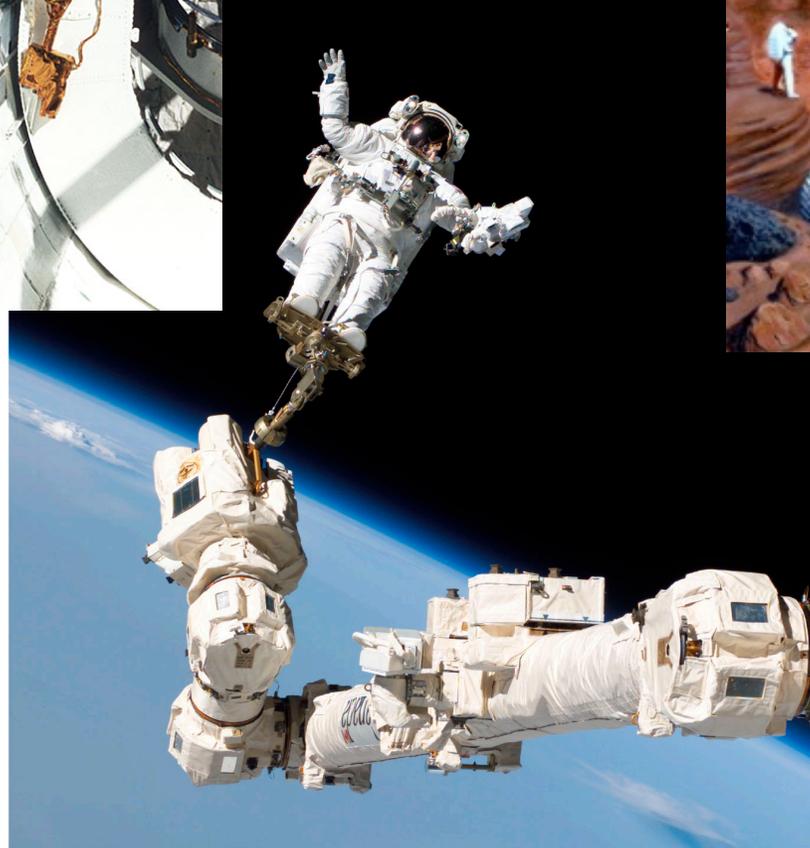
- Frequent narrowing of the central sulcus, upward shift of the brain, and narrowing of CSF spaces at the vertex, predominantly after long-duration flights
- Volumetric gray matter decreases, including large areas covering the temporal and frontal poles and around the orbits
- For some regions of the 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



# Effects of Spaceflight on Operational Performance



Review of Spaceflight Induced Effects:  
Operational Performance



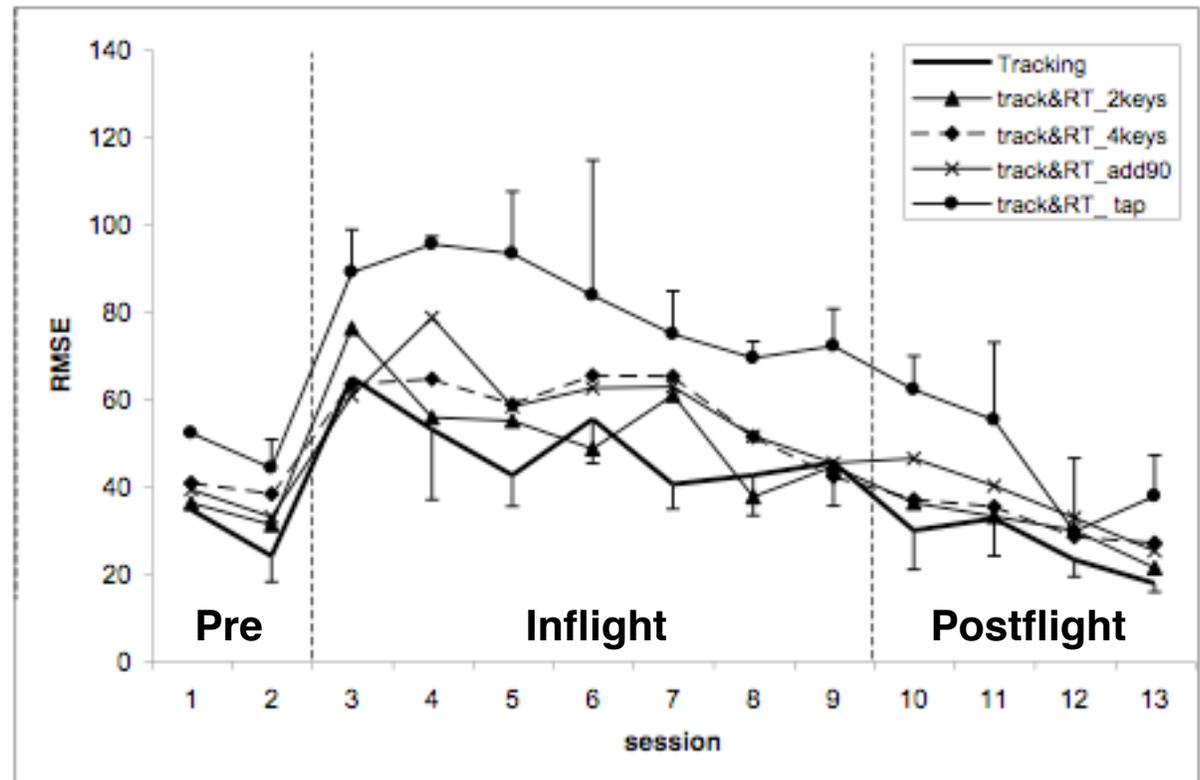
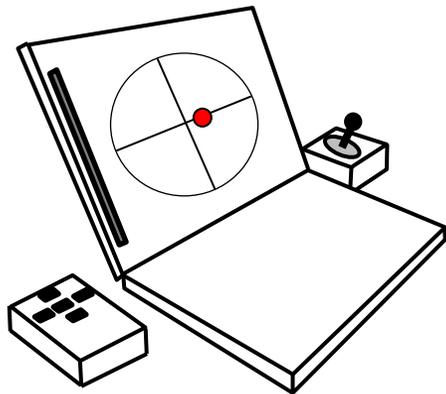


