

Neurologic Effects in Spaceflight

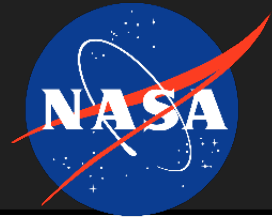
Aerospace Medicine Residency annual summer course,
Principles of Aviation and Space Medicine, UTMB
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Ajitkumar Mulavara, Ph.D., HHPC/KBR
ajitkumar.p.mulavara@nasa.gov

“I do not have any relevant financial disclosures for this presentation and attest that the clinical recommendations are evidence-based and free of commercial bias (e.g., peer-reviewed literature, adhering to evidence-based practice guidelines).”



Risks Associated with Spaceflight



The effects of multiple spaceflight hazards might interact combinatorially and affect operationally relevant tasks

Balance Disorders
Fluid Shifts
Cardiovascular
Deconditioning
Muscle Atrophy
Bone Loss



Drives the need for additional “autonomous” medical care capacity – cannot come home for treatment

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



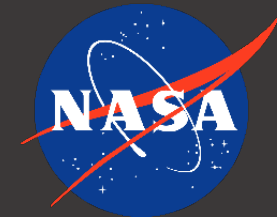
Vehicle Design
Acceleration/Vibration/ Noise
Environmental – CO₂ Levels, Toxic Exposures, Water, Food
Decreased Immune Function



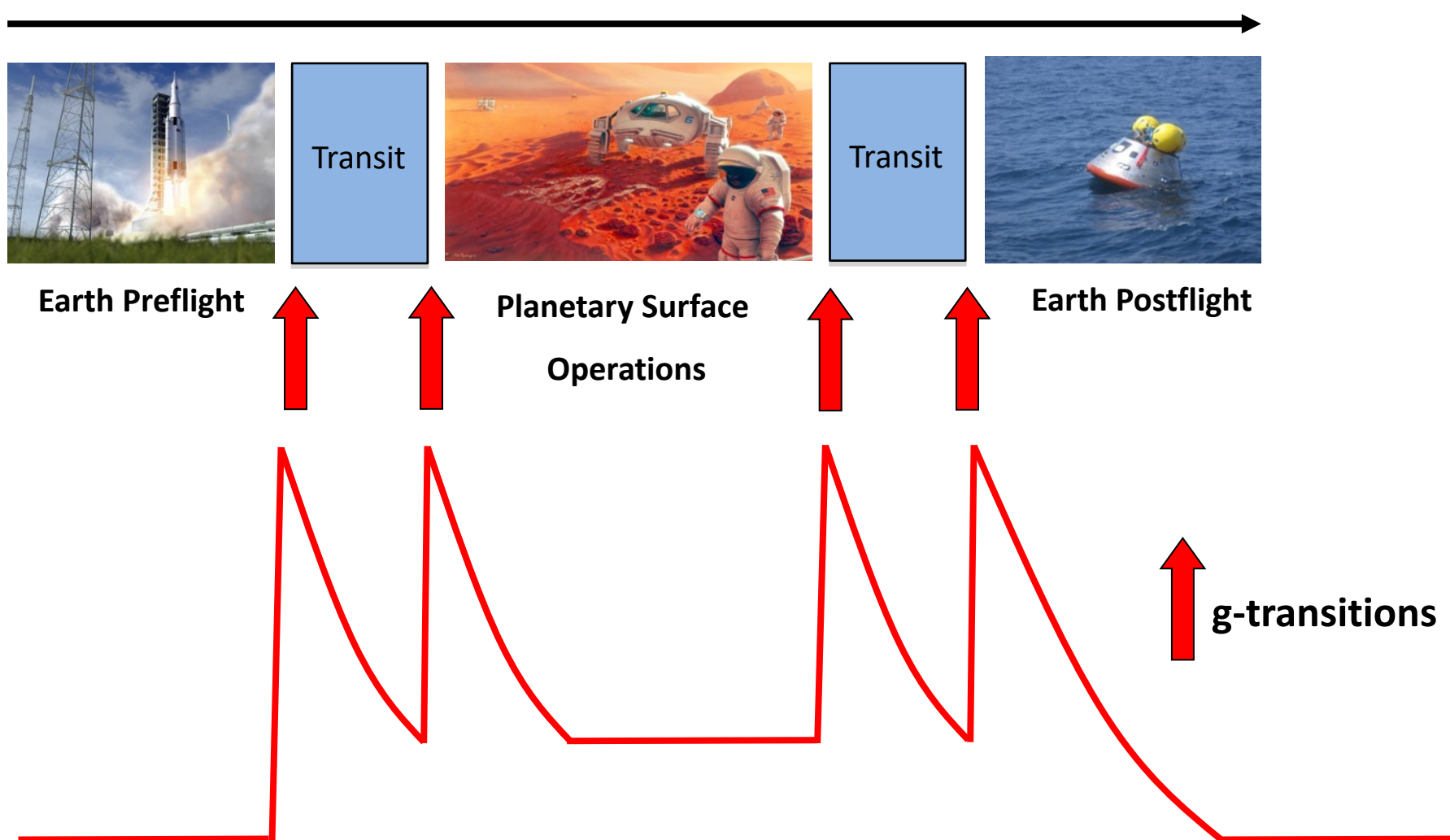
Behavioral aspect of isolation
Sensory deprivation
Sleep disorders (circadian dysregulation)



Astronauts Experience Sensorimotor Deficits During Gravity Transitions



Exploration mission profile

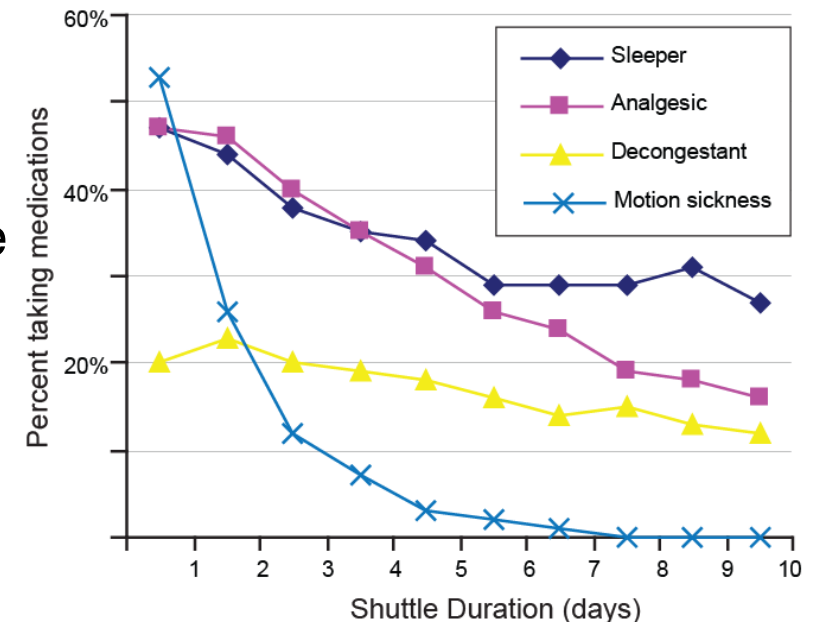




Space Motion Sickness



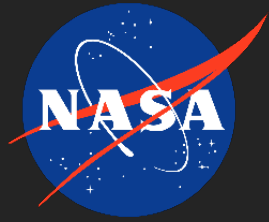
- Incidence inflight ~70%, developing within hours and resolving within 2-3 days but may persist in a few (Jennings, 1998, Reschke et al, 2018)
- Incidence of “re-entry sickness” on return ~30% after 1–2-week missions, greater after longer duration flights (100% after 6 m based on recent field tests)
- Severity highly variable across crews, with decreased incidence in repeat flyers (Davis et al, 1988)
- Difficult to predict susceptibility from terrestrial analogs
- Most promising CMs: reversing prisms (Oman et al., 1986), torsional disconjugacy (Markham & Diamond, 1993), 90m exposure to 3Gx (Bles et al., 1997)
- Symptoms alleviated by:
 - Medications (e.g., IM Phenergan)
 - Restriction of early activities
 - Maintain familiar orientation with respect to visual environment
 - Maintain contact cues



Courtesy, Wood S



Post-flight neurological exam



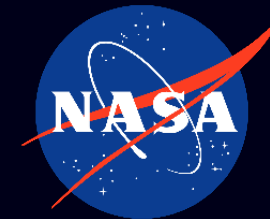
Rank Order	Neurological Function Test	% with positive signs on Landing Day
1	Tandem/Heel to Toe Walk (eyes open)	57.0%
2	Gaze/Ocular Movements	55.0%
3	Dynamic Equilibrium	47.2%
4	Leg lift-Hop	39.6%
5	Standing/ Romberg	22.2%
6	Finger to Nose	19.4%
7	Dizziness/Faintness	16.5%
8	Rising from Chair	13.8%
9	Vertigo/Spinning	11.9%
10	Drift	10.2%
11	Headache	7.5%



Clark JB. J Vestib Res (2002) 11:321-322

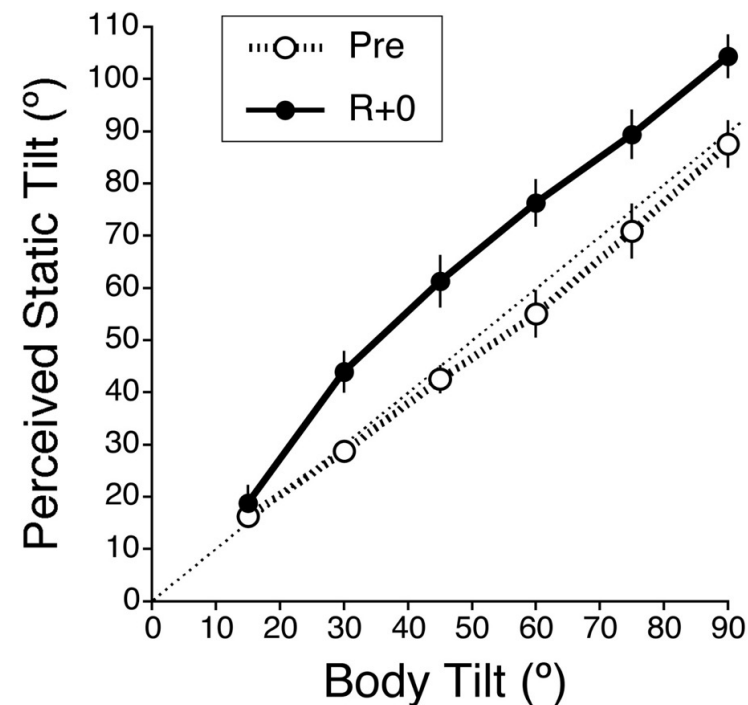


R+0 Perceptual Disturbances: Shuttle



High percentage of subjects experience perceptual disturbances (illusions of self and surround motion associated with head/body movements) during and immediately after g-transition.

Harm DL, Reschke MF, Parker DE (1999). Extended Duration Orbiter Medical Project, NASA/SP-1999-534



Offaxis Vertical Axis Rotation protocol

Roll-tilt perception is overestimated on R+0

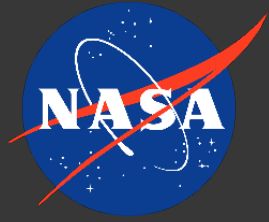
No change in Ocular Counter Rolling

Clément et al. (2007). Journal of Vestibular Research 17: 209–215

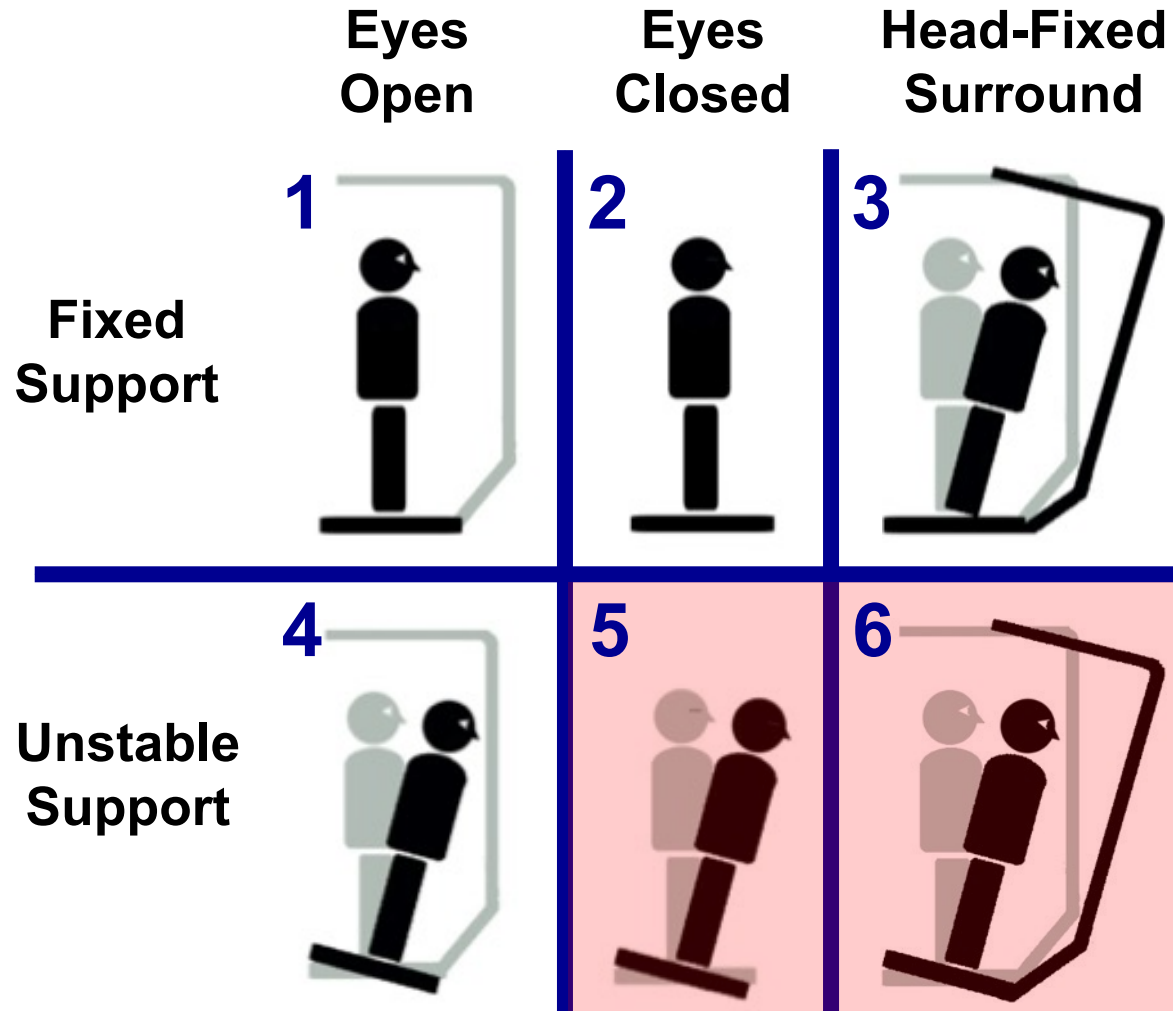
Scott Wood, PI



Sensory Organization Tests (SOT)



Altered Vision



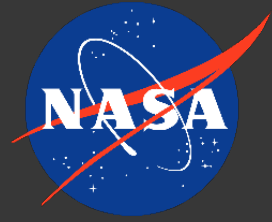
Altered Somatosensory



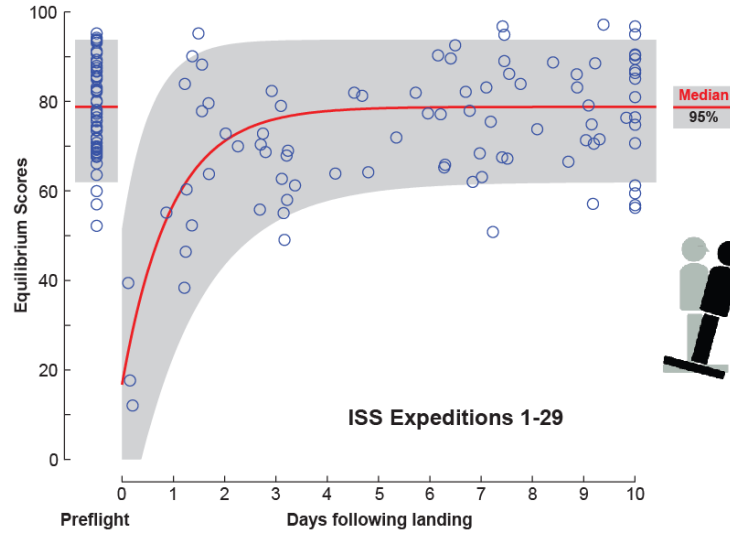
Nashner et al., J Neurosci
(1982) 2:536-544