# Manual Control and Dual Tasking



Review of Spaceflight Induced Effects:  
Operational Performance

Dual tasking increases error in manual control during periods of adaptive change – implications for cognitive reserve



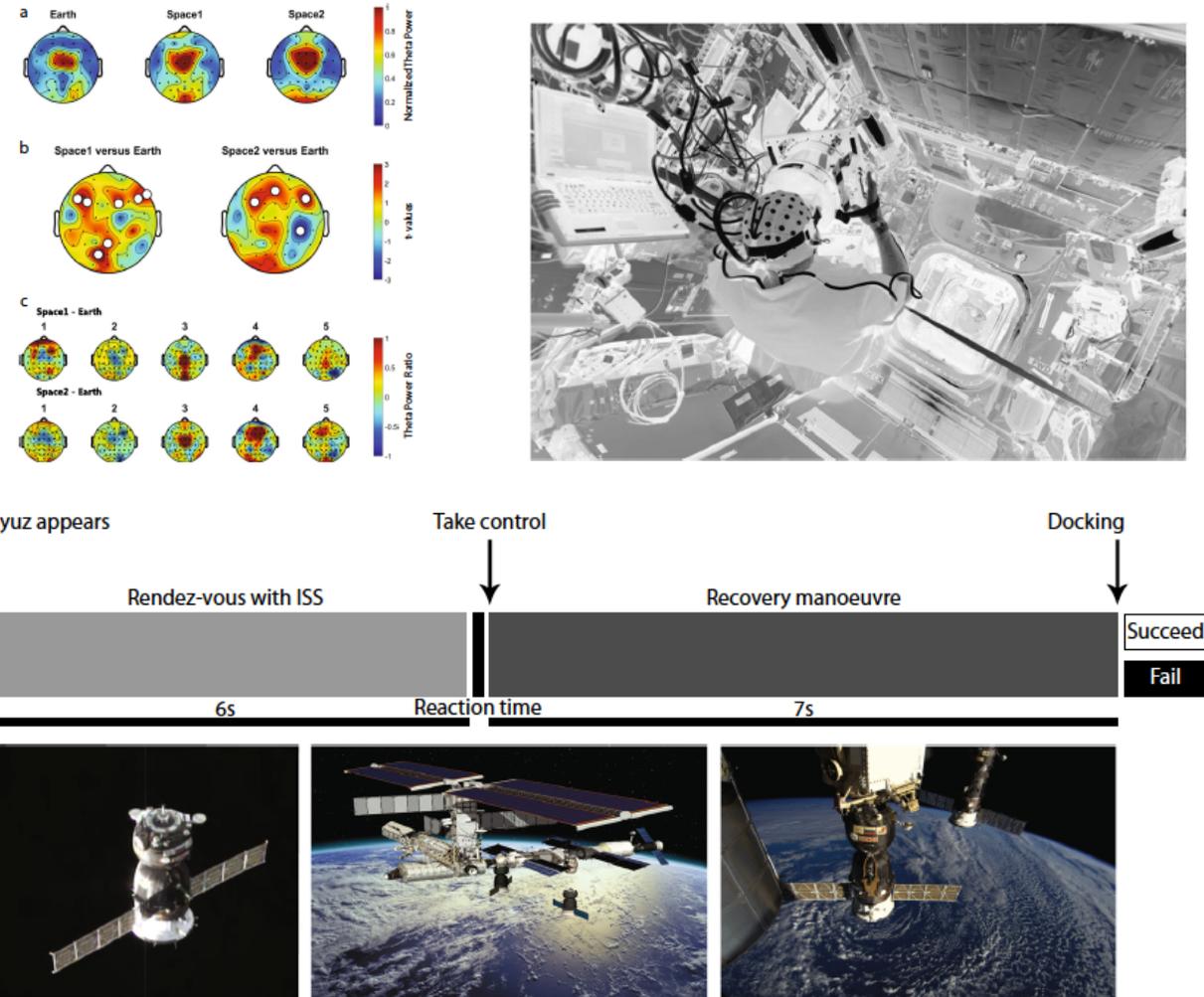


# Sleep Pressure Markers Associated with Reduced Performance During Spaceflight



## Review of Spaceflight Induced Effects: Operational Performance

- Sleep pressure markers during wakefulness were measured in five astronauts throughout their 6-month ISS mission using electroencephalographic recordings
- Performance on a Soyuz docking simulation was associated with an increase in sleep pressure markers when reaction times were slower
- Reaction time on the docking simulation slowed over two months in space