Sensory Organization Test 5 Sharpen Tests With Head Tilts

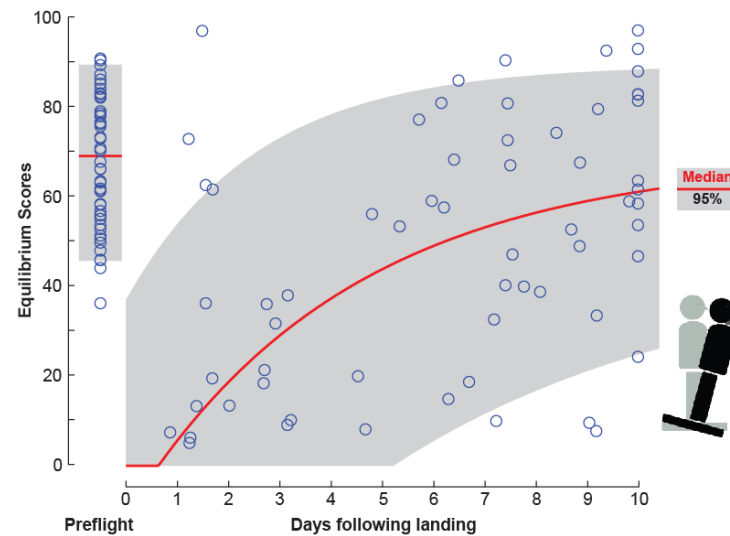


**Head
Erect**

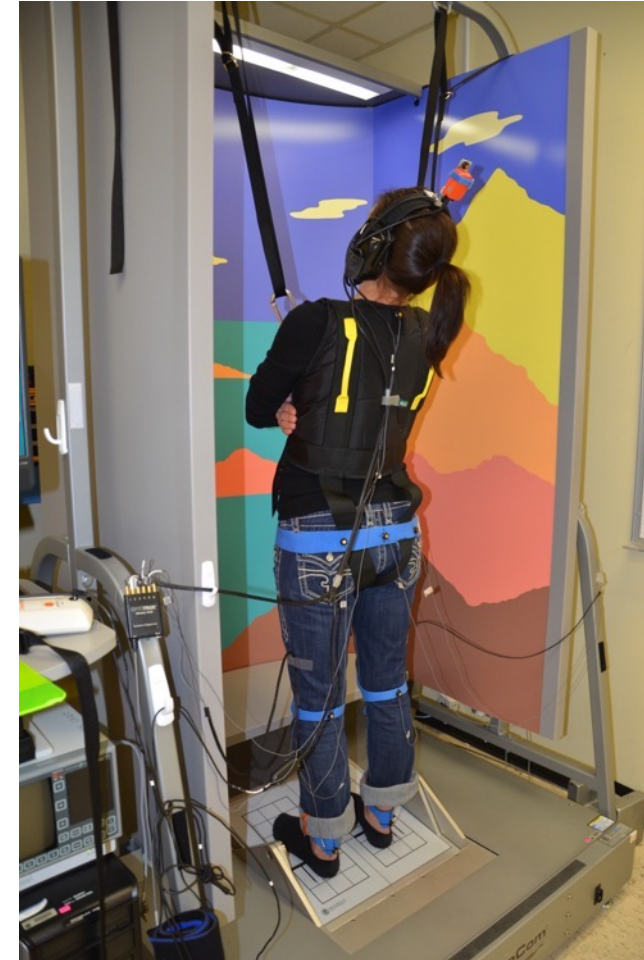


**Time constant:
19h vs 111h**

**Head
Moving**

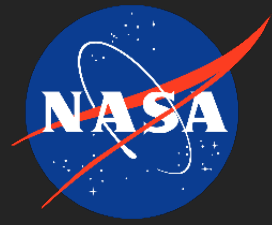


**Pitch
0.33 Hz
±20°**

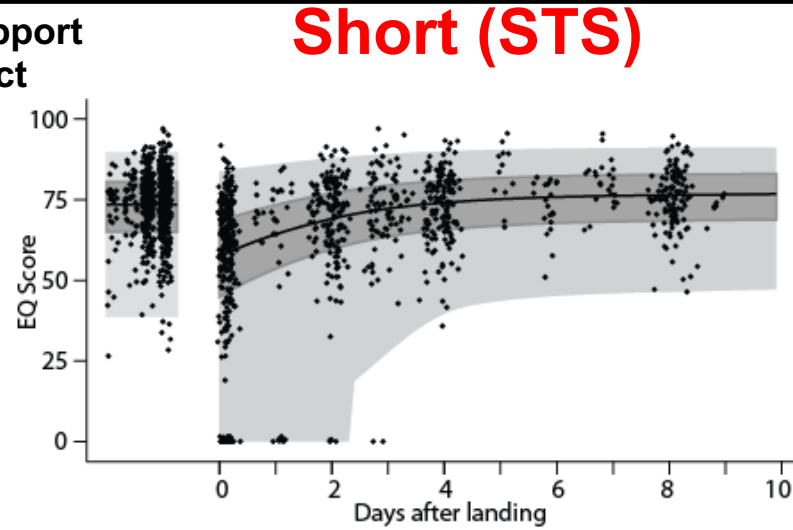




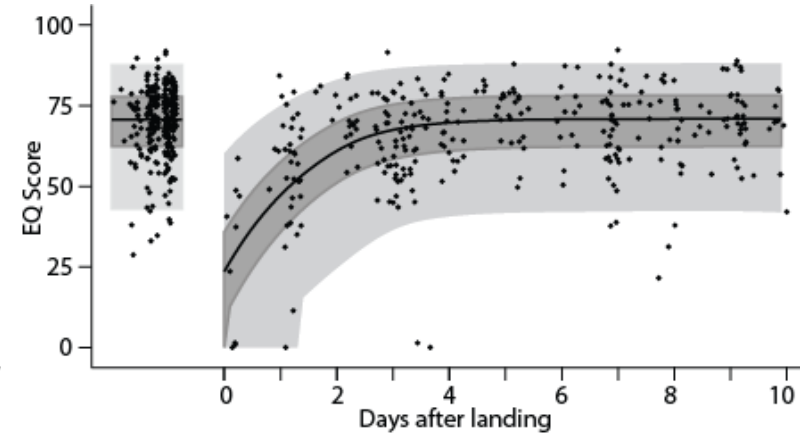
Short versus long duration



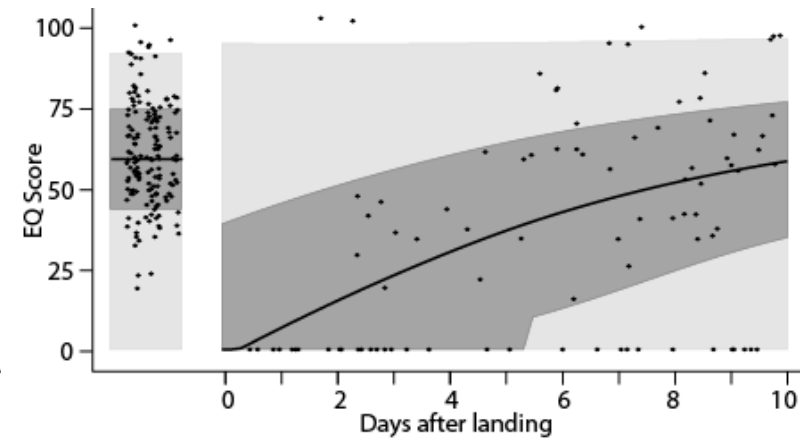
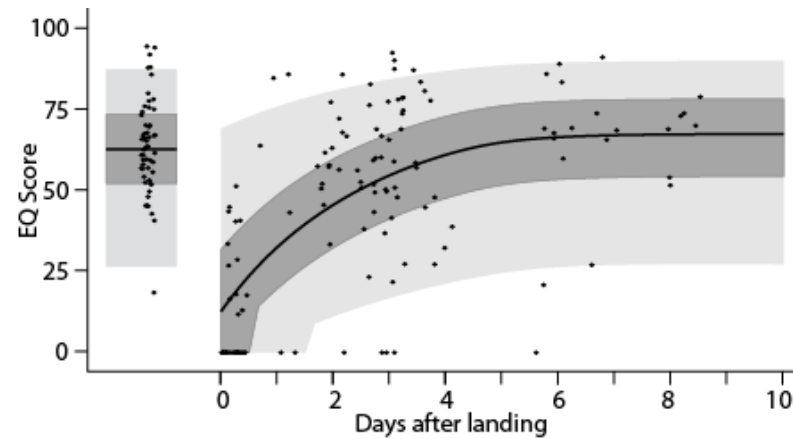
Unstable support
Head Erect



Long (MIR / ISS)

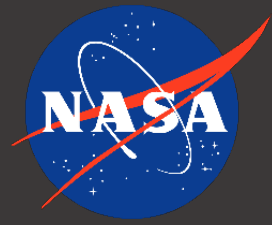


Unstable support
Head Moving





Behavioral Medicine Risk

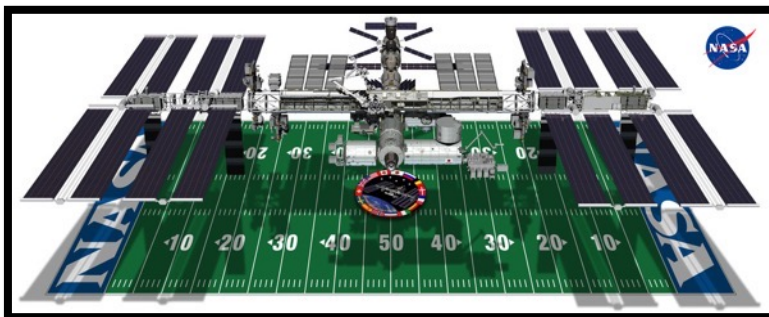


Current Operations

Low Earth Orbit

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

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



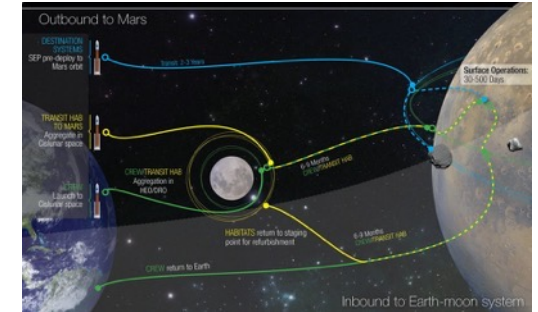
Exploration Class Missions

Deep Space

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

Major Challenges

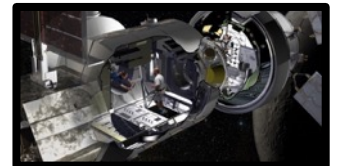
- Sleep, fatigue, workload & circadian
- Stress, conflict, mood & morale
- Selection and crew composition
- Psychosocial adaptation & training
- Meaningful work, motivation
- Growth and resiliency
- Family connectedness and communication
- Net habitable volume, sensory stimulation
- Earth out of view



Orion
Capsule
316 Ft³

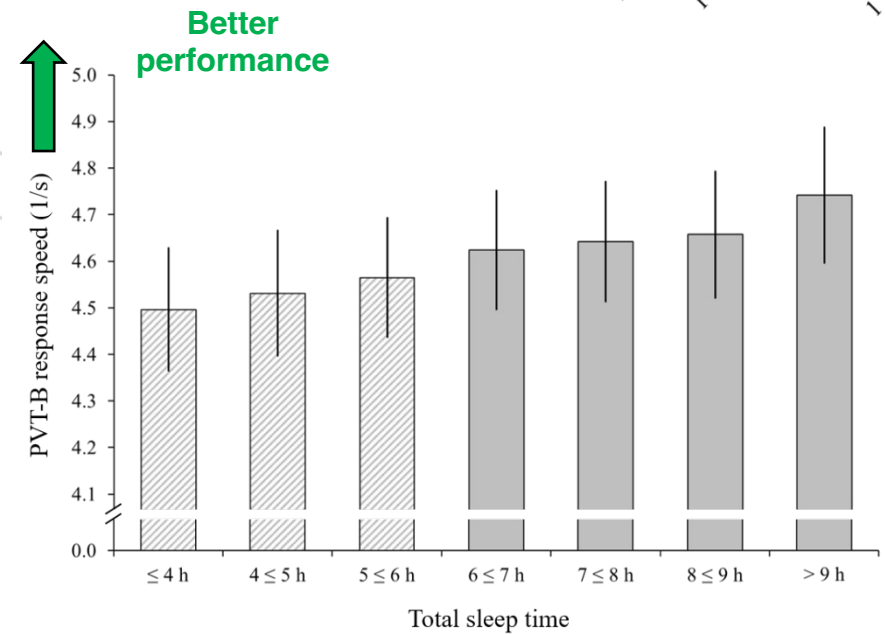
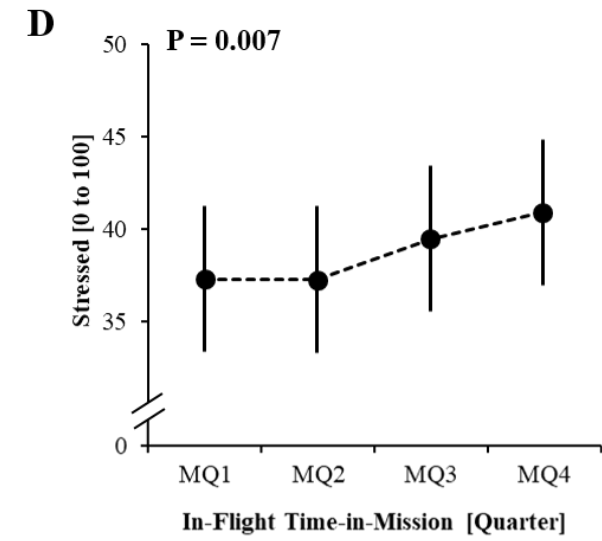
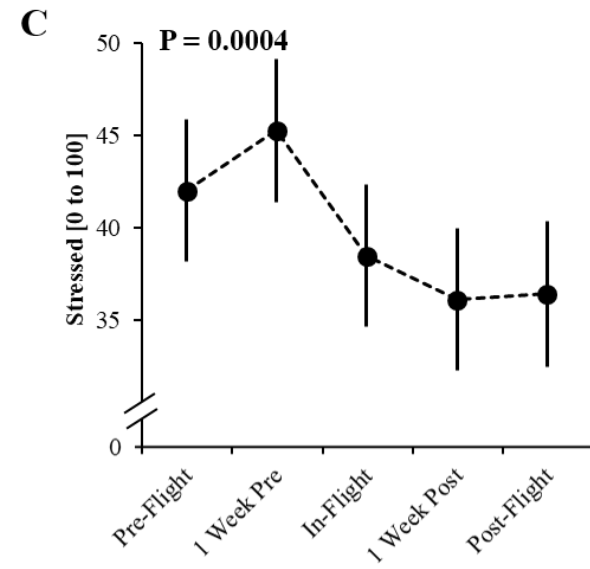
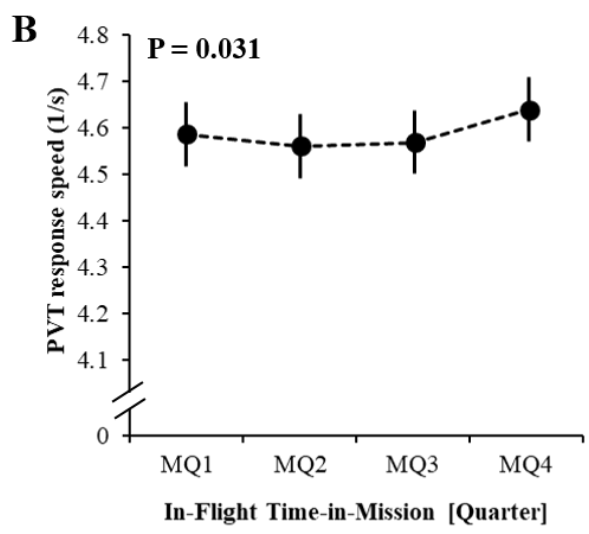
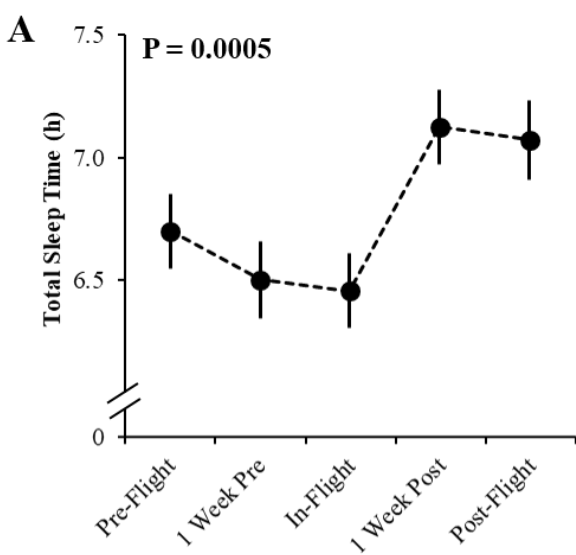
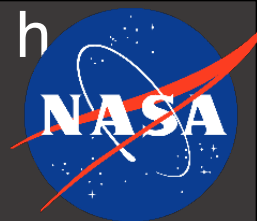


Gateway
Habitat
4415 Ft³





Astronauts reported sleeping ~6.5 h in-flight. Sleep durations of 6 h or less are associated with slower psychomotor speed, increased negative somatic behavioral states, and elevated stress



- n=24 astronauts on the ISS
- Reaction SelfTest (RST) –
 - I. sleep timing, duration, and quality
 - II. visual analog scale (VAS) ratings of behavioral states
 - III. neurobehavioral performance (i.e. PVT-B)

OXFORD Sleep Research Society®
 SLEEPJ, 2022, 1–9
<https://doi.org/10.1093/sleep/zsac006>
 Advance Access Publication Date: 12 January 2022
 Original Article

ORIGINAL ARTICLE
 Sleep deficiency in spaceflight is associated with degraded neurobehavioral functions and elevated stress in astronauts on six-month missions aboard the International Space Station

Christopher W. Jones^{1,†,*}, Mathias Basner^{1,†,*}, Daniel J. Mollicone², Christopher M. Mott² and David F. Dinges^{1,*}



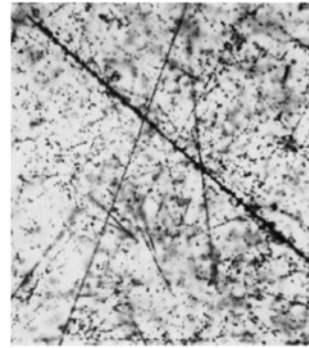
Acute Effects on CNS from Space Radiation Exposure



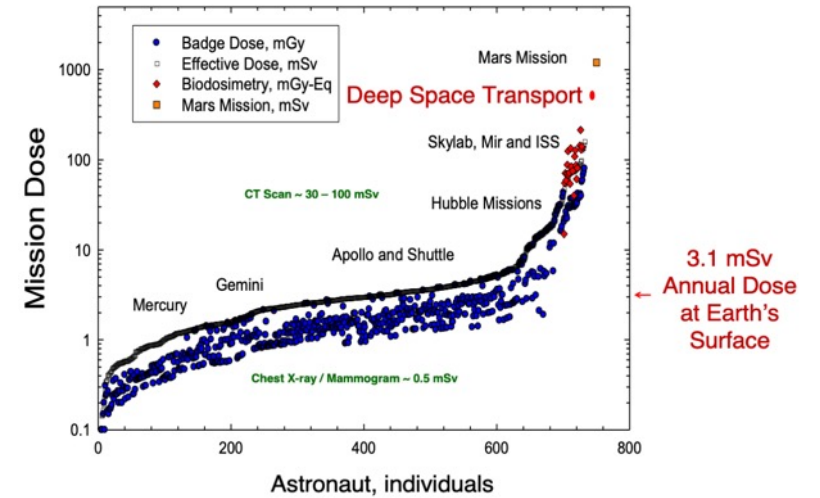
Human Space Radiation Exposure



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).



Modified from Cucinotta et al. (2002)

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

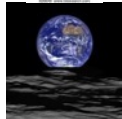


Table 1. Summary of exploration mission exposures.

Exploration Mission	Mission Duration	Dose (mGy)	Gray Equivalent (mGy-Eq) ^a	Dose Equivalent (mSv) ^b
ISS in LEO	6 months	30–60	–	50–100
ISS in LEO	1 year	60–120	–	100–200
Sortie to Gateway (free space)	30 days	20	35	55
Lunar Surface Mission (2 weeks on surface)	42 days	25	45	70
Sustained Lunar Operations	1 year	100–120	180–220	300–400
Deep-Space Habitat	1 year	175–220	300–400	500–650
Mars Mission	650 to 920 days	300–450	550–800	870–1,200

^aConversion of dose to gray equivalent uses RBE values recommended by NCRP No. 132 [25]

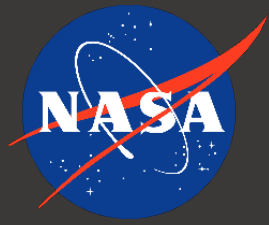
^bBoth NASA-defined quality factors [26] and ICRP 60 quality factors [11] considered in range of estimates.

Abbreviations: ICRP, International Commission on Radiological Protection; ISS, International Space Station; LEO, low Earth orbit; NCRP, National Council on Radiation Protection; RBE, relative biological effectiveness

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



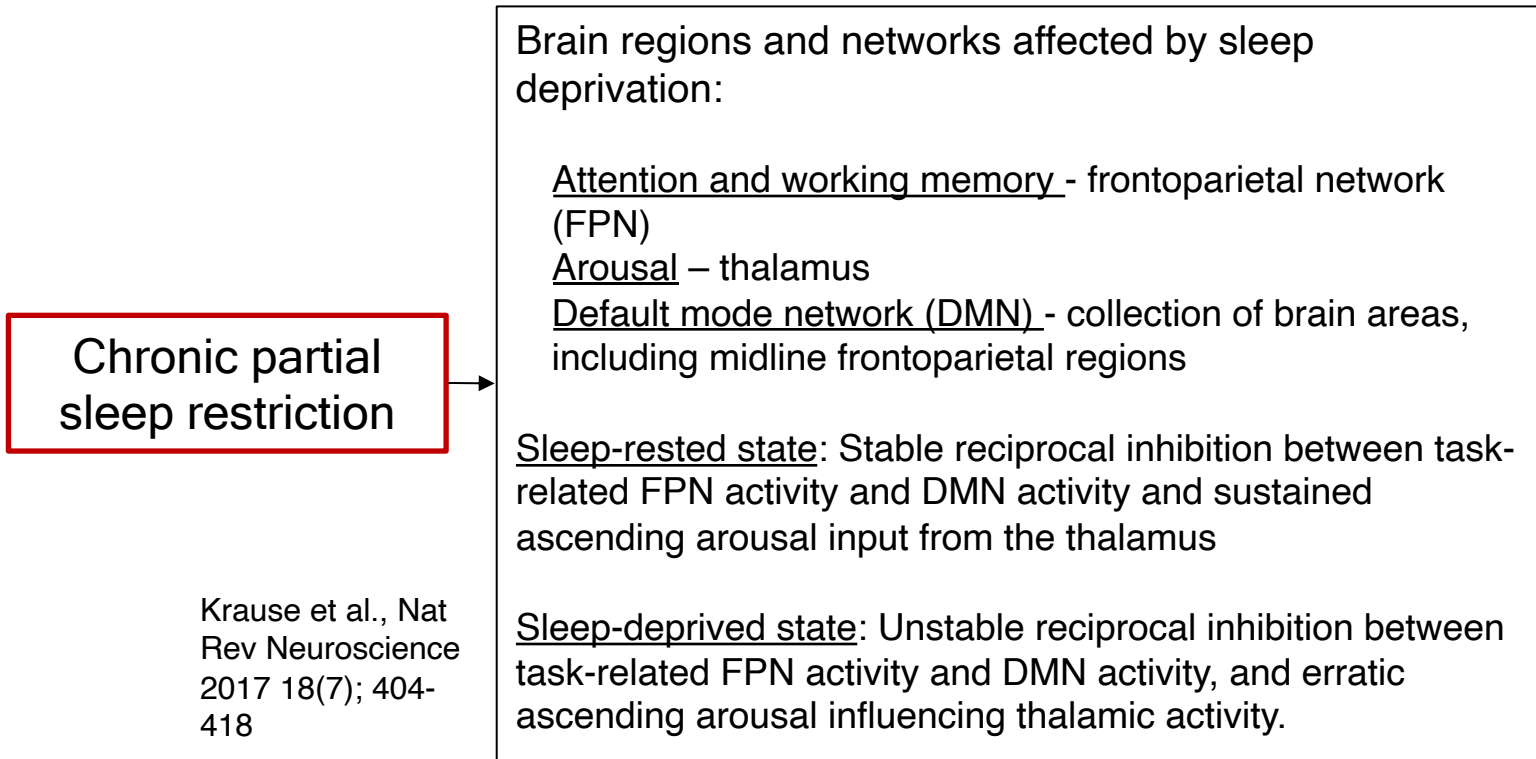
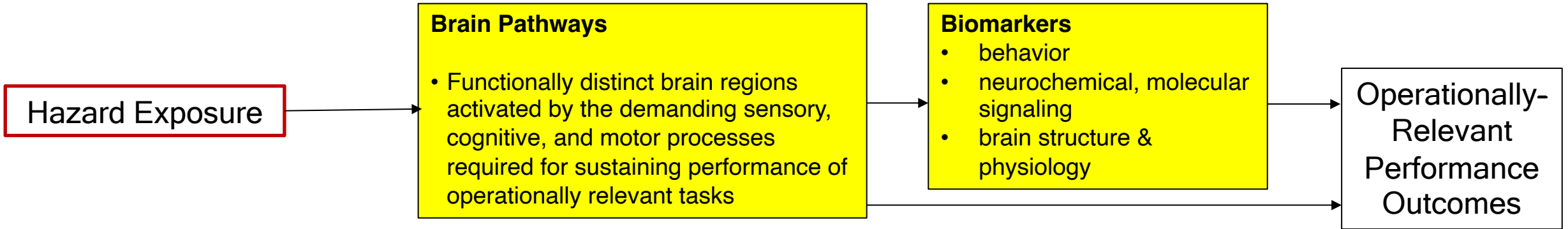
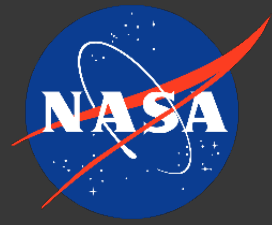
Summary of Evidence: Space Radiation Simulation Rodent Studies



- 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)
- Minimum dose to observe 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
- Preliminary evidence show that persistent compensatory process(es) may outlast radiation-induced impairments and sequelae in male and female mice (Miry et al. 2021; Garrett et al. 2022)



Biomarkers of Operationally Relevant Performance & Brain Pathways



Krause et al., Nat Rev Neuroscience 2017 18(7); 404-418

- Eye lid droop
- Psychomotor Vigilance Test (PVT)
- Dual task

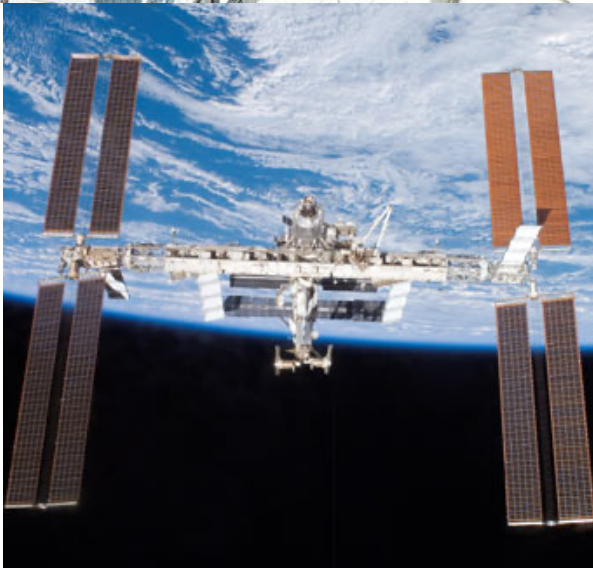
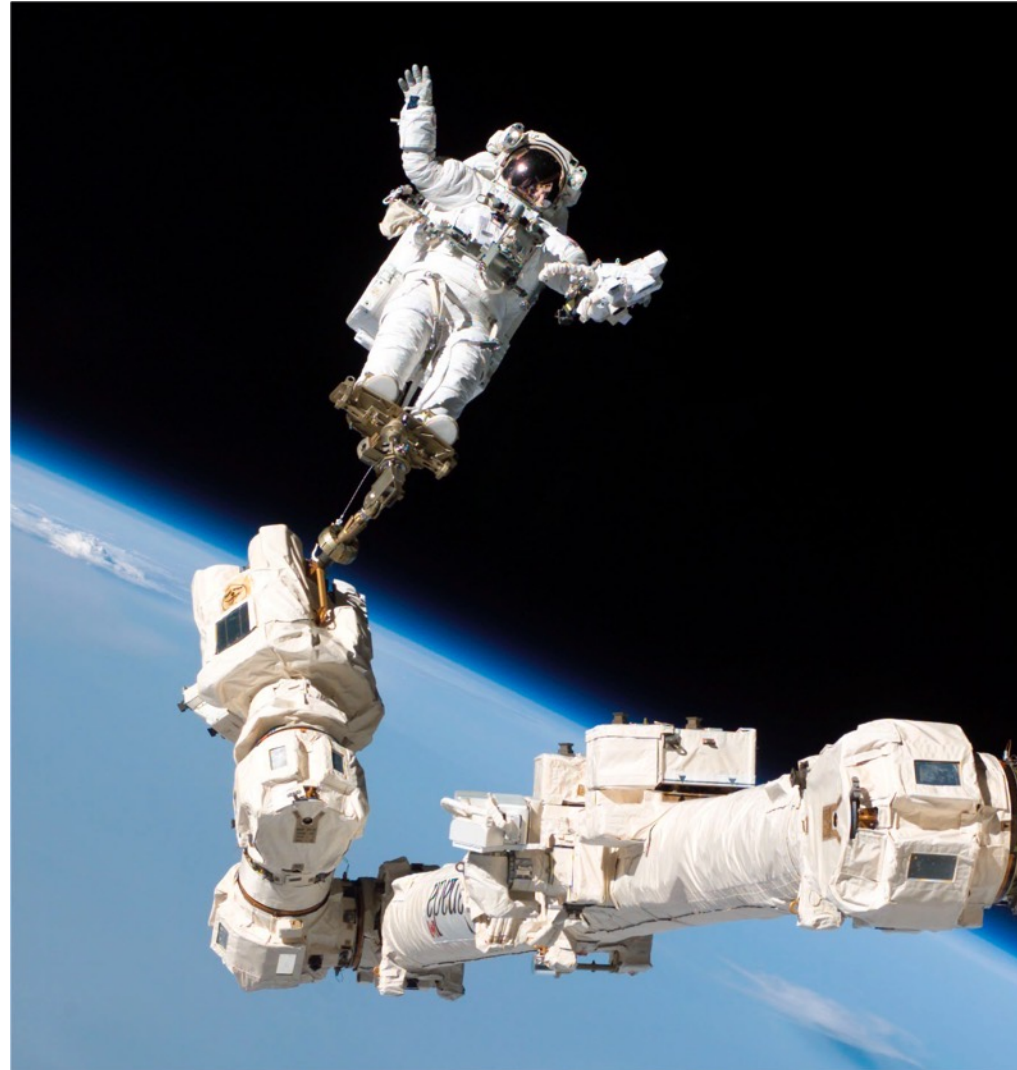
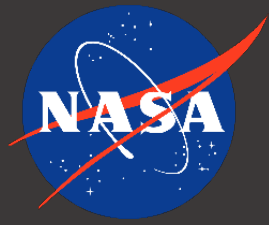
Control of Robot on International Space Station



Allows for translation in animal model

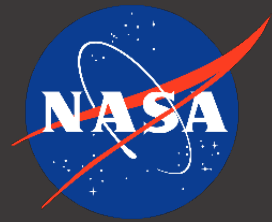


Effects of Spaceflight on Operational Performance

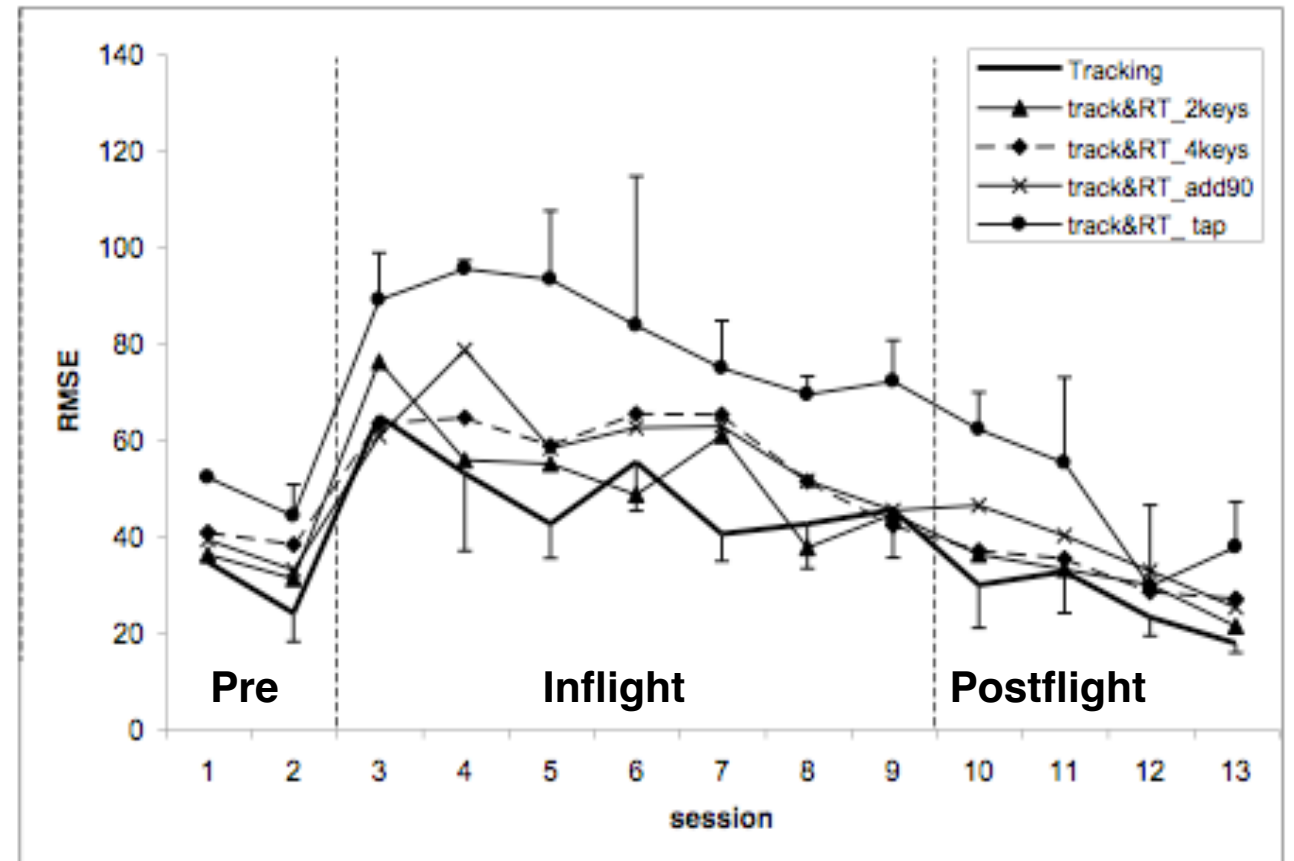
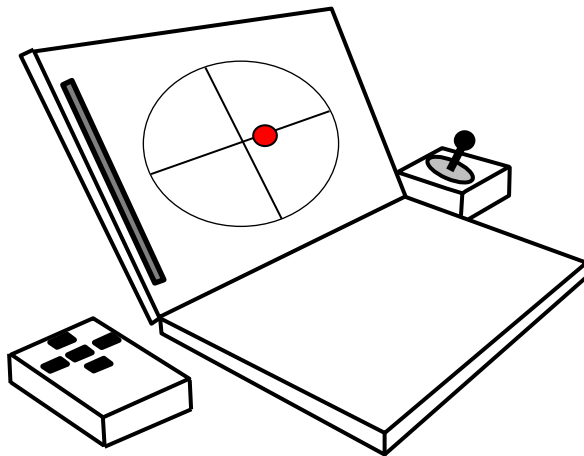




Manual Control and Dual Tasking



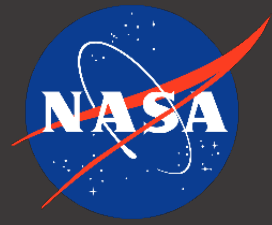
Dual tasking increases error in manual control during periods of adaptive change – implications for cognitive reserve



RMSE: Root mean square error for manual control

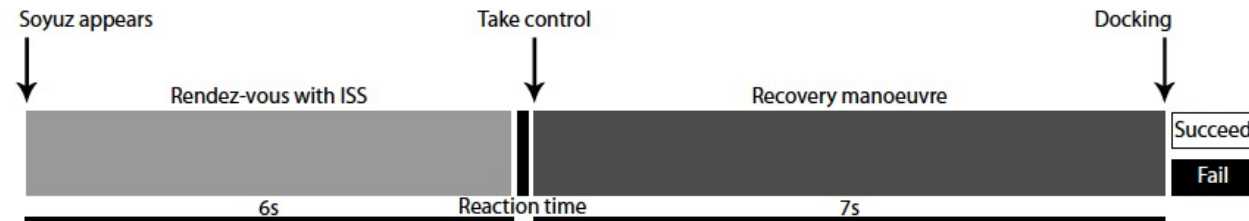
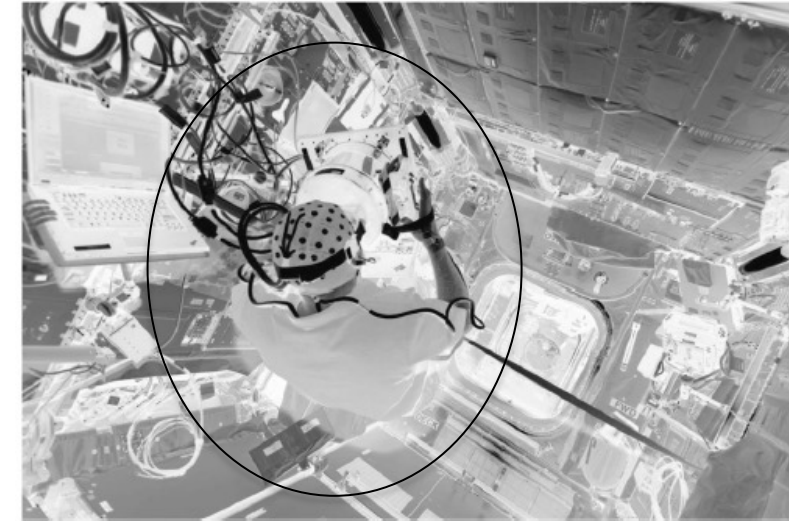
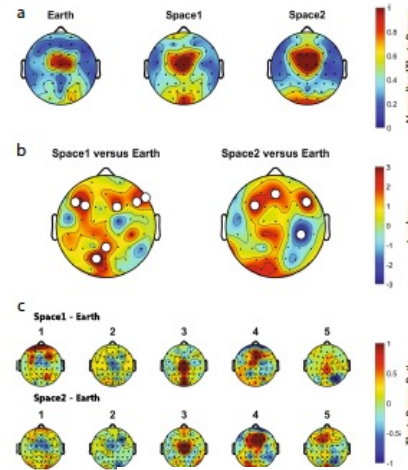


Sleep Pressure Markers Associated with Reduced Performance During Spaceflight



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

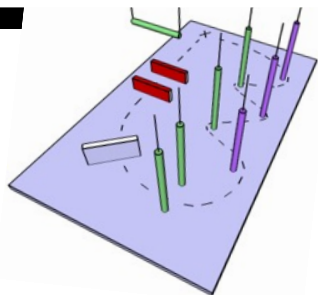
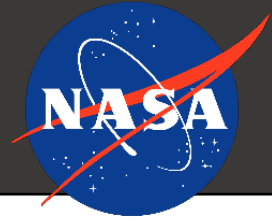
Theta power topographical distribution (5-7 Hz)



Visuo Motor Task



Functional Mobility after Long-Duration Space Flight

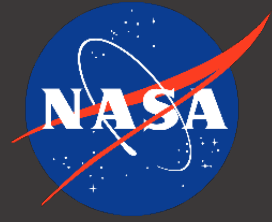


Functional Mobility Test

PI: Jacob Bloomberg

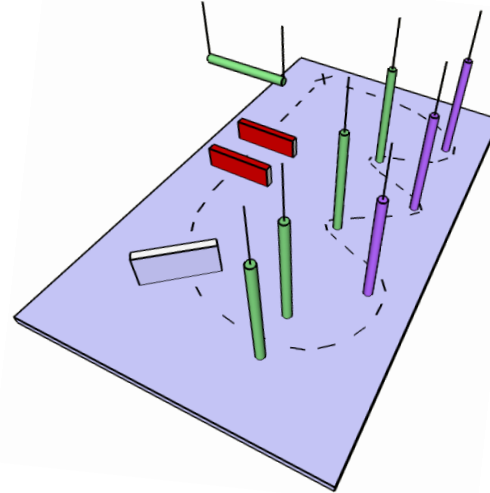


Functional Mobility after Long-Duration Space Flight



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

Functional Mobility Test



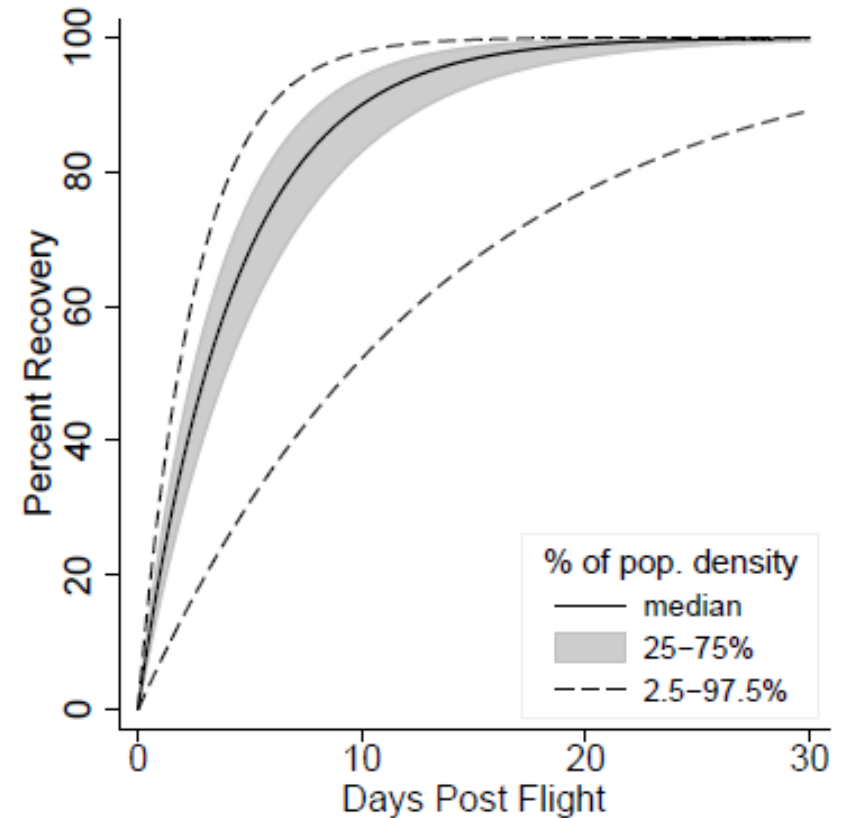
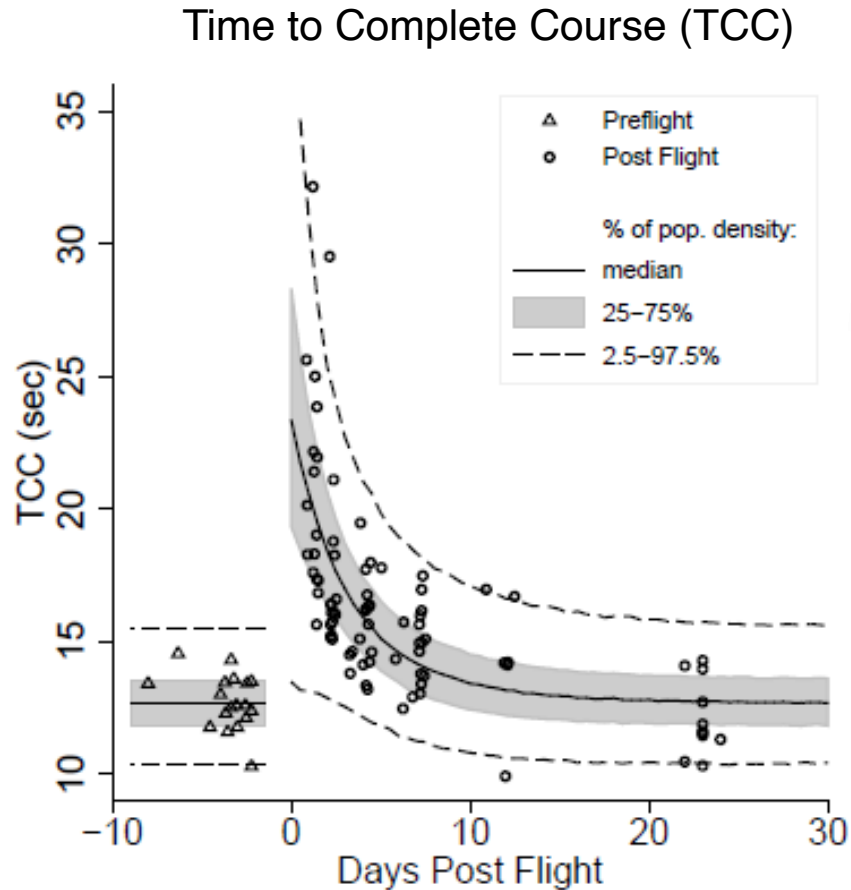
N = 18

Exp Brain Res
DOI 10.1007/s00221-010-2171-0
RESEARCH ARTICLE

Locomotor function after long-duration space flight: effects and motor learning during recovery

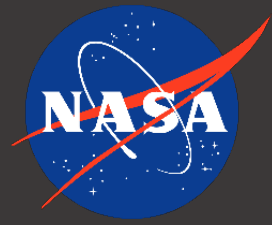
Ajitkumar P. Mulavara · Alan H. Feiveson · James Fiedler · Helen Cohen · Brian T. Peters · Chris Miller · Rachel Brady · Jacob J. Bloomberg

Percent Recovery

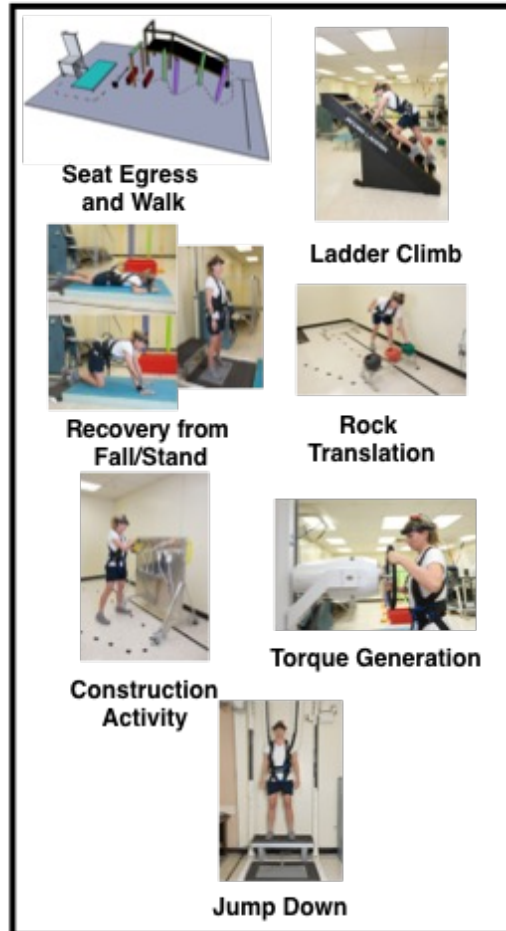




Functional Task Test



Functional Performance



> [Med Sci Sports Exerc.](#) 2018 Sep;50(9):1961-1980. doi: 10.1249/MSS.0000000000001615.