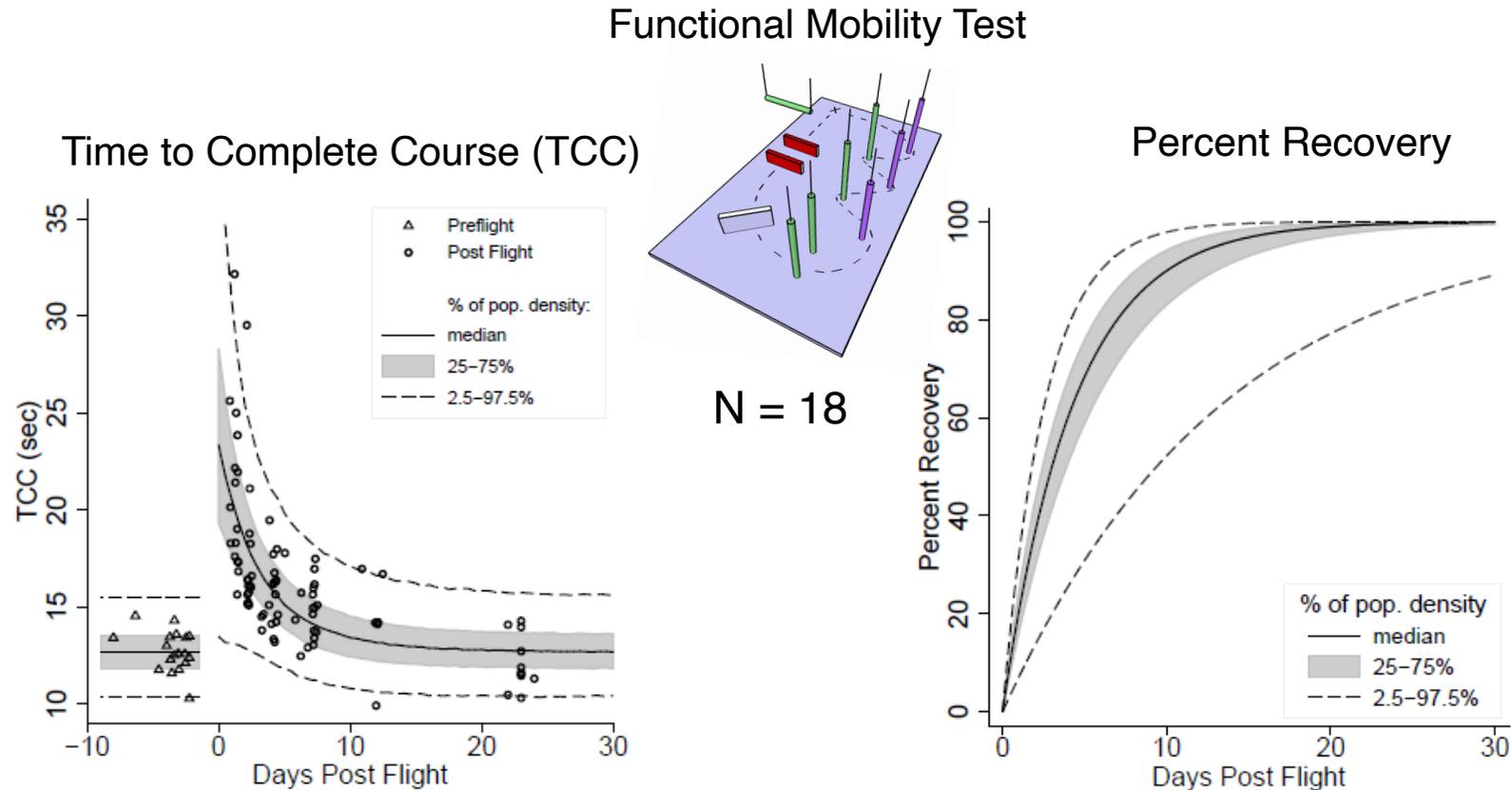




# Functional Mobility after Long-Duration Space Flight



**Recovery of functional mobility to 95% of preflight level took 15 days.**



Review of Spaceflight Induced Effects:  
Operational Performance



# Driving Simulation after 6 Months on the International Space Station

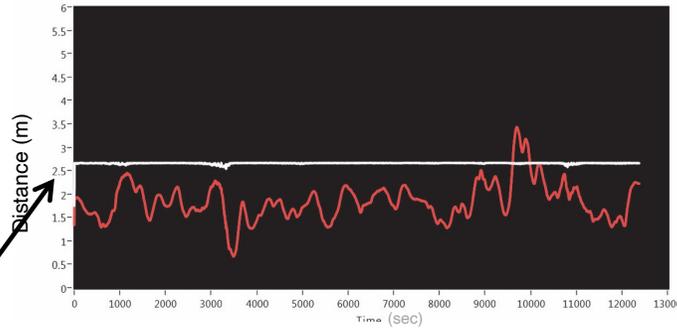


Review of Spaceflight Induced Effects:  
Operational Performance

Postflight increases in lane crossing, time in wrong lane and time to return to correct lane

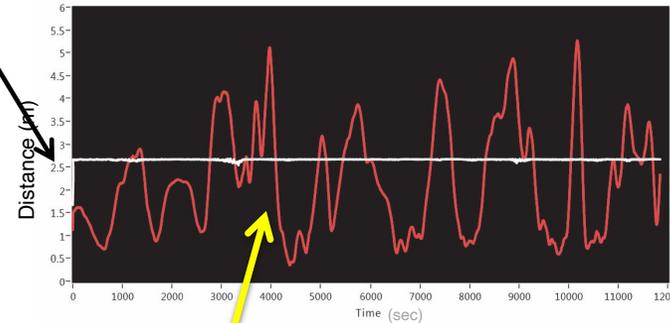
Driving (Mountain Course)

Preflight

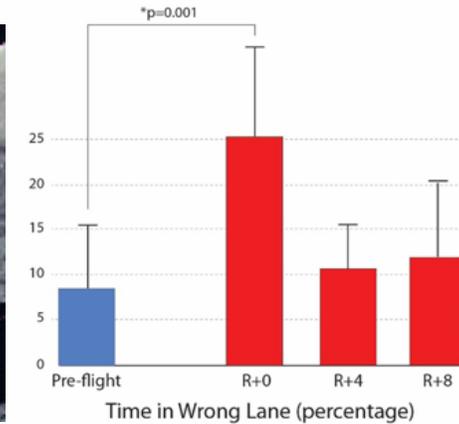
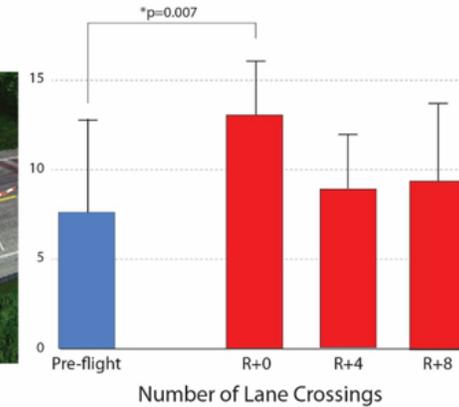
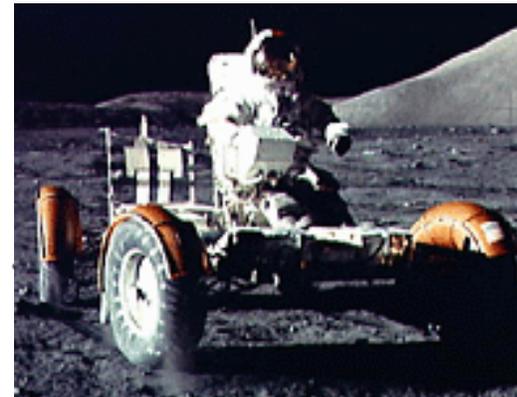
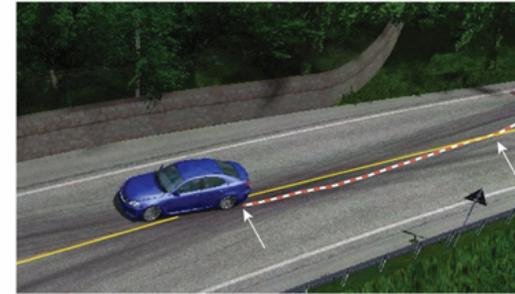


Lane divider

Postflight (R+0)



Car position



Moore et al. (2019)