Physiological and Functional Alterations after Spaceflight and Bed Rest

Ajitkumar P Mulavara ¹, Brian T Peters ¹, Chris A Miller ¹, Igor S Kofman ¹, Millard F Reschke ², Laura C Taylor ¹, Emily L Lawrence ¹, Scott J Wood ², Steven S Laurie ³, Stuart M C Lee ³, Roxanne E Buxton ⁴, Tiffany R May-Phillips ³, Michael B Stenger ⁵, Lori L Ploutz-Snyder ⁶, Jeffrey W Ryder ⁴, Alan H Feiveson ⁷, Jacob J Bloomberg ²

Affiliations + expand

PMID: 29620686 PMID: PMC6133205 DOI: 10.1249/MSS.0000000000001615

[Free PMC article](#)

> [Aerosp Med Hum Perform.](#) 2018 Sep 1;89(9):805-815. doi: 10.3357/AMHP.5039.2018.

Functional Task and Balance Performance in Bed Rest Subjects and Astronauts

Chris A Miller, Igor S Kofman, Rachel R Brady, Tiffany R May-Phillips, Crystal D Batson, Emily L Lawrence, Laura C Taylor, Brian T Peters, Ajitkumar P Mulavara, Alan H Feiveson, Millard F Reschke, Jacob J Bloomberg

PMID: 30126513 DOI: 10.3357/AMHP.5039.2018

> [Compr Physiol.](#) 2019 Dec 18;10(1):171-196. doi: 10.1002/cphy.c190005.

Exercise Countermeasures to Neuromuscular Deconditioning in Spaceflight

Kirk L English ^{1 2}, Jacob J Bloomberg ³, Ajitkumar P Mulavara ⁴, Lori L Ploutz-Snyder ⁵

Affiliations + expand

PMID: 31853963 DOI: 10.1002/cphy.c190005

PI: Jacob Bloomberg



STS - Sho

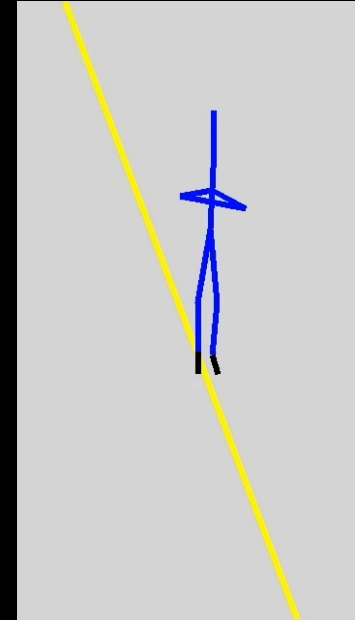
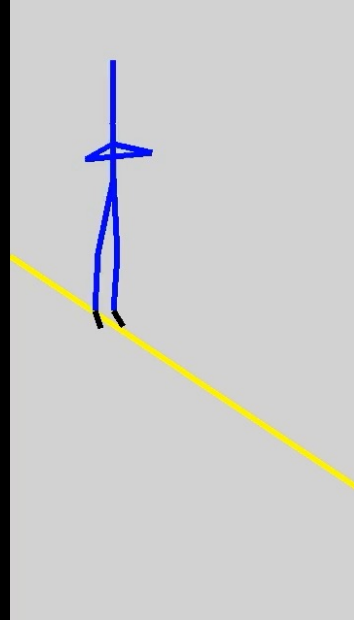


Preflight



R+0/R+1

ISS - Long

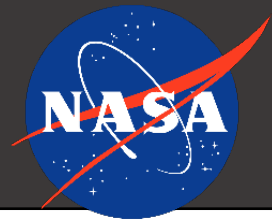


Tandem Walk Eyes Closed

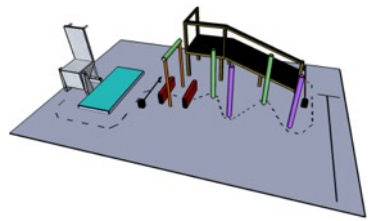
PI: Jacob Bloomberg



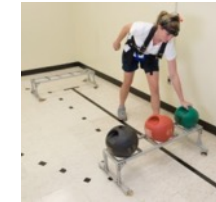
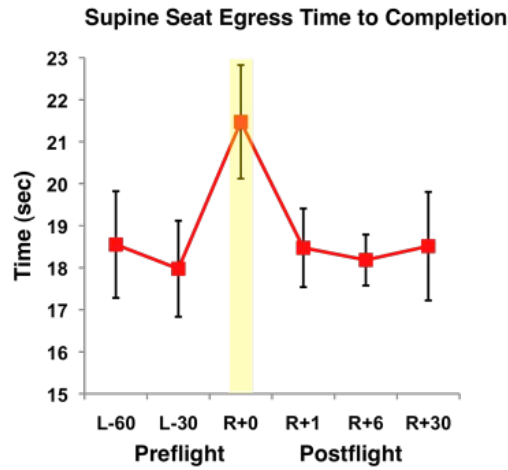
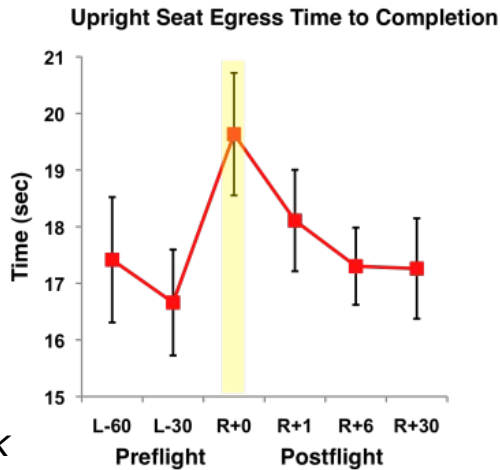
Functional Task Test



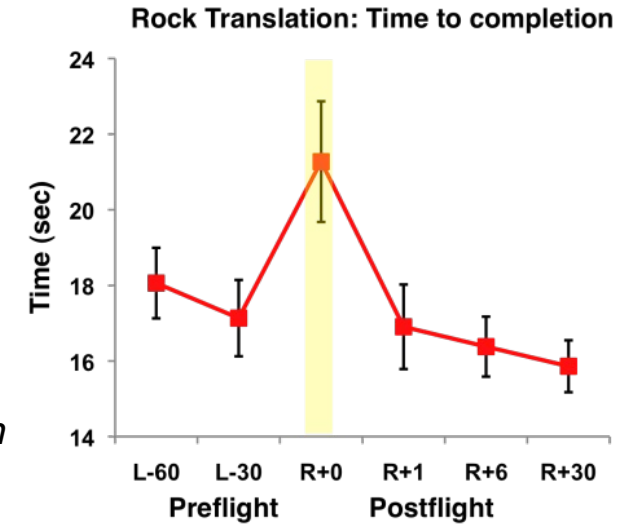
Functional tasks with a postural equilibrium challenge show the greatest change shortly after Shuttle landings (n=7)



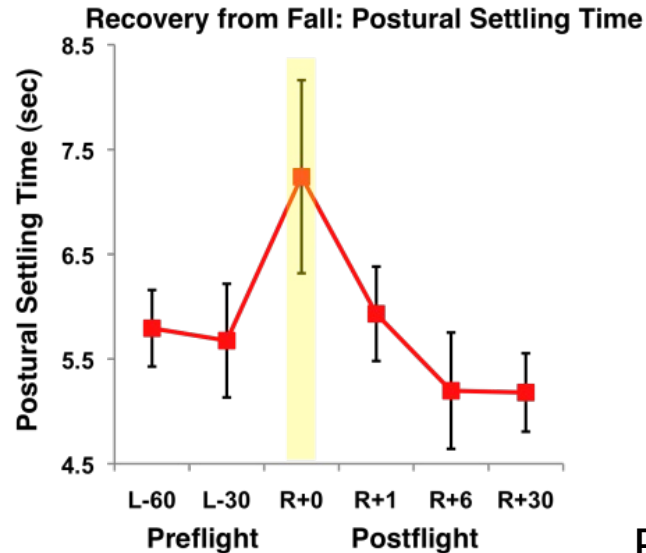
Seat Egress and Walk



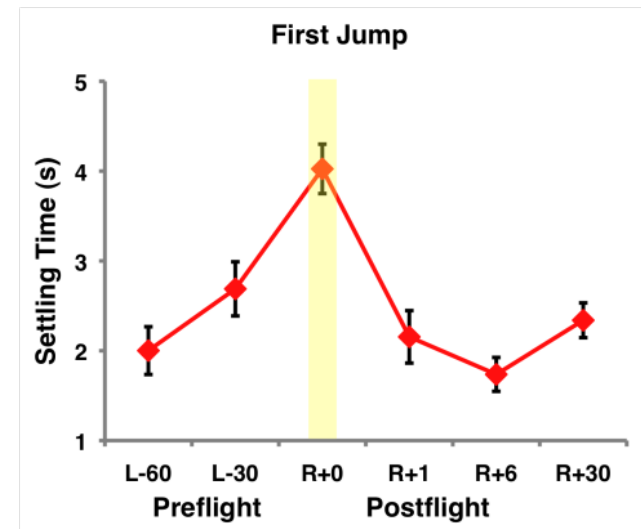
Rock Translation



Recovery from Fall/Stand



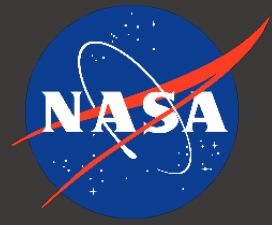
Jump Down



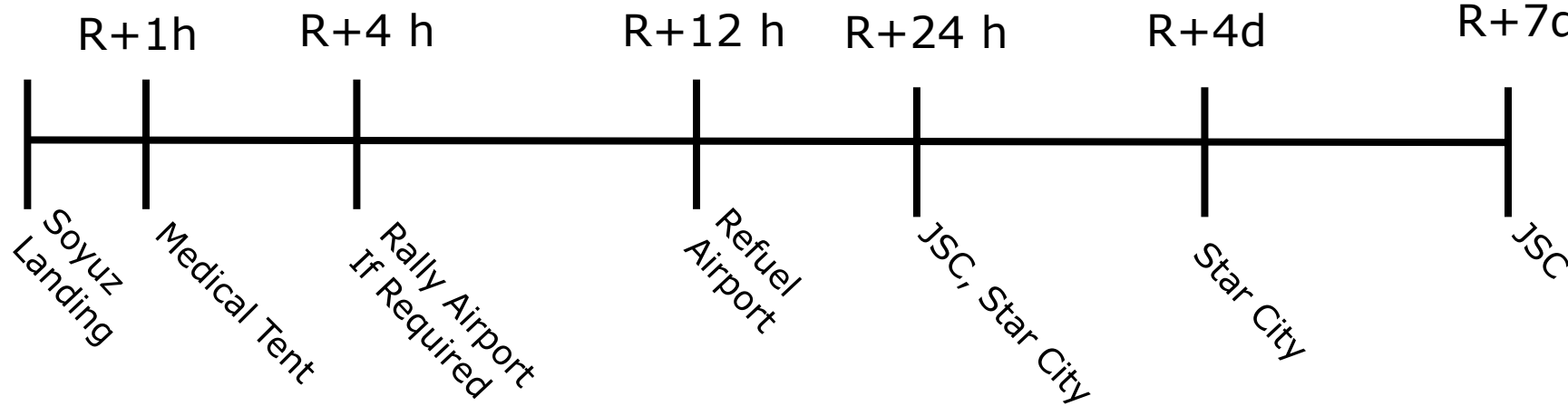
PI: Jacob Bloomberg



Field Test: Early Postflight Testing after Long Duration Spaceflight



PIs: M. Reschke, I. Kozlovskaya



Recovery from Fall



Sit-to-stand



Tandem Walk

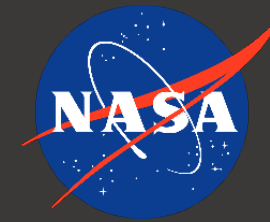


Eyes Open (EO)
Eyes Closed (EC)





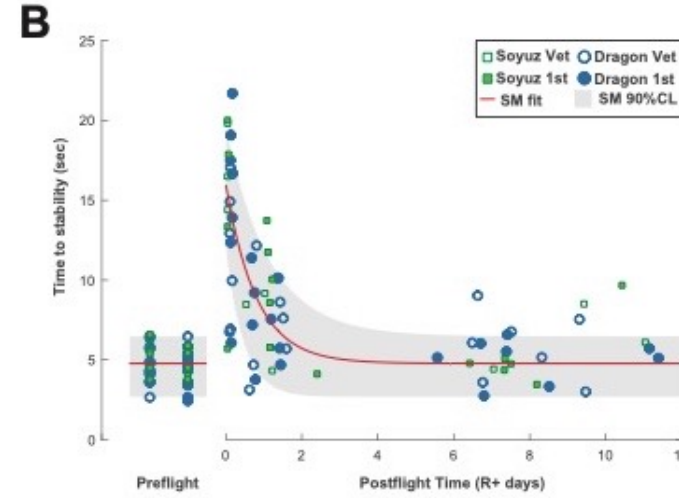
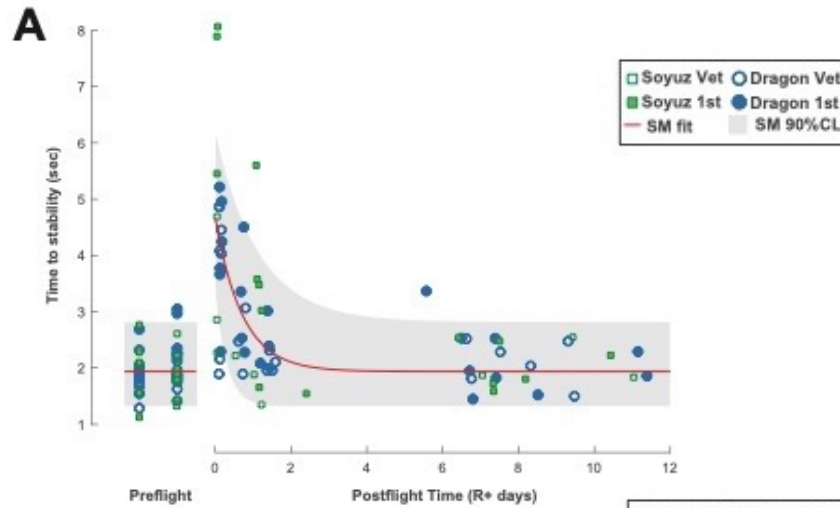
Field Test: rookies vs veterans & Dragon vs Soyuz landings



Sit-to-stand



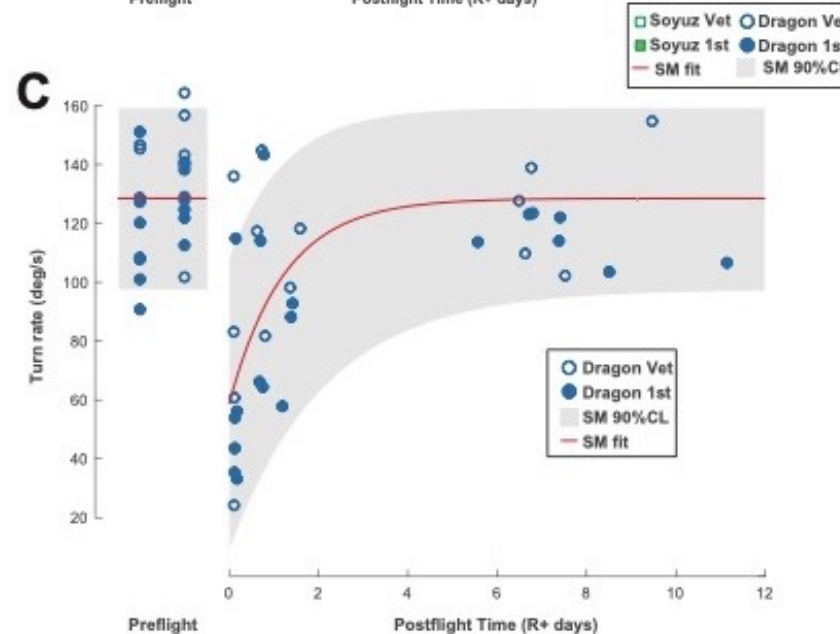
Time to stability



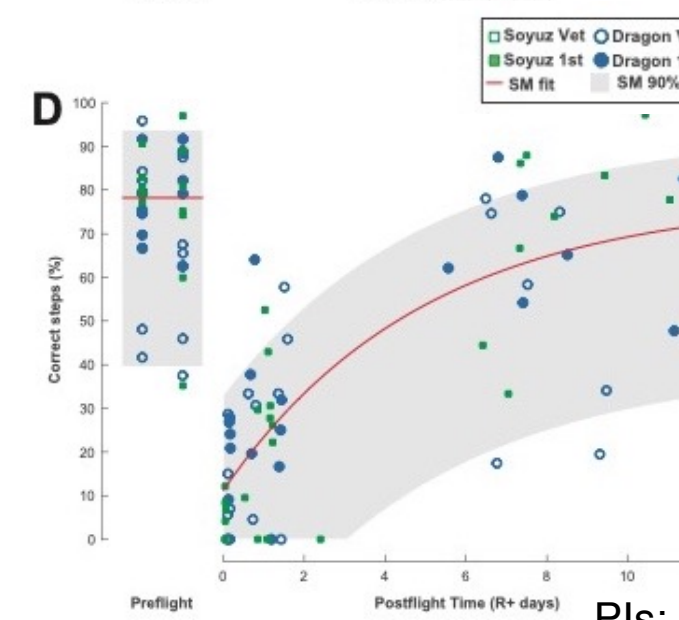
Recovery from Fall



Time to stability



Walk and Turn task Turn rate



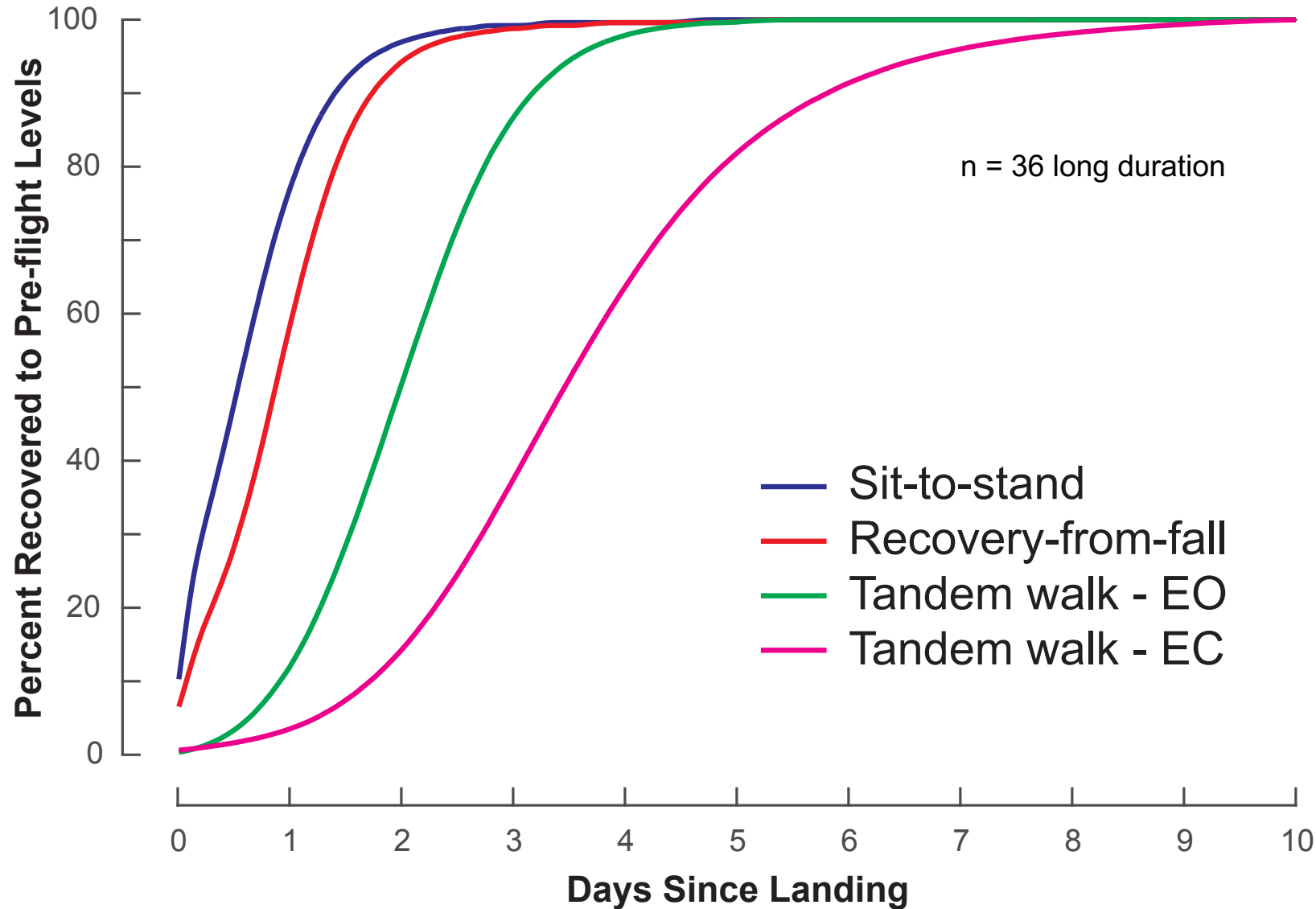
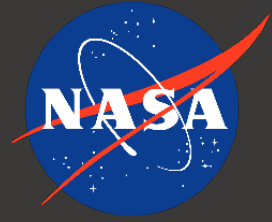
Tandem Walk