# Summary of Evidence – Operational Performance



## Review of Spaceflight Induced Effects: Operational Performance

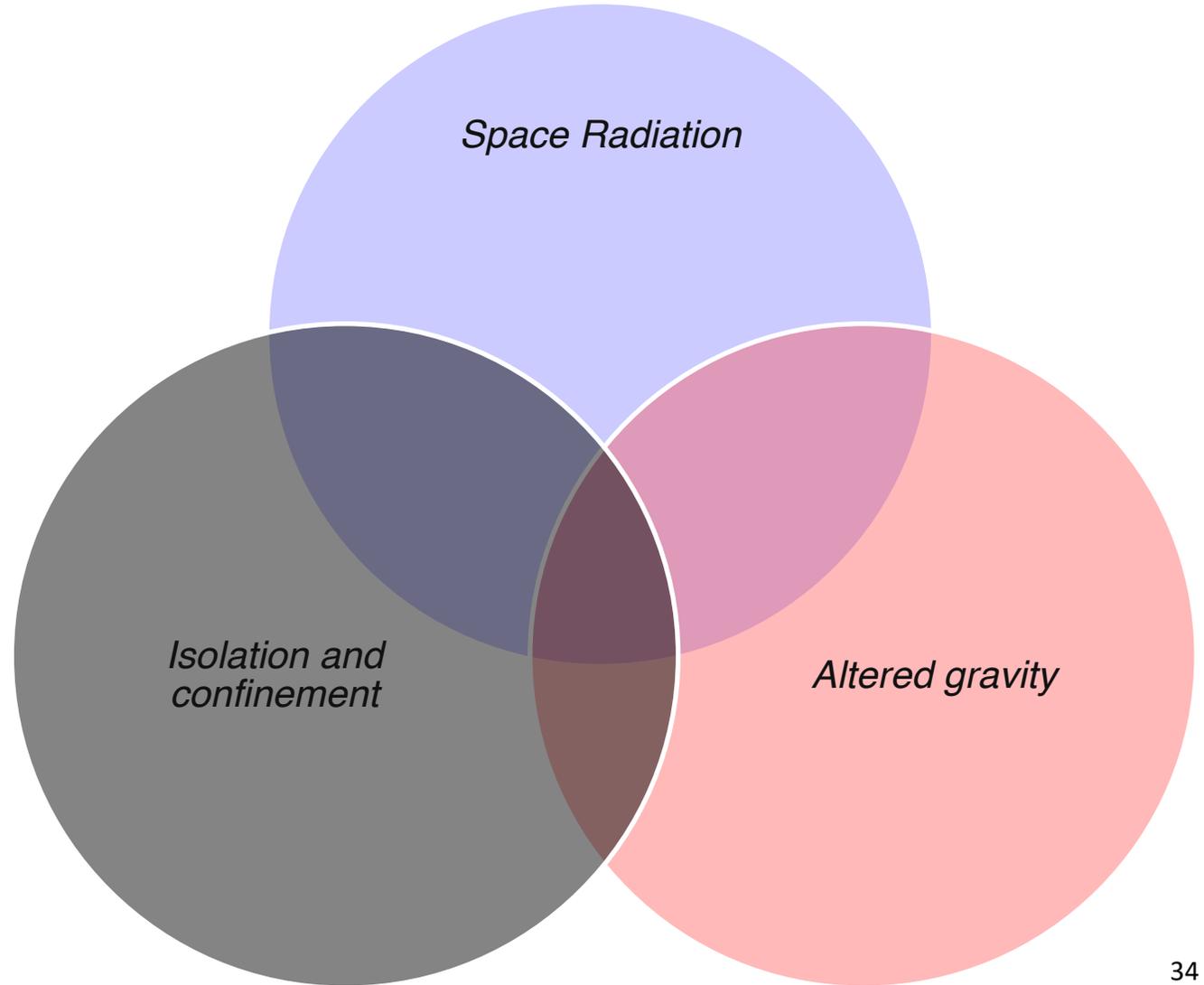
- Reduced cognitive reserve may relate to the commonly experienced “space fog” - cognitive and perceptual changes that manifest as attention-lapses, short-term memory problems, spatial disorientation, and confusion when performing tasks; affecting in-flight performance (e.g. manual control)
- Increase 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)



# Interactions Between Multiple Stressors



Review of Spaceflight Induced Effects:  
Interactions between stressors





# Combined Space Radiation and Altered Gravity

## Chronic Gamma Irradiation ± Hindlimb Unloading



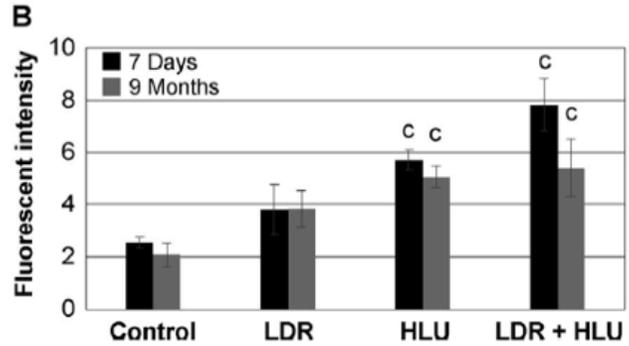
Review of Spaceflight Induced Effects:  
Interactions between stressors

### Stressors:

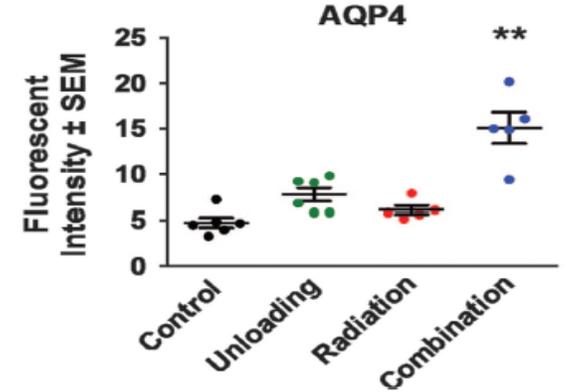
- Low dose gamma radiation (LDR) using a <sup>57</sup>Co source (0.01 cGy/h for a total dose of 0.04 Gy)
- Hindlimb unloading (HLU)
- Combination of both for 3 weeks

### Measurements of LDR+ HLU Effects on:

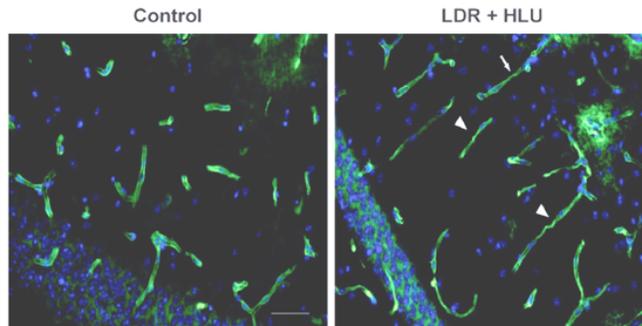
- Mouse Brain Oxidative Stress increases (4-HNE)
- Blood Brain Barrier modified (AQP4)
- Microvessel changes



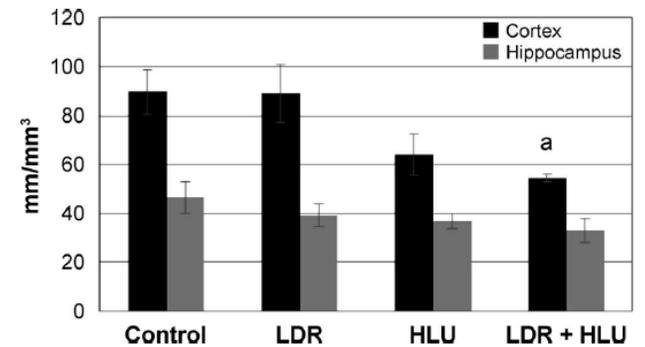
4-hydroxynonenal (4-HNE) staining in the hippocampus (panel B) at 7 days or 9 months.



Water transporter aquaporin 4, astrocyte foot / endothelium interface marker at 9 months.



Microvessel morphological changes in cortex at 9 months after combination treatment with LDR + HLU and in control.



Microvessel length density (mm/mm<sup>3</sup>) in the cortex and hippocampus at 9 months.