Eyes Closed (EC) # of correct steps



Recovery curves: Functional Tasks



Recovery from Fall



Sit-to-stand



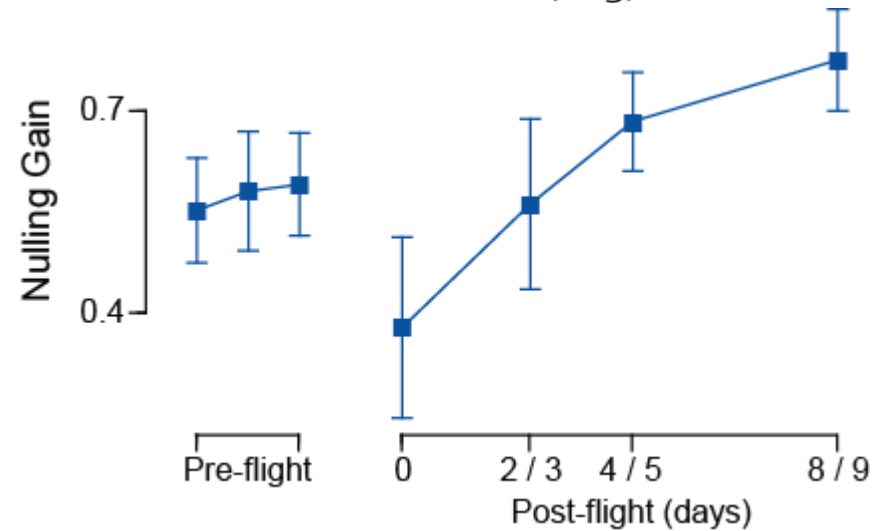
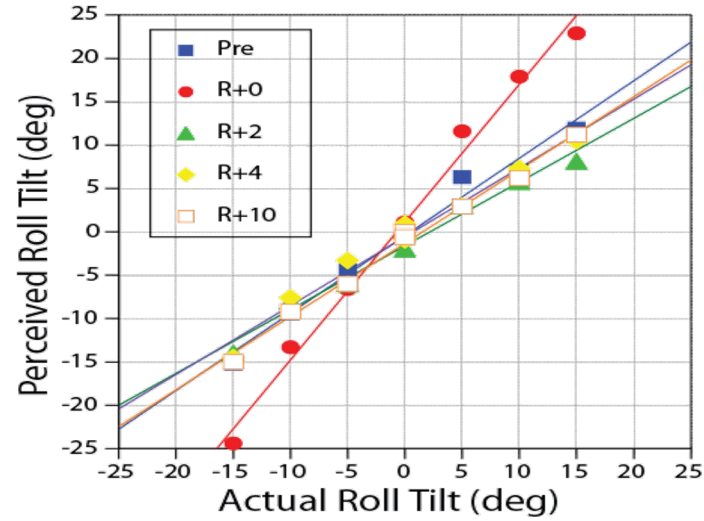
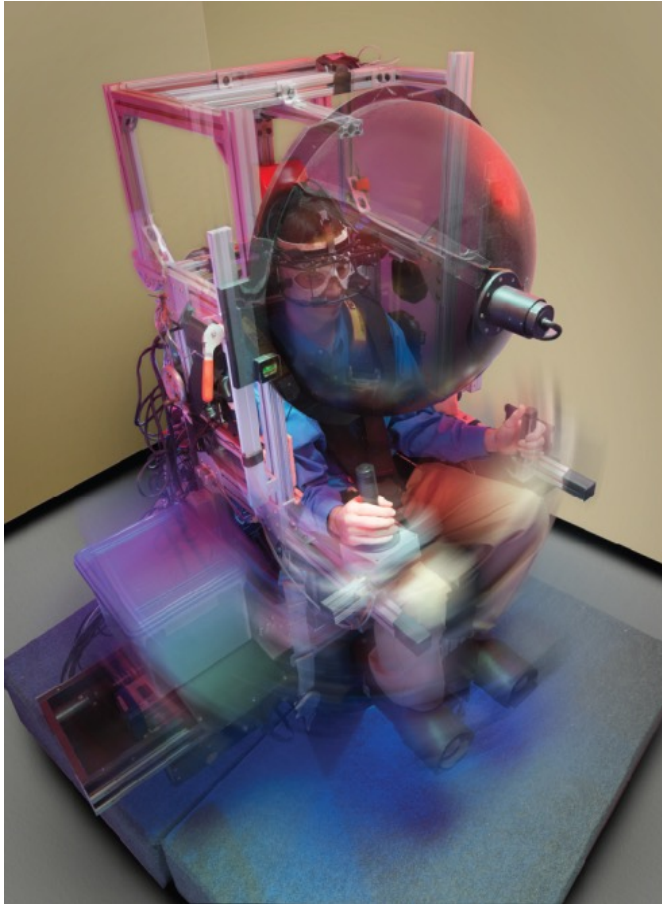
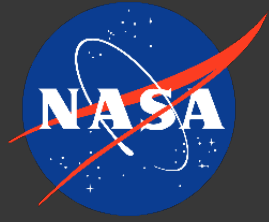
Tandem Walk



Eyes Open (EO)
Eyes Closed (EC)



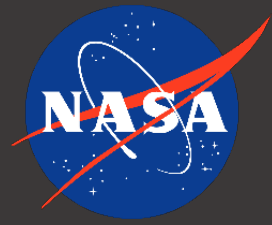
Tilt perception versus manual control



Scott Wood, PI



Driving Simulation after 6 Months on the International Space Station

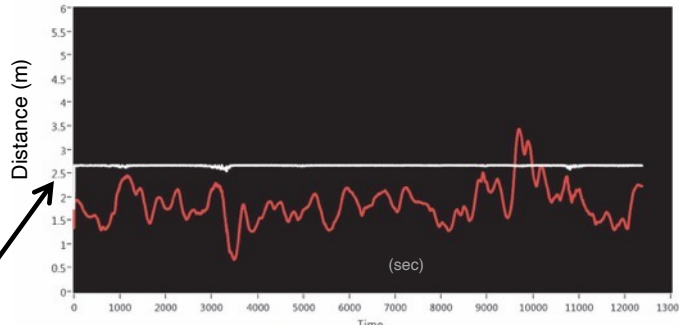


Postflight increases in: # of lane crossings, time in wrong lane and time to return to correct lane.

Manual control function shows decrement after gravity transitions following long duration missions.

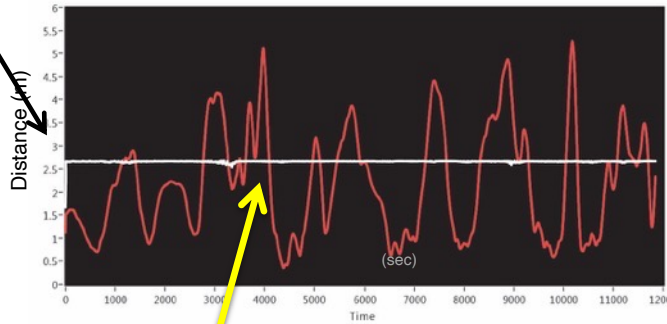
Driving (Mountain Course)

Preflight

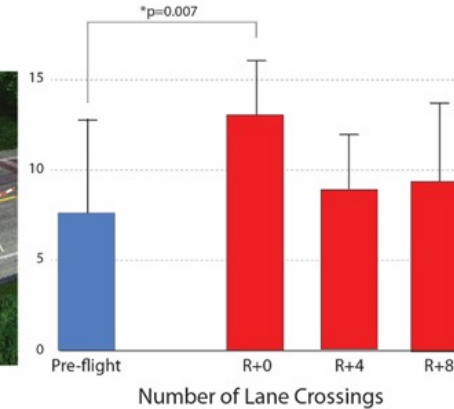
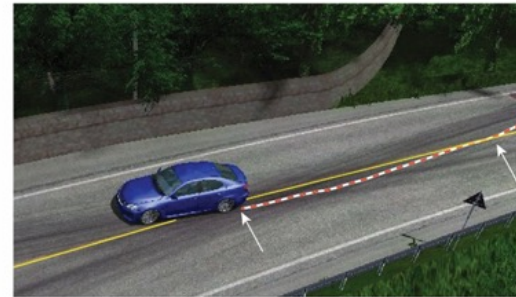


Lane divider

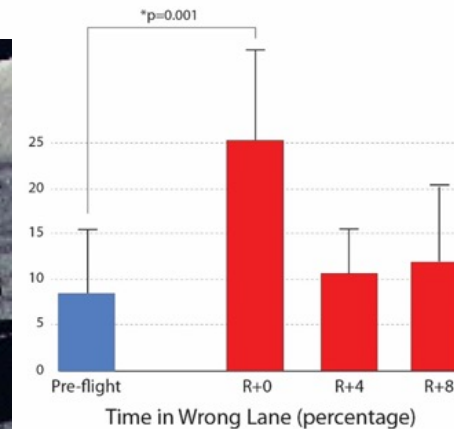
Postflight (R+0)



Car position



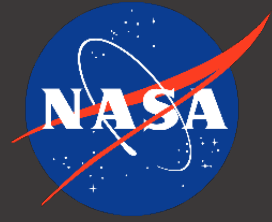
of Lane Crossings



Time in Wrong Lane



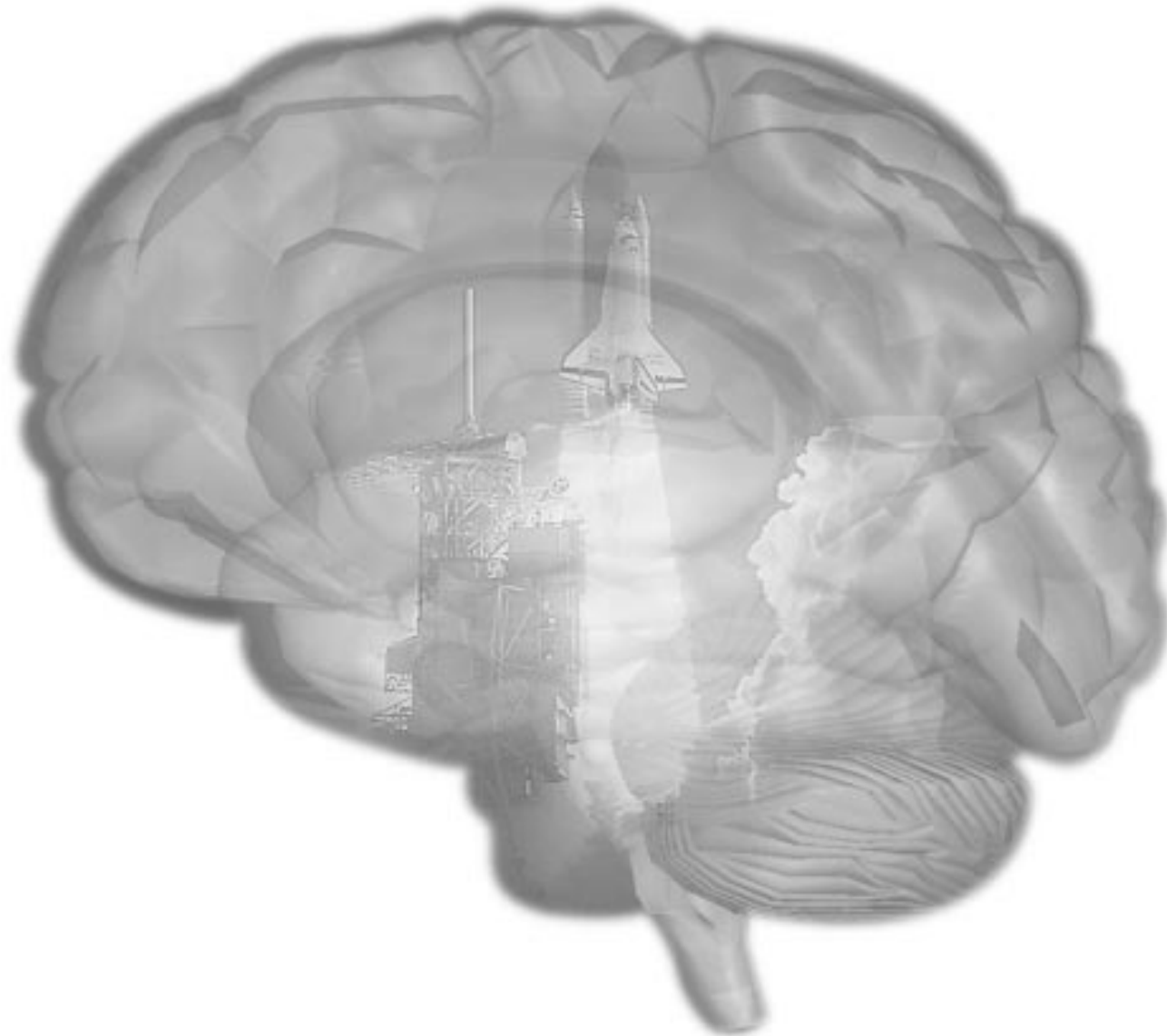
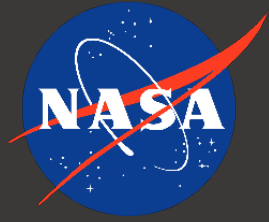
Summary of Evidence Operational Performance



- Postural control and mobility function show decrement after gravity transitions during short and long duration missions (e.g. egress task)
- Manual control function shows decrement during and after gravity transitions following short and long duration missions (e.g. landing, driving, docking)
- 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)

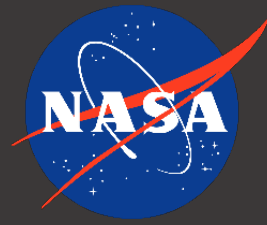


Effects of Spaceflight on Brain Structure and Function





Alterations to the Brain During Spaceflight



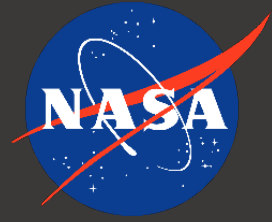
Study	Population	Imaging Protocol	Main Findings
Roberts et al. 2019 ¹⁹	n=19, 7 SD and 12 LD Pre- and post flight scans	T1-weighted MRI (3T) - Brain tissue and CSF volumes	<ul style="list-style-type: none"> Increase in total ventricular volume in LD crew. Significant increase in lateral ventricles and third ventricle, but not in fourth ventricle. Change in ventricular volume associated with increasing flight duration and decreasing crewmember age. 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. <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
Van Ombergen et al. 2019 ²¹	n=11, LD Pre- and post flight scans, 7-month follow-up	T1-weighted MRI (3T) - CSF volumes	<ul style="list-style-type: none"> 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. Ventricular volume increases associated with increasing mission duration
Riascos et al. 2019 ¹⁷	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"> Trend for cortical thinning of R occipital lobe; reduced volume of L thalamus; increased lateral ventricular volume. WM changes in R posterior thalamic radiations, trend towards greater effects in LD crew.
Pechenkova et al. 2019 ²³	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"> Stimulation-specific increase in connectivity of R posterior supramarginal gyrus with the rest of the brain 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 Connectivity modifications at vestibular nuclei, R parietal cortex, anterior cerebellar network, R posterior insula and L posterior insula <u>Clinical Correlate:</u> Space motion sickness severity associated with connectivity between R posterior supramarginal gyrus and L insular region
Kramer et al. 2020 ²²	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"> 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 Increased aqueductal stroke volume and CSF peak-to-peak velocity magnitude Pituitary depression seen in 6/11 crewmembers
Hupfield et al. 2020 ²⁴	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"> 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 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
Jillings et al. 2020 ²⁵	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"> GM changes driven by local volume shifts rather than tissue loss, largely reversed at 7-month follow up WM volume increases in the cerebellum, CST, PMC GM volume increases in the basal ganglia Larger visual acuity decreases post-flight associated with greater ventricular expansion

Structure	Function	System	Functional Symptoms
Superior Longitudinal Fasciculus (Right) ⁶	Connects the frontal, occipital, parietal, and temporal lobes. Visuospatial attention (goal-directed, stimulus driven) and motor control. ⁷	Visual, motor, cognitive, behavioral	Observed: Crewmembers with the largest spaceflight-associated balance disruptions had greater WM structure changes in the SLF ⁶ Potential: Visuospatial cognitive dysfunction (searching, shifting spatial attention, performing mental rotations, detecting patterns) ⁷
Inferior Longitudinal Fasciculus ⁵	Connects temporal and occipital lobes. Visual modality, object/face/place processing, emotional processing, visual memory. ⁸	Visual, cognitive, behavioral	Potential: Visual neglect, visual amnesia, visual hallucinations, prosopagnosia, visual hypo-emotionality ⁸
Inferior Occipitofrontal Fasciculus ⁵	Connects frontal and occipital/temporal lobes. Hypothesized role in spatial attention and cognition (non-dominant), goal-oriented behavior, social cognition, attention ⁹	Visual, cognitive, behavioral	Potential: Reduced verbal fluency, spatial neglect, anosognosia, potential for inability to identify facial emotions ⁹
R. posterior thalamic radiations ¹⁰	Posterior radiations connect thalamus and occipital cortex, contain optic radiations. ¹¹	Visual	Potential: Visual pathway deficits ¹¹
Calcarine, middle occipital, inferior occipital gyri ¹⁰	Location of the primary visual cortex and secondary visual association cortex. ¹²	Visual, cognitive	Potential: Visual hallucinations, visual field cuts ¹²
Right fusiform gyrus ¹⁰	Facial and word recognition, within-category identification ¹³	Visual, cognitive, behavioral	Potential: Prosopagnosia, dyslexia ¹³
Inferior cerebellar peduncle ⁵	Connects the cerebellum to the spinal cord and medulla. Carries input from vestibular receptors (afferent and efferent) to help with posture, balance, coordination. ¹⁴	Cerebellar, vestibular	Potential: Vertigo and imbalance mimicking a peripheral vestibular issue, ocular tilt, spontaneous nystagmus ¹⁴
Middle cerebellar peduncle ⁵	Afferent pathway from pons to cerebellum. Controls the initiation, planning and timing of volitional motor activity. ¹⁵	Cerebellar, motor	Potential: Cerebellar ataxia (limb, gait, speech) ¹⁵
Corticospinal Tract ⁶	Efferent motor information from the cerebral cortex to the body. ¹⁶	Motor	Potential: Central motor weakness ¹⁶
White matter underlying primary motor and sensory cortices ⁵	Afferent and efferent motor and sensory information, sensory integration. ^{17,18}	Motor, somatosensory, vestibular, cognitive	Potential: Impairment in voluntary movement, sensory weakness or sensory loss, deficits in perception of somatosensory input and vestibular equilibrium. ^{17,18}
Inferior and posterior parietal lobe ⁵	Body spatial representation, central vestibular and proprioceptive processing, vertical upright perception. ¹⁹	Somatosensory, vestibular, cognitive	Potential: Sensorimotor deficits, including deficits in perception and spatial memory, inaccurate reaching and grasping, inattention, deficits in trunk and limb orientation. ^{19,20}
Thalamus ¹⁰	Relays information between cortex and subcortical areas. ²¹	Visual, somatosensory, cognitive, behavioral	Potential: Neuropsychological disturbances, motor weakness or sensory loss, deficits in episodic memory, executive function, processing speed, directed attention, working memory. ²¹
Frontal poles ²²	Higher order cognition, emotion, goal directed behavior, task prioritization. ²³	Cognitive, behavioral	Potential: Loss of empathy, difficulty re-prioritizing tasks. ²³

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, January 2021

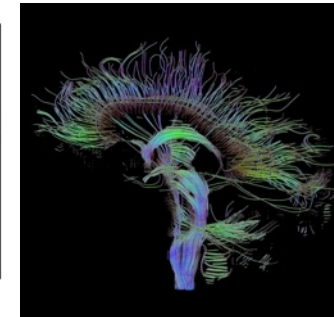
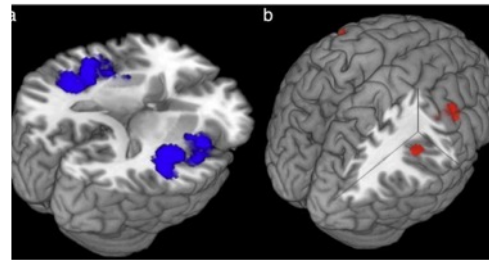
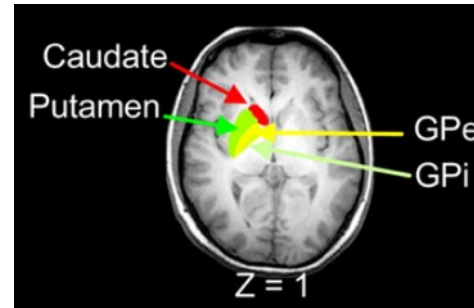


“Neuromapping” Experiment Persistence of Alterations to the Brain after Spaceflight



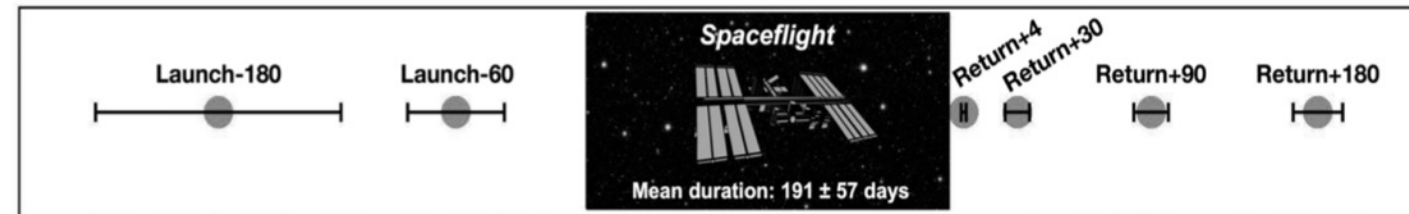
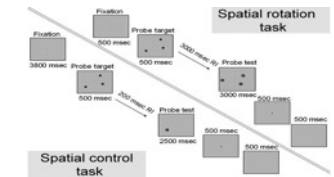
Brain Structure & Function

(PI: Seidler)



1. Structural MRI
2. Diffusion weighted MRI (dMRI)
3. Functional MRI –
 1. Short Term Working Memory
 2. Vestibular Stimulation
 3. Dual Task Performance
 4. Motor Adaptation
 5. Resting state functional connectivity

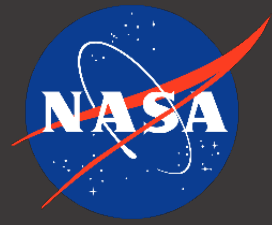
Short Term Working Memory – Brain mapping during mental rotation



Time (Days)



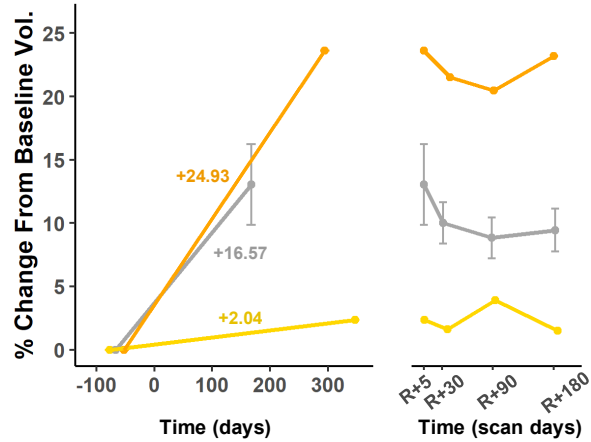
Spaceflight Associated Ventricular Expansion



N=15

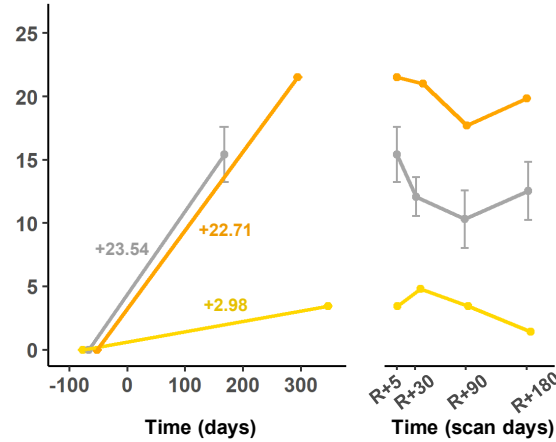
Left Lateral Ventricle

Spaceflight Changes Postflight Recovery

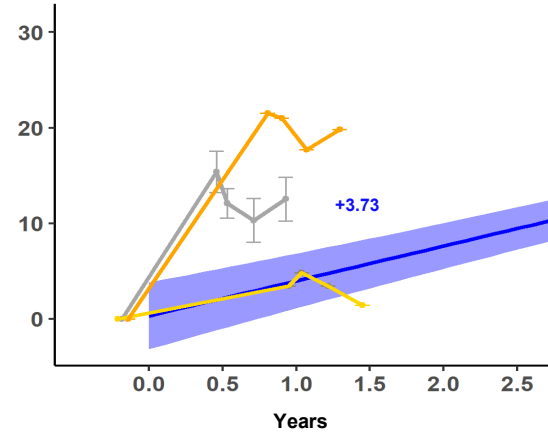
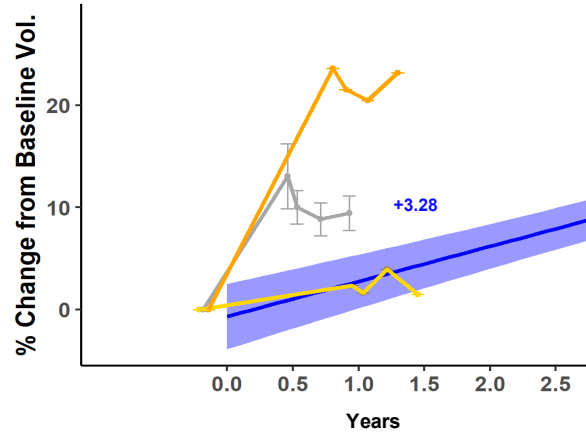


Right Lateral Ventricle

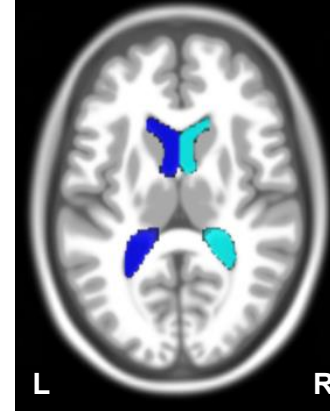
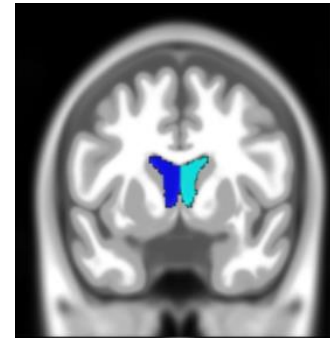
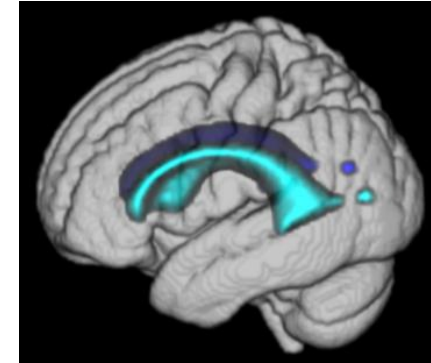
Spaceflight Changes Postflight Recovery



TM₁ TM₂ = 12-month astronauts; ■ = 6-month astronauts; Day 0 = Start of flight; R = Return



TM₁ TM₂ = 12-month astronauts; ■ = 6-month astronauts; ■ = Control Group



Ventricular expansion with flight; incomplete recovery by 6/7/12 months postflight

Roberts et al. (2017, 2019)

Riascos et al. (2019)

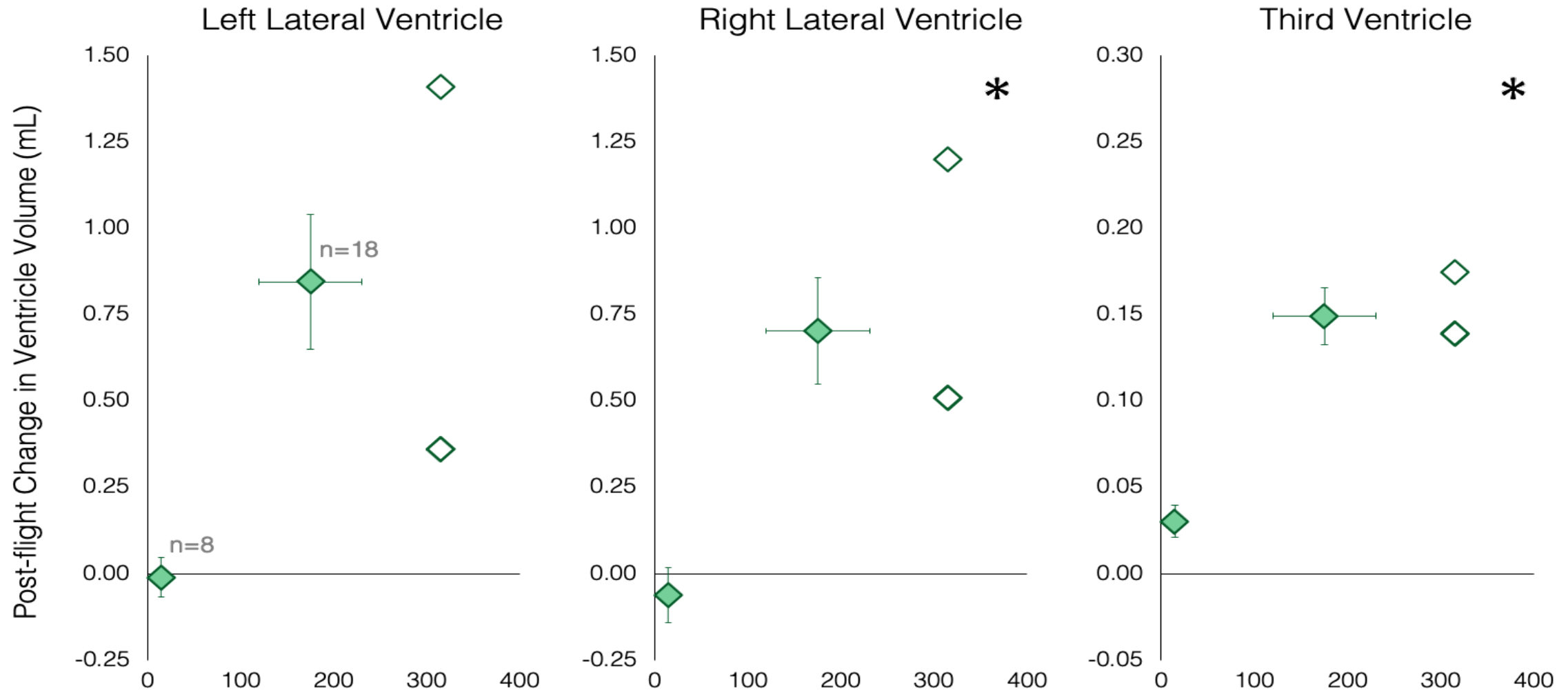
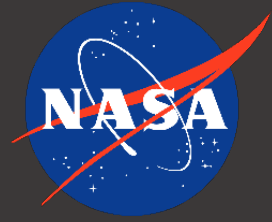
Ombergen et al. (2019)

Kramer et al. (2020)

Hupfeld et al. 2020. *Cereb Cortex Comm.*



Effects of Flight Experience Difference Study: Current flight duration

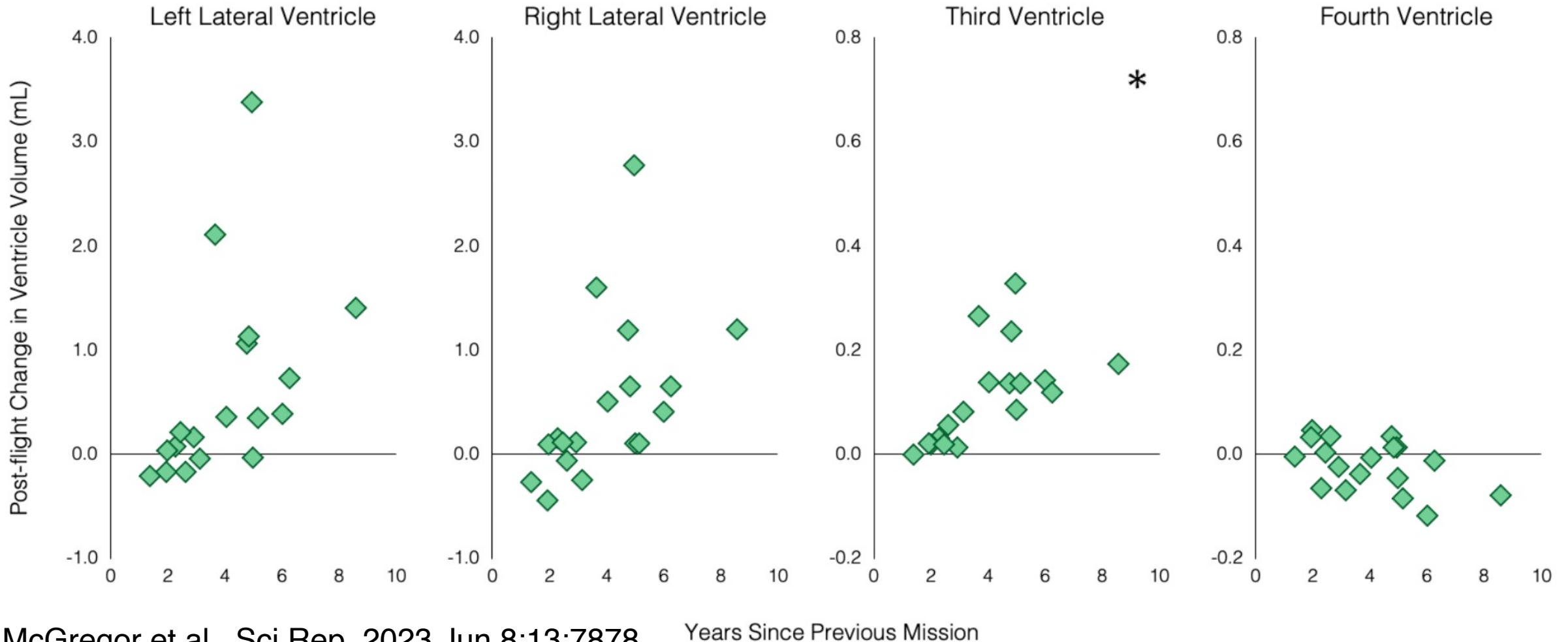




Effects of Flight Experience Difference Study: Inter-mission intervals

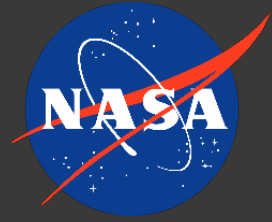


Post-flight ventricle volume changes associated with inter-mission intervals – recovery of expansion capacity



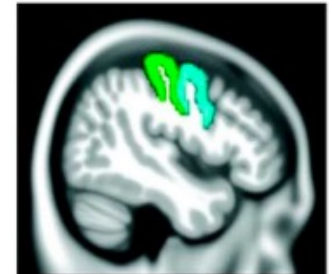
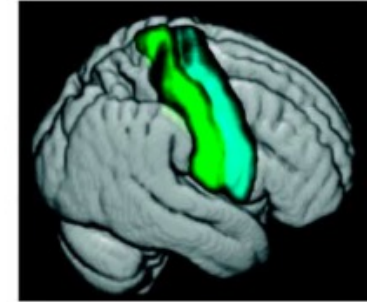
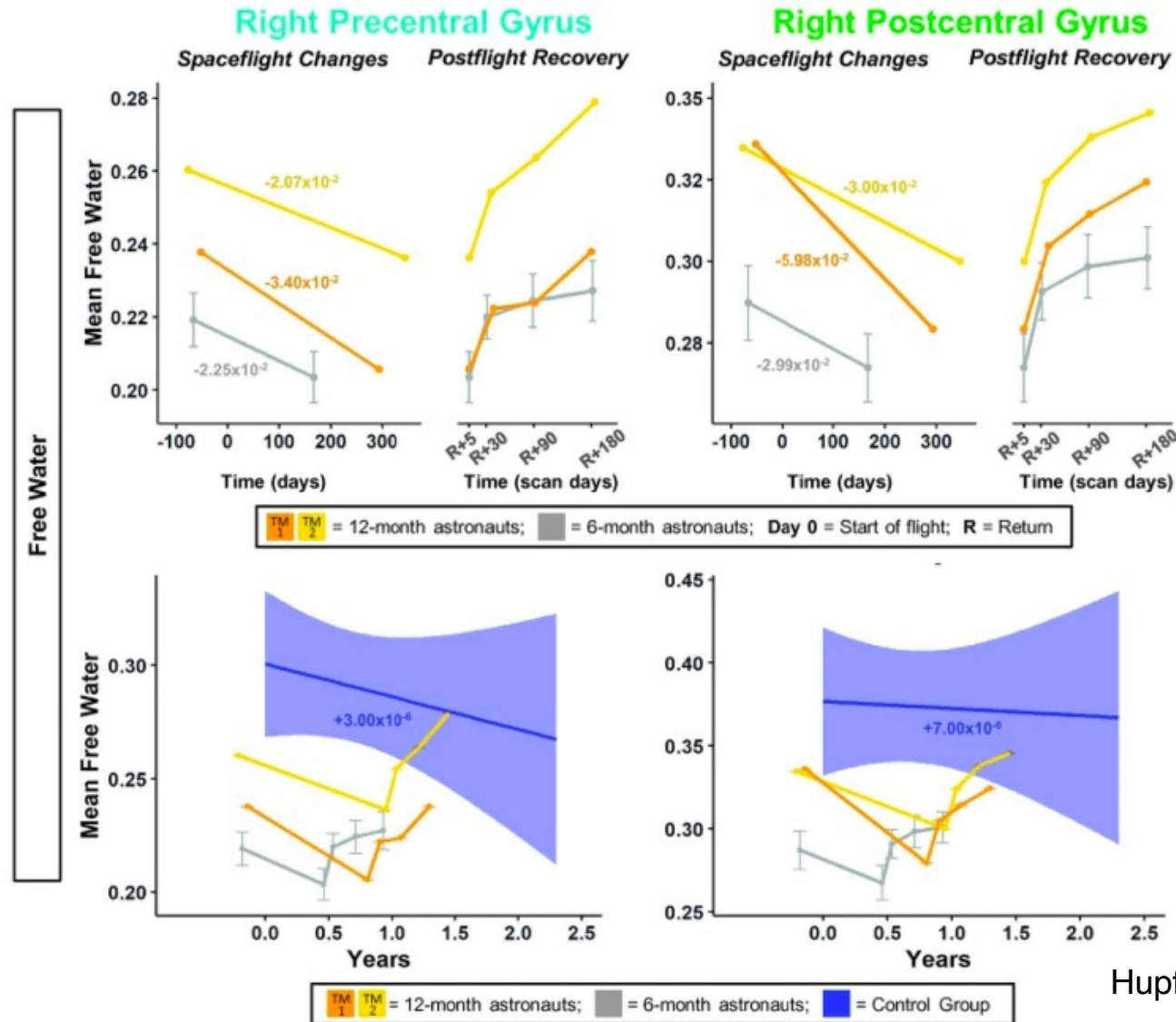


Spaceflight Associated Extracellular Fluid Shifts: Brain Free Water



- Free-water is defined as self-diffusing water molecules that do not experience restriction or hindrance from their surrounding
- Free water parameter is expected to measure molecules that are in the extracellular space, ventricles, and around the brain parenchyma

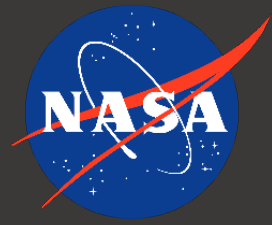
Pasternak et al., 2009



Hupfeld et al. 2020. *Cereb Cortex Comm.*



Spaceflight Associated Brain White Matter Microstructural Changes



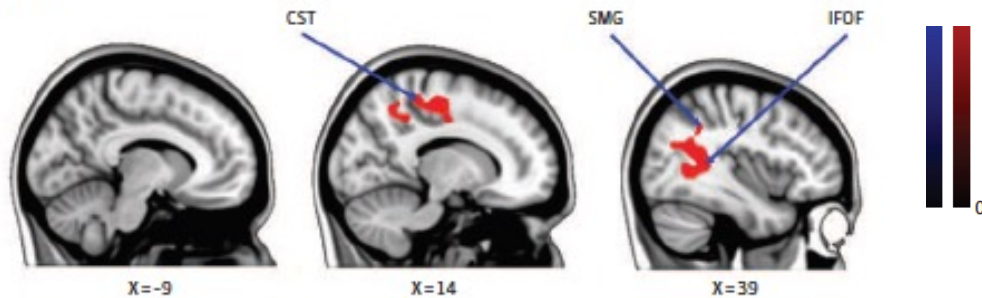
A FA_T Decrease in Fractional Anisotropy (FA)



- Areas:**
- visuospatial processing,
 - vestibular function,
 - movement control

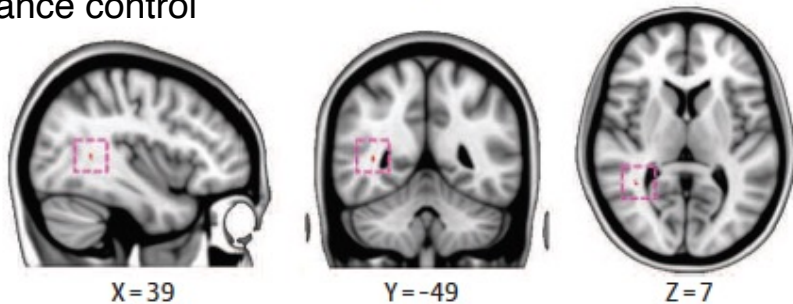
Fractional anisotropy (FA): decrease, right superior and the inferior longitudinal fasciculi, inferior fronto-occipital fasciculus, the corticospinal tract, the inferior and middle cerebellar peduncles.