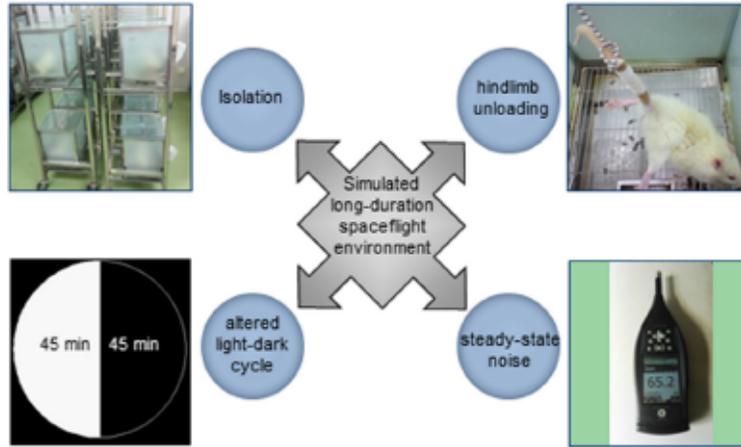


# Combined Isolation and Altered Gravity Hindlimb Unloading, Isolation, Sleep and Noise (SLSE)

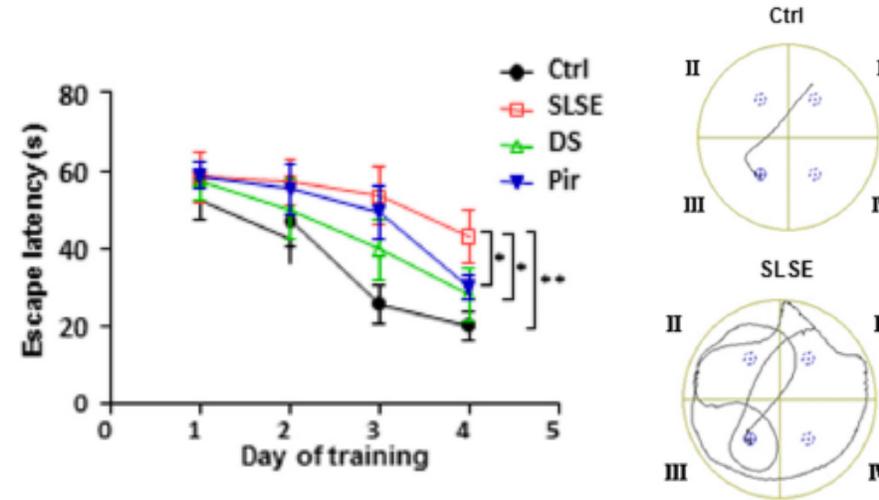


Review of Spaceflight Induced Effects:  
Interactions between stressors

## Simulation of combined stressors



## Spatial learning



## Neurotransmitter content changes in the cortex (C) and hippocampus (H) of rats

- Decreases: 5-hydroxytryptamine (C,H), dopamine (C), norepinephrine (C,H), epinephrine (C), glutamate(C,H), acetylcholine (C)
- Increases: gamma-aminobutyric acid (C)

## Changes in numbers and arrangements of neurons in the hippocampus (H) and cortex (C)

- Significantly fewer neurons (H: CA3 - subfields 1, 3 and C)
- Neurons were larger in the intercellular space, loosely and irregularly arranged, and weakly stained, indicating that they were injured



# Synergistic Effect Between Inflammation and Stress in Prefrontal Cortex



Review of Spaceflight Induced Effects: Interactions between stressors

- Prefrontal Cortex (PFC):**
- Executive functions
  - Memory
  - Visual search, gaze control

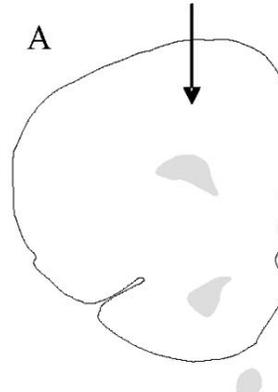
**Table 1. Schedule of stressing agents used during the chronic stress treatment**

Day of treatment	Agent used	Duration
1	Forced swimming	10 min
2	Restraint	3 h
3	Water deprivation	24 h
4	Restrain at 4°C	1.5 h
5	Restraint	3 h
6	Food deprivation	24 h
7	Water deprivation	24 h
8	Restrain at 4°C	2 h
9	Food deprivation	24 h

LPS=lipopolysaccharide (a potent pro-inflammogen)

De Pablos et al. (2006)

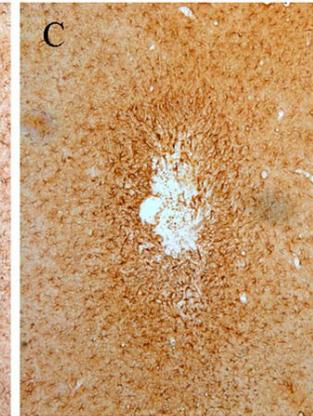
The injections site in the PFC



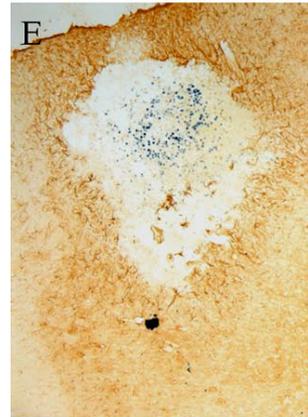
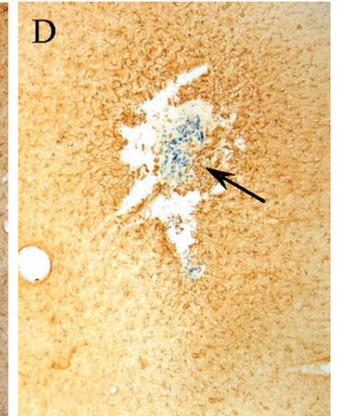
Saline-injected non-stressed



Vehicle injected non-stressed animal



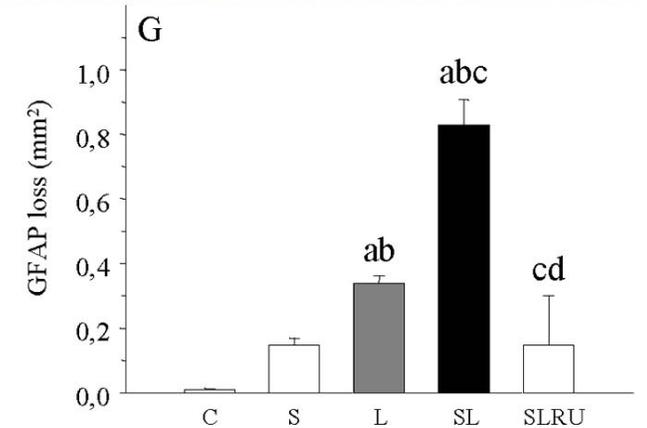
LPS-injected non-stressed animal



LPS-injected stressed animal



Treatment with RU486



Quantification of areas showing loss of astrocytes at the end of the treatments

Coronal section showing GFAP immunoreactivity



# Synergistic Effects?



**Null-hypothesis** - Risks are non-interacting and do not disproportionately act on different receptors within crewmembers that cannot be predicted based on response to single risk alone

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



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

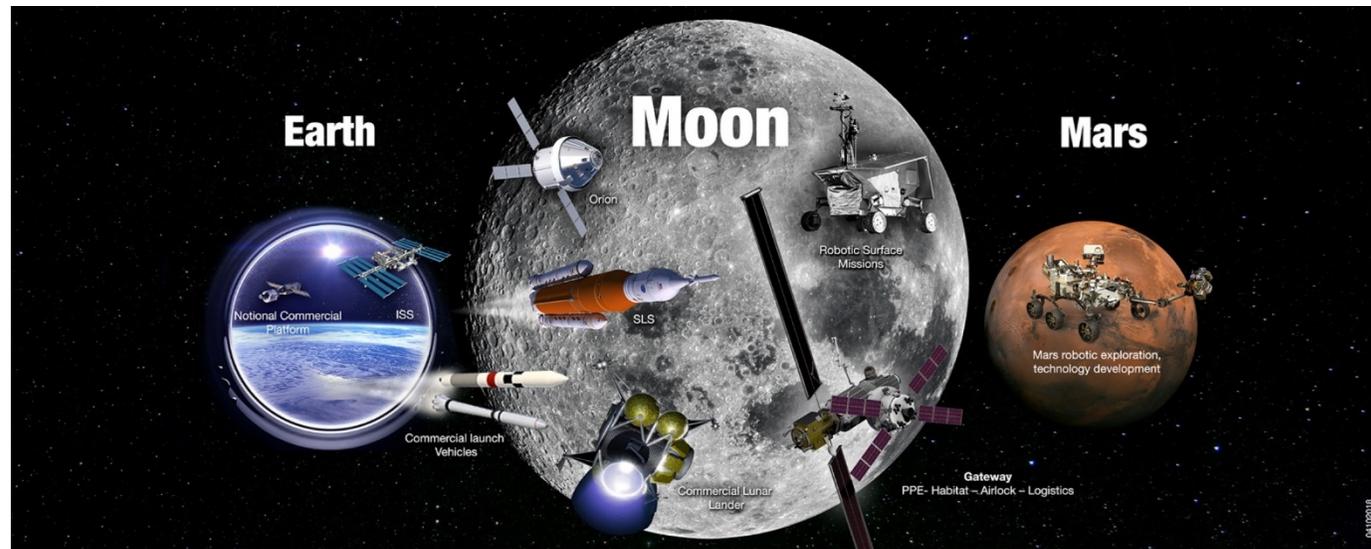
Liess et al. (2016)



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



- **End-state:** Identification and validation of **monitoring capabilities, countermeasures, and risk mitigation of synergistic impacts** the **SR/BMed/SM hazard** pose to **operationally relevant performance domains.**



**In LEO**  
Commercial & International  
partnerships

**In Cislunar Space**  
A return to the moon for  
long-term exploration

**On Mars**  
Research to inform future  
crewed missions

Implementation Strategy:  
Summary



# Team Acknowledgement



- Thomas Williams, Ph.D., Human Factors and Behavioral Performance (HFBP) Element Scientist
- Alexandra Whitmire, Ph.D., HFBP Element Scientist (acting)
- Aaron Allcorn, HFBP Element Manager
- Ahsan Sheikh , HFBP Deputy Element Manager
- Andrea Hanson, Ph.D., CBS Portfolio Manager
- Jayati Roy Choudhury, Ph.D., CBS Science Integrator
- Kerry George, Ph.D., CBS Scientist
- Gregory Nelson, Ph.D., Space Radiation CNS Discipline Scientist
- Scott Wood, Ph.D., Sensorimotor Discipline Co-Lead
- Millard Reschke, Ph.D., Sensorimotor Discipline Co-Lead





# Grand Challenge. Great Responsibility.



Introduction:  
Responsibilities of Human Space Flight





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# Definitions

- Biomarker (Institute of Medicine definition) - Characteristics that indicate biological processes. Could include, but not limited to blood serum/urine markers, function test measurements, cognitive test measurements, etc.
- Risk – A measure of uncertainty where there is potential for uncontrolled loss of something of value.
- POLs and PELs - Define numerically what risk levels are acceptable.
- Countermeasure – An action taken to counteract a danger or threat.
- Translational Research - Discipline in biomedical research that aims to expedite the discovery of new diagnostic tools and treatments by using a multi-disciplinary, highly collaborative, "bench-to-bedside" approach.
- Exploration Missions (EM)- Any space mission planned beyond those scheduled to visit the ISS.