C RD_T Increase in Radial Diffusivity (RD)

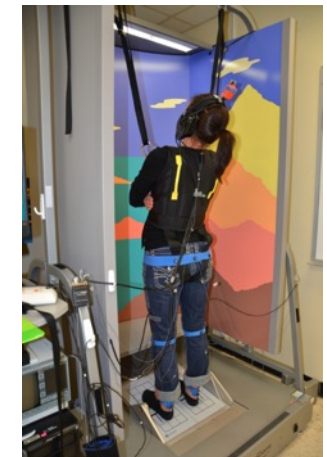
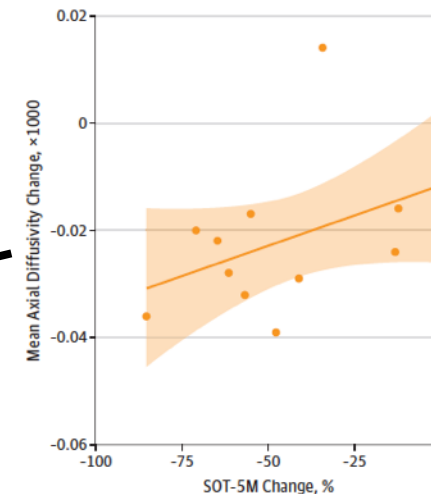


Radial Diffusivity: increase, white matter structures underlying the precentral and postcentral gyrus, the supra marginal gyrus, and angular gyrus

Changes of Axial Diffusivity (AD_T) associated with balance control

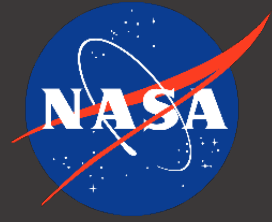


Changes of Axial Diffusivity (AD_T) and Sensory Organization Test (SOT) 5M Balance Score





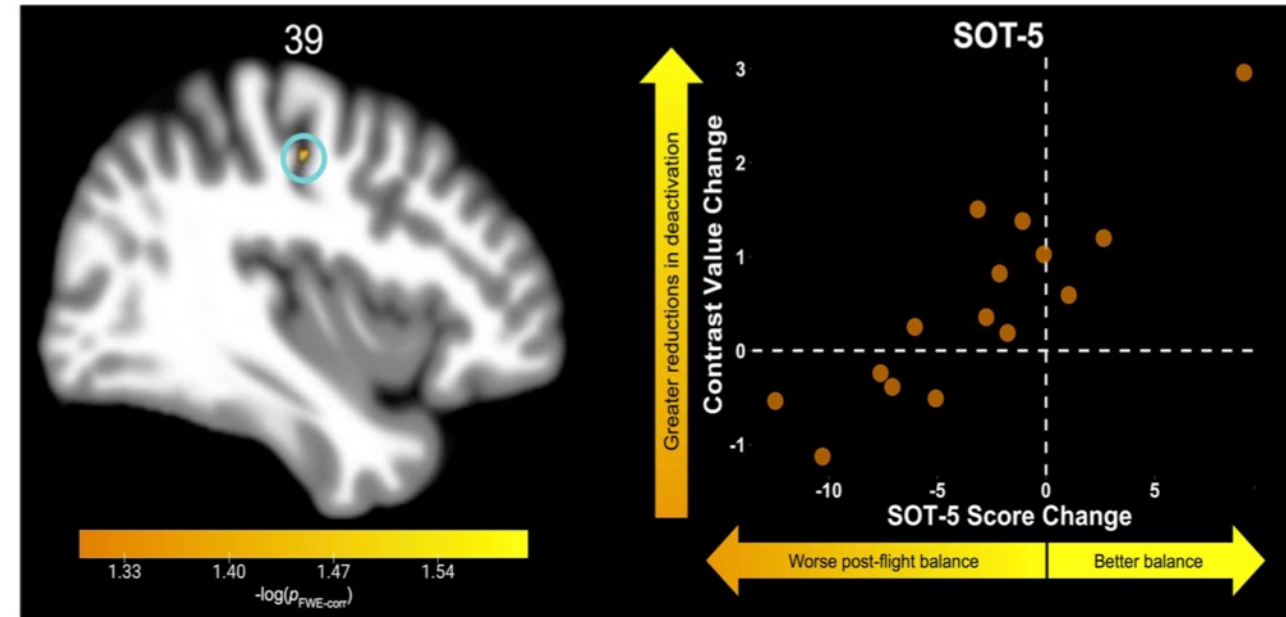
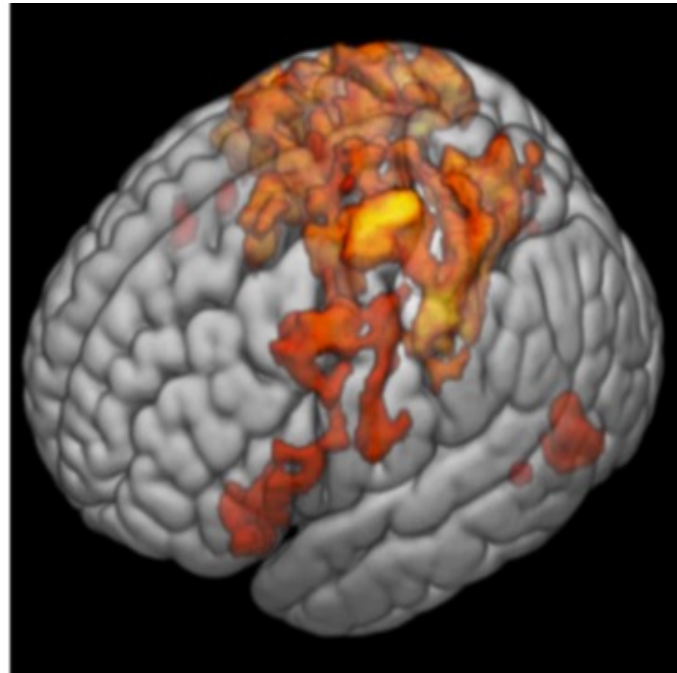
Brain Activation During Vestibular Stimulation After Long Duration Spaceflight



Widespread pre- to post-flight decreases in cortical suppression during vestibular stimulation

Hupfeld et al., Cerebral Cortex, 2021;00: 1–15

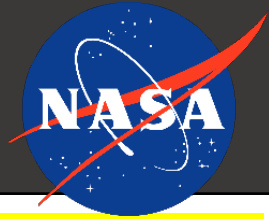
right pre-central gyrus



MRI Protocol: T2-weighted echo-planar imaging sequence to collect the vestibular fMRI scans: TR = 3.66 s, TE = 39ms, flip angle = 90°, FOV= 250 x 250mm, matrix = 94 x 94, slice thickness = 4 mm, slice gap = 1 mm, voxel size = 2.66 x 2.66 x 5.0 mm³, 36 axial slices, 66 volumes.



MRI-visible Peri-Vascular Space (PVS)



scientific reports Hupfeld, Richmond, et al., 2022

OPEN Longitudinal MRI-visible perivascular space (PVS) changes with long-duration spaceflight

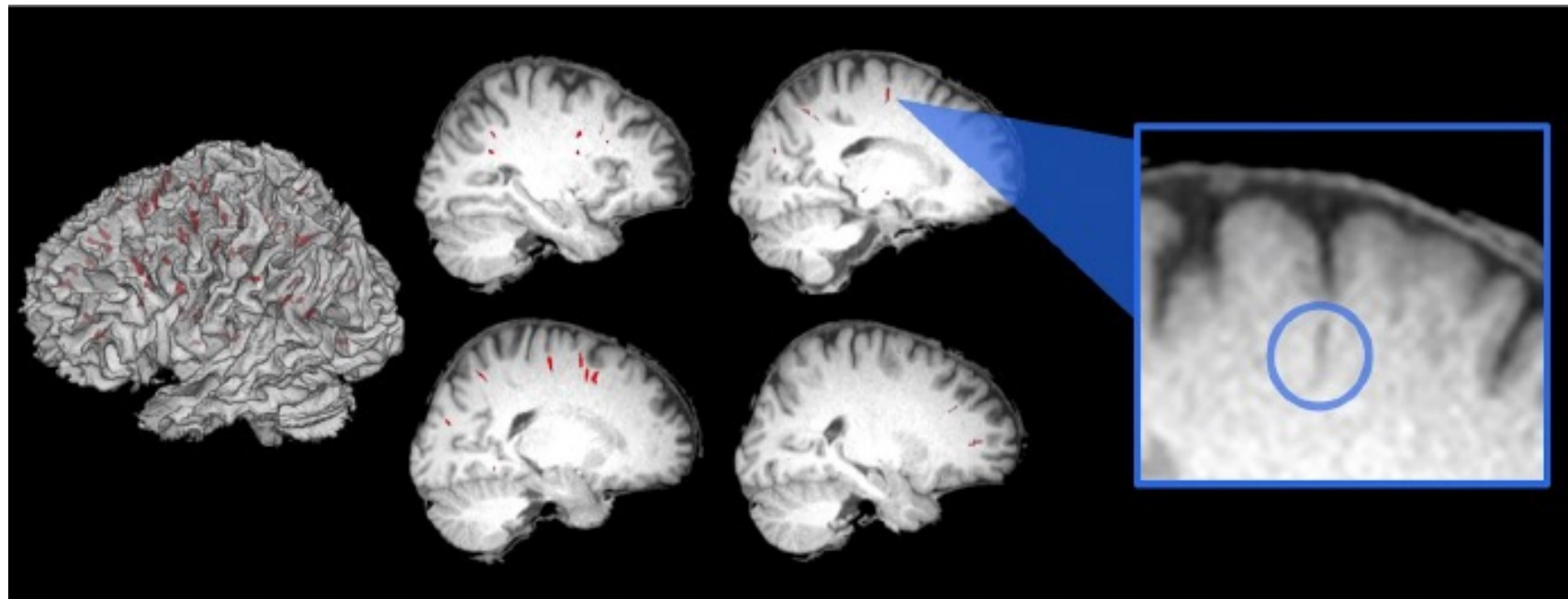
Kathleen E. Hupfeld^{1,13}, Sutton B. Richmond^{1,13}, Heather R. McGregor¹, Daniel L. Schwartz^{2,3}, Madison Luther⁴, Nichole E. Beltran⁵, Igor S. Kofman⁵, Yiri E. De Dios⁵, Roy F. Riascos⁶, Scott J. Wood⁷, Jacob J. Bloomberg⁷, Ajitkumar P. Mulavara⁵, Lisa C. Silbert^{2,8}, Jeffrey J. Iliff^{9,10,11}, Rachael D. Seidler^{1,12} & Juan Piantino^{4,23}

- Cerebrospinal fluid (CSF) in the subarachnoid space also flows into the brain parenchyma through the periarterial spaces surrounding the penetrating arteries
- Once in the brain parenchyma, CSF exchanges with interstitial space fluid (ISF), eventually returning to the cisternal CSF along the perivenous pathway
- Perivascular exchange of CSF and ISF along what has been termed the “glymphatic pathway” plays an important role in the removal of cerebral interstitial solutes and wastes

- PVS - facilitate fluid drainage and brain homeostasis
- N = 15 astronauts, ISS

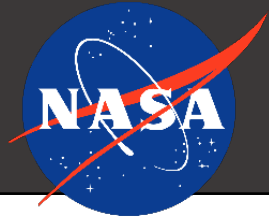
• T1 weighted MRI:
 MPRAGE, TR = 1.9 s, TE = 2.32 ms, flip angle = 9°, FOV = 250 x 250 mm, slice thickness = 0.9 mm, 176 sagittal slices, matrix = 512 x 512, voxel size = 0.488 x 0.488 x 0.9 mm = 0.214 mm³.

• White matter PVS identification:
 Auto detection and manual verification by single trained rater - Piantino et al. (2020, 2021), Schwartz et al. (2019)



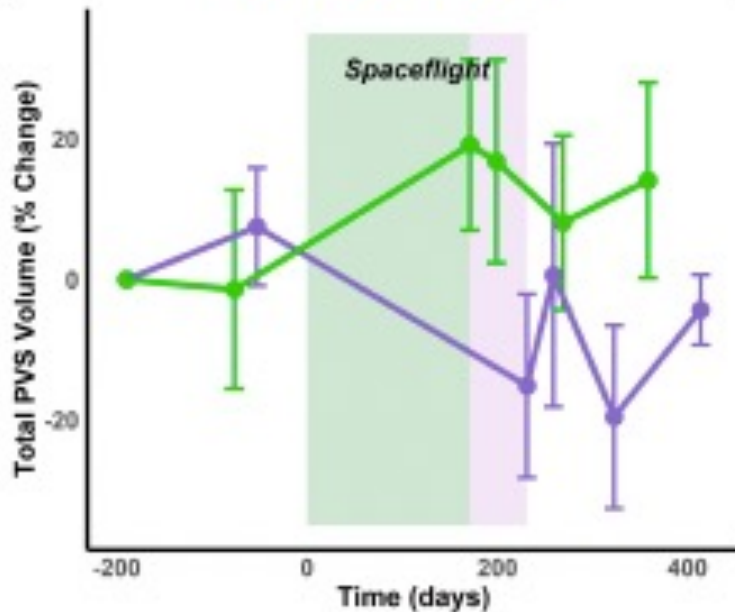


MRI-visible perivascular space (PVS) changes with long duration spaceflight

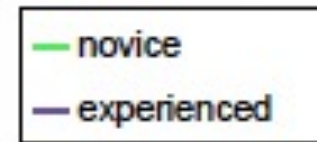
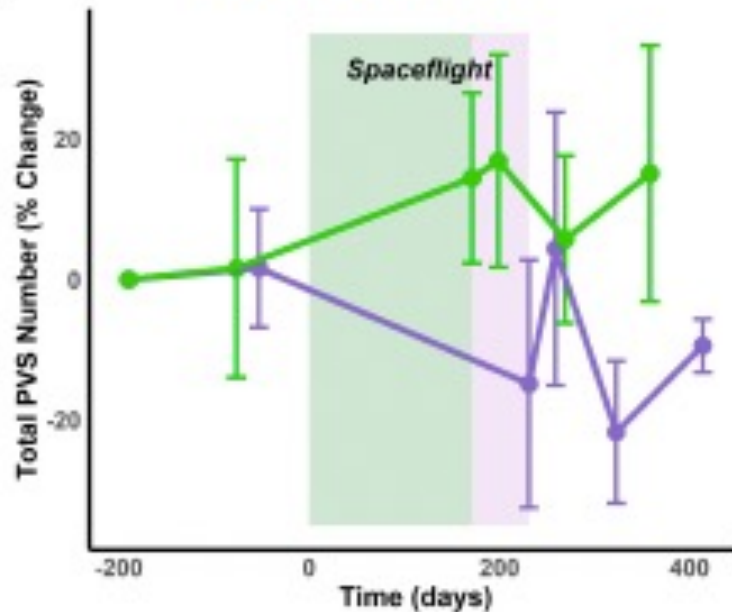


- Novice astronauts show an increase in total PVS volume from pre- to post-flight, whereas experienced crewmembers did not
- Significant positive correlation for experienced astronauts between more previous flight days and greater PVS median length at baseline
- The presence of spaceflight associated neuro-ocular syndrome (SANS) was not associated with PVS number or morphology

Total PVS Volume



Total PVS Number



Hupfeld, Richmond, et al., 2022
Scientific Reports



MRI-visible Peri-Vascular Space (PVS) Changes With Long Duration Spaceflight



- Increased volume of basal ganglia PVS and white matter PVS (WM-PVS) after spaceflight, which was more prominent in the NASA crew than the Roscosmos crew.
- NASA and Roscosmos crews demonstrated a similar degree of lateral ventricle enlargement and decreased subarachnoid space at the vertex, which was correlated with WM-PVS enlargement.
- NASA astronauts who developed SANS had greater pre- and postflight WM-PVS volumes than those unaffected. These results provide evidence for a potential link between WM-PVS volume and SANS
- N = NASA - 24 ISS, 7 Shuttle; ROS & ESA –13+ ISS

PNAS













BRIEF REPORT

NEUROSCIENCE

OPEN ACCESS



The effect of prolonged spaceflight on cerebrospinal fluid and perivascular spaces of astronauts and cosmonauts

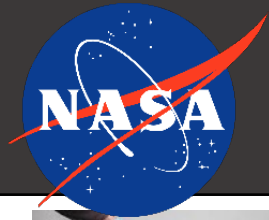
Giuseppe Barisano^{a,1} , Farshid Sepehrband^a , Heather R. Collins^b, Steven Jillings^c, Ben Jeurissen^d, James A. Taylor^b , Catho Schoenmaekers^c, Chloë De Laet^c, Ilya Rukavishnikov^e, Inna Nosikova^e , Alena Rumshiskaya^f, Jitka Annen^g , Jan Sijbers^d, Steven Laureys^g, Angelique Van Ombergen^c, Victor Petrovichev^f, Valentin Sinitsyn^h , Ekaterina Pechenkovaⁱ , Alexey Grishin^j, Peter zu Eulenburg^k , Meng Law^l, Stefan Sunaert^m , Paul M. Parizelⁿ , Elena Tomilovskaya^{a,2} , Donna R. Roberts^{b,1,2}, and Floris L. Wuyts^{c,1,2} 

Barisano et al., 2022

Edited by Thomas Albright, Salk Institute for Biological Studies, La Jolla, CA; received December 3, 2021; accepted March 3, 2022



Blood Brain Barrier (BBB) Integrity After Spaceflight



Letters

RESEARCH LETTER

Changes in Blood Biomarkers of Brain Injury and Degeneration Following Long-Duration Spaceflight

JAMA Neurology Published online October 11, 2021

Peter zu Eulenburg, MD, PhD
Judith-Irina Buchheim, MD
Nicholas J. Ashton, PhD, MD
Galina Vassilieva, MD
Kaj Blennow, MD, PhD
Henrik Zetterberg, MD, PhD
Alexander Choukér, MD

jamaneurology.com

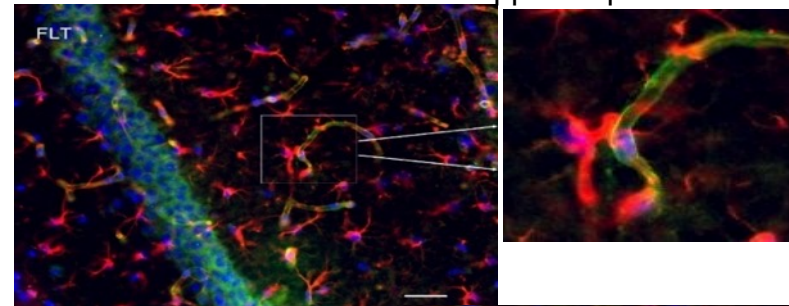
- neurofilament light chain protein was significantly elevated compared with preflight levels directly postflight, 1 week, and 3 weeks after return to Earth
- coherent reparatory processes, from cephalad fluid shift, in the brain with subsequent restoration of the blood-brain barrier integrity
- N = 5 cosmonauts, 20 days preflight and (1 day, 1week, and 21 to 25 days after landing)
- Single molecule array (Simoa) immunoassay quantification of neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), total tau, and 2 amyloid- β ($A\beta$) proteins ($A\beta$ 40 and $A\beta$ 42), hemoglobin as a control protein

Mao et al., Spaceflight induces oxidative damage to blood-brain barrier integrity in a mouse model. *Faseb J*, (2021)

Changes in BBB integrity biomarkers including AQP4, GFAP, and PECAM-1 in the hippocampus, impact was less substantial in the cortex

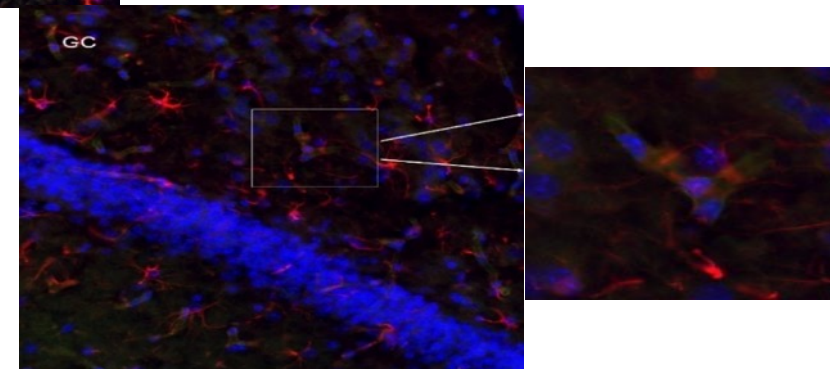
Spaceflight impacts on BBB integrity -AQP4 dysregulation in the hippocampus of mouse brain

Glial fibrillary acidic protein (GFAP, red) and aquaporin4 (AQP4, green) staining in the hippocampus



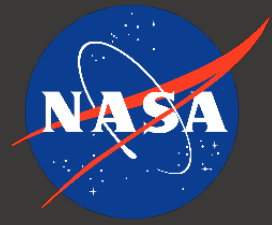
Flight

Ground Control





Preflight Brain Morphology covariation with changes in functional performance postflight – Implications on preflight training



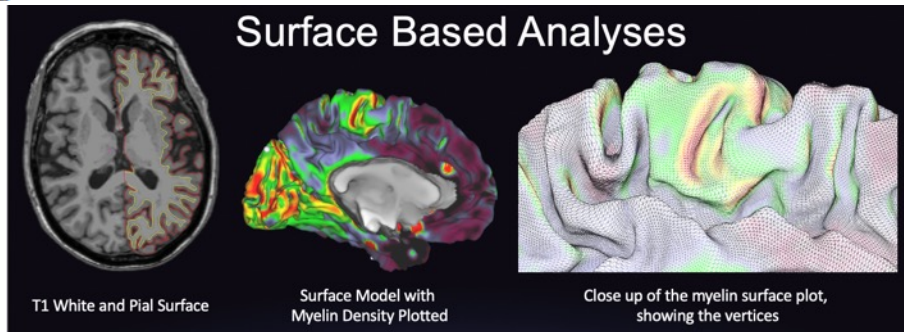
Brain Structure and Function
<https://doi.org/10.1007/s00429-022-02492-z>

Koppelmans et al., 2022

ORIGINAL ARTICLE

Cortical thickness of primary motor and vestibular brain regions predicts recovery from fall and balance directly after spaceflight

Vincent Koppelmans¹ · Ajitkumar P. Mulavara² · Rachael D. Seidler³ · Yiri E. De Dios² · Jacob J. Bloomberg⁴ · Scott J. Wood⁴



N=14, ISS astronauts, LSAH

T1-weighted MPRAGE sequence: 0.49 x 0.49 x 0.9 mm

T2-weighted SPACE sequence: 0.49 x 0.49 x 1.0 mm

Diffusion-weighted sequence: 1.95 x 1.95 x 3 mm, 20 non-collinear directions each sampled 3x, 3-volumes without diffusion weighting

Cortical Thickness Maps and Myelin Density Maps as predictors to postflight performance in Recovery from fall and Balance control (SOT5) tasks

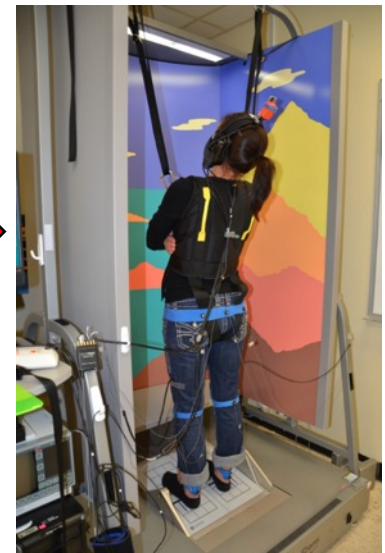
Time to recover from falling post-flight is predicted by cortical thickness of brain regions involved in planning, execution of movement, and sensory perception.

Recovery from Fall



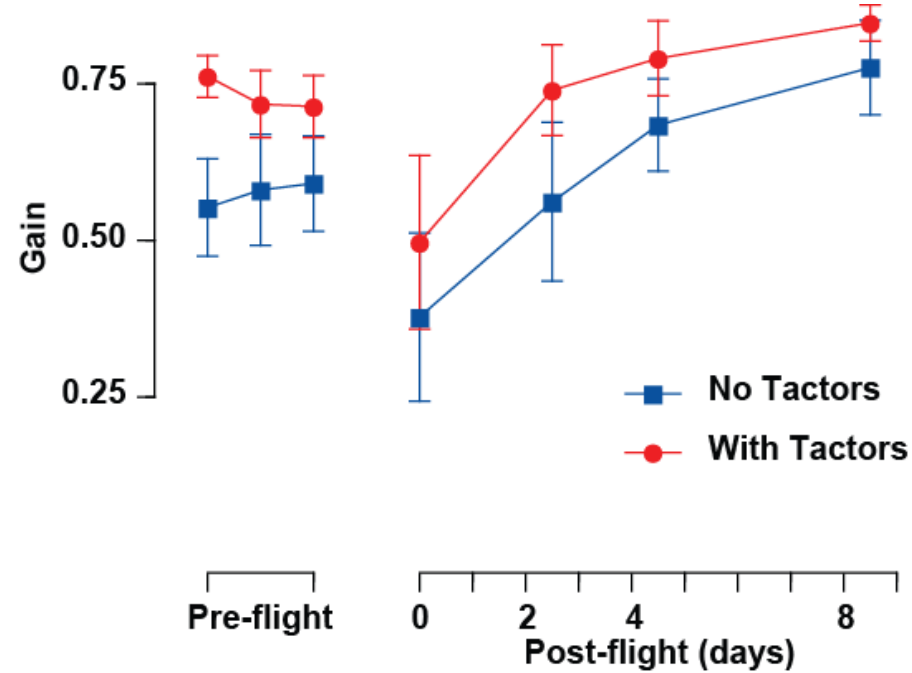
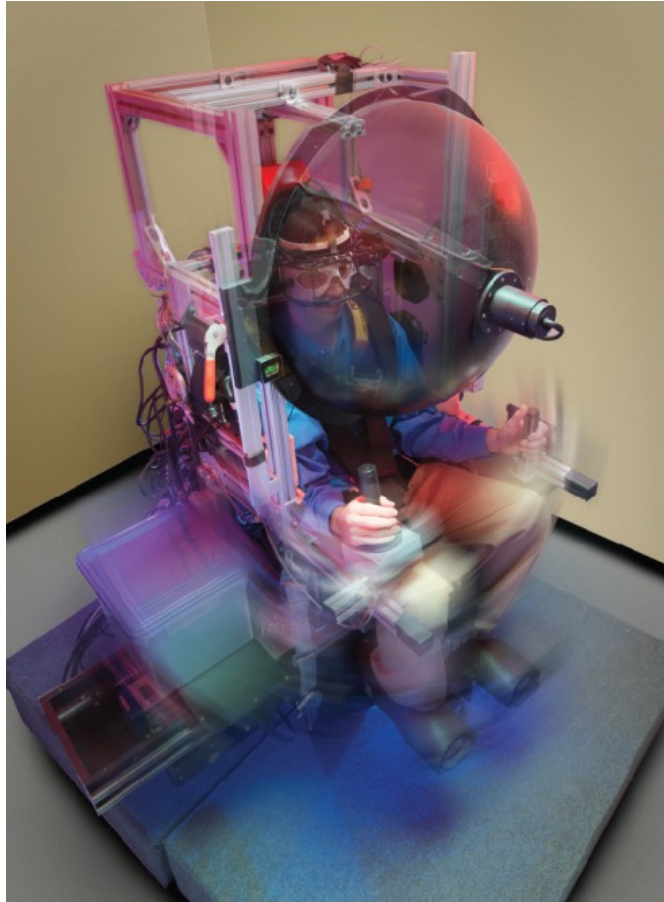
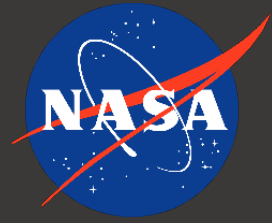
Balance performance (decrements) post-flight are predicted by cortical thickness of brain regions involved in vestibular processing, sensory perception, and sensory integration.

Balance Control - Sensory Organization Test (SOT 5M)





Ambiguous Tilt and Translation Motion Cues after Space Flight – Clément/Wood



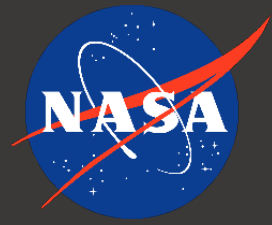
- On R+0 nulling gain reduced by >30%.
- Performance improved with tactors.
- R+0 with tactors similar to preflight without.

Clément & Wood, Acta Astronautica (2013) 92:48–52

Scott Wood, PI



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 (Roberts et al. 2019, Lee et al. 2019, Barasino et al. 2022)
- Free Water fractions in brain decreases, including large areas covering the temporal, frontal poles, around the orbits and may be affected by time spent during and between spaceflight missions (Hupfeld et al., 2022; McGregor et al., 2022)
- Ventricular expansion with flight; incomplete recovery by 6/7/12 months postflight (Roberts, et al. 2017, 2019; Riascos et al., 2019; Ombergen et al., 2019; Kramer et al., 2020)
- Changes in white matter microstructure can affect communication between brain regions and contribute to operational task performance deficits (Lee et al. 2019; Jillings et al. 2020; Doroshin et al., 2022)
- Changes in coordinated functional activation between different brain regions during task performance indicates neural plasticity after adaptation to long duration spaceflight (Salazar et al., 2022, Pachenkova et al. 2019, Burles et al. 2023)
- MRI-visible peri-vascular space changes with long duration spaceflight with potential implications for glymphatic clearance (Barasino et al. 2022, Hupfeld et al, 2022)
- Preflight morphological features of the cortex predicted postflight functional task deficits (Koppelmans, et al., 2022)



Current Tasks: Spaceflight Alterations to the Brain



CIPHER - Spatial Cognition (Co-PIs: Basner M. & Stahn A.)

Objective:

- Effects of long-duration low-earth orbit missions on cognitive performance
- Brain structural, functional and connectivity substrates of changes in cognitive performance
- Visuospatial brain domain changes and the biological basis of neurocognitive changes

Deliverable:

- A single comprehensive set of integrated neuroimaging, neurocognitive data and tools

Investigating Long-term Structural and Functional Changes to the Eye and Brain after Spaceflight (Co-PIs: Macias B., Basner M., Bershad E., Seidler R., Stahn A.)

Objective:

- Quantify long-term changes in ocular and brain structure that remain or develop long after spaceflight and to determine the functional consequences of those changes

Deliverable:

- Long-term consequences of spaceflight on the eye and brain

Call Back Cohort Protocol

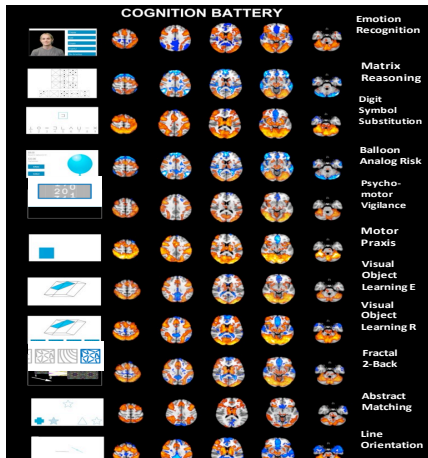
Measure Name	Primary Variable
Neuro exam	Neurologic status
Neuropsych battery	Neuropsychological status
Cognition battery	Familiarization Cognition battery
Cognition battery	Cognition battery
Pneumatometry	Intraocular pressure
Visual fields	Visual Function (MD, PSD)
Optical biometry	Axial length, anterior chamber depth, corneal curvature
OCT/OCT-A	Total retinal thickness
ERG	Visual Function (PhNR, PERG)
3D Sag T1 Brain	Brain Structure
3D Sag T1 Pituitary	Pituitary Shape
Resting state Bold fMRI	Functional connectivity
Diffusion MRI	FW shifts and white matter changes

Prospective Cohort Protocol

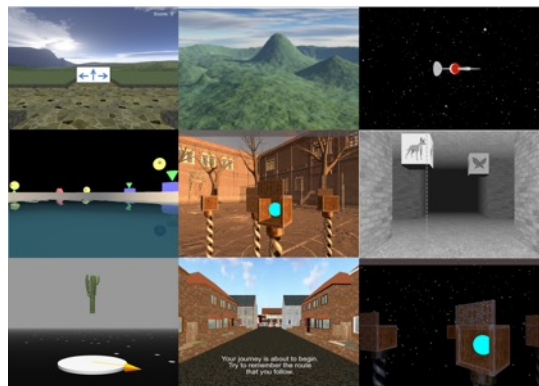
WinSCAT battery
Cognition battery
Spatial cognition batteries
Blood draw
Neuro exam
Neuropsych battery
MedB Eye Exam
Pneumatometry
Visual fields
Optical biometry
OCT
ERG
OCT-A
Questionnaires

Long Term Health from Multiple Stressors

Cognition Test Battery

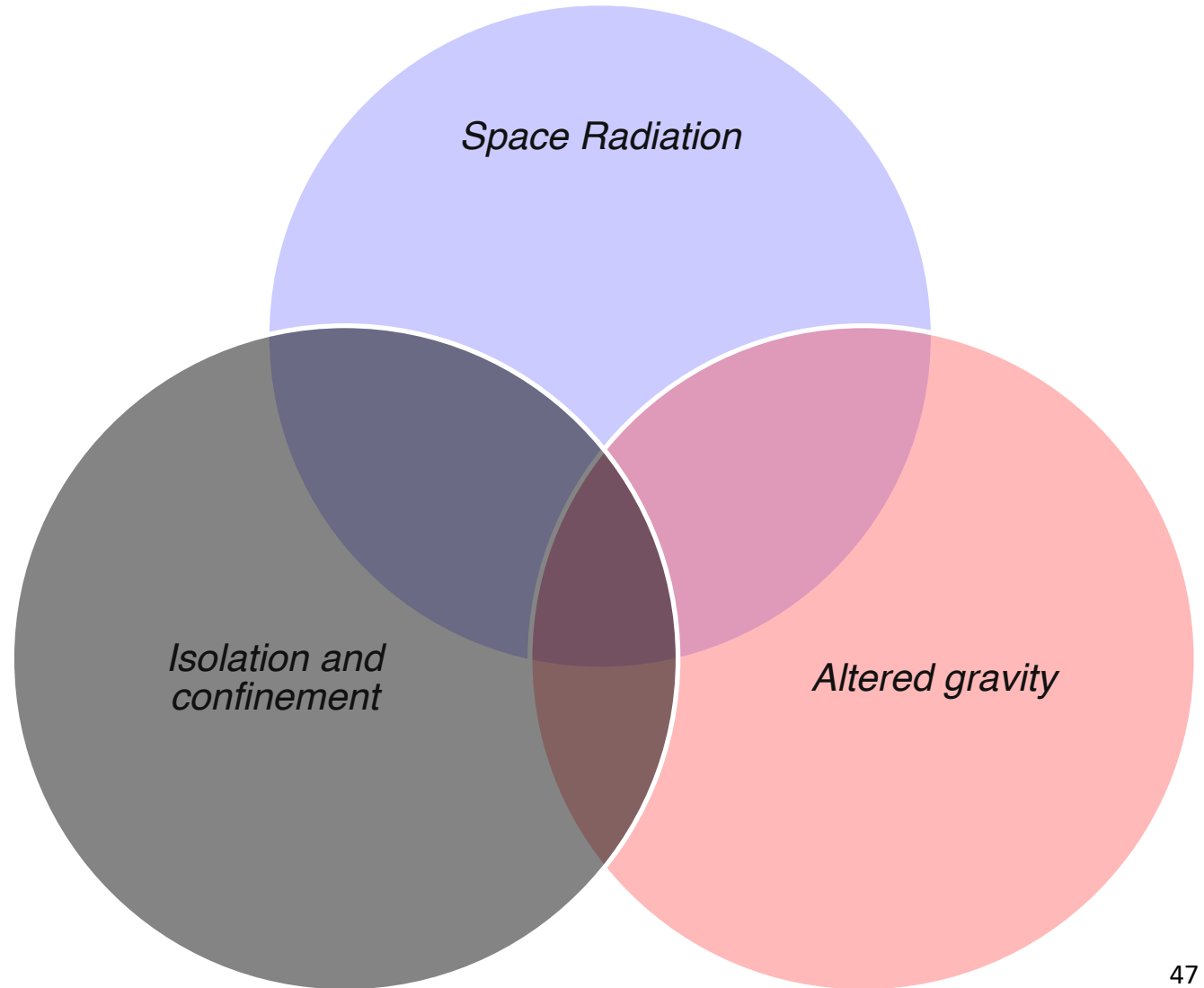
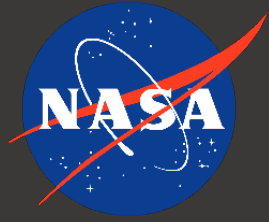


Spatial Cognition





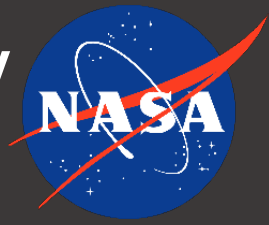
Interactions Between Multiple Stressors



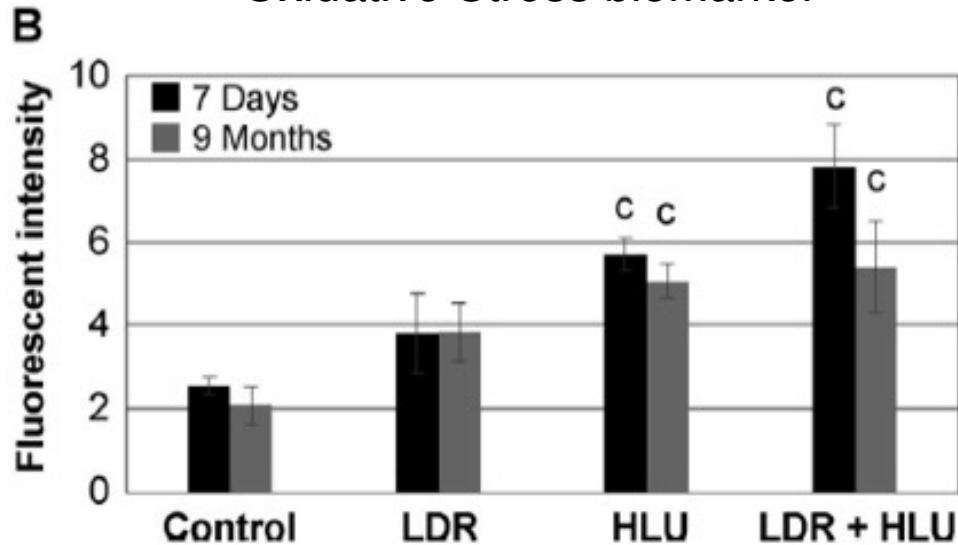


Combined Space Radiation and Altered Gravity

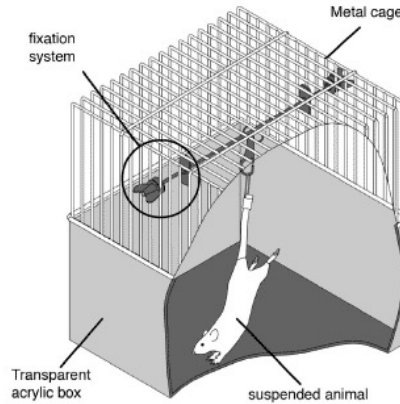
Chronic Gamma Irradiation ± Hindlimb Unloading



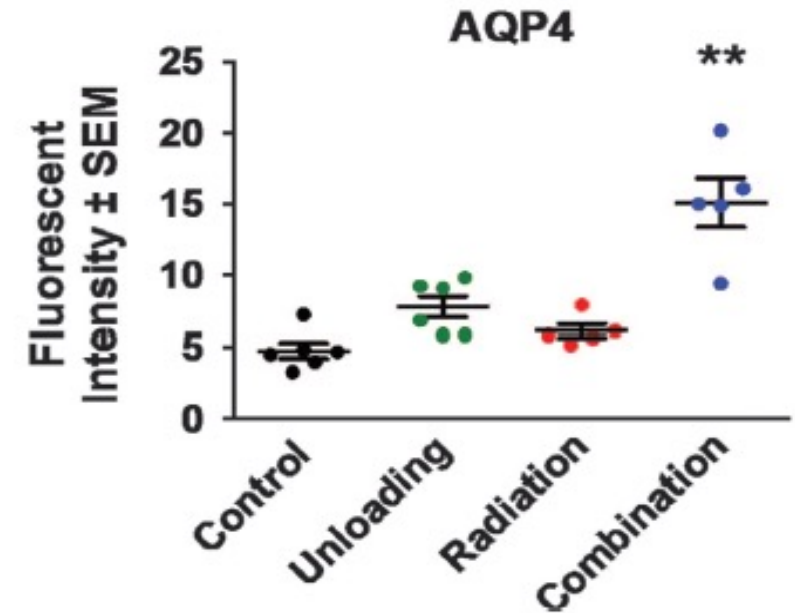
Oxidative Stress biomarker



Hind Limb Unloading



BBB biomarker



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.

Stressors:

- Low dose gamma radiation (LDR) using a ⁵⁷Co 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



Sleep fragmentation unmasks latent ATSET deficits following Space Radiation & Sleep Quality neutron and Si radiation exposures



Sleep Fragmentation Exacerbates Executive Function Impairments Induced by Low Doses of Si Ions

Richard A. Britten,^{a,b,c,d,1} Arriyam S. Fesshaye,^a Vania D. Duncan,^a Laurie L. Wellman^{c,e} and Larry D. Sanford^{c,e}

RADIATION RESEARCH **194**, 116–123 (2020)
0033-7587/20 \$15.00
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DOI: 10.1667/RADE-20-00080.1

Si Radiation

Whole-body irradiation with 600 MeV/n Si ions 5 cGy (n = 11)

Attention Shift assay modeled after the intra-dimensional /extra-dimensional component of the Cambridge Neuropsychological Test Automated Battery (CANTAB) – testing complex decision making cognitive function (Humans & Primates)

“Good Rats” exposed to sleep fragmentation

ATSET reassessment

ATSET – attentional set-shifting
ATRC – attempts to reach criteria
SR – space radiation
EVMS – Eastern Virginia Medical school
BNL – Brookhaven National Laboratory

Original Articles

Sleep fragmentation exacerbates executive function impairments induced by protracted low dose rate neutron exposure

Richard A. Britten ✉, Vania D. Duncan, Arriyam S. Fesshaye, Laurie L. Wellman, Christina M. Fallgren & Larry D. Sanford
Received 25 Jul 2019, Accepted 29 Oct 2019, Accepted author version posted online: 14 Nov 2019, Published online: 06 Dec 2019

Download citation <https://doi.org/10.1080/09553002.2019.1694190>

INTERNATIONAL JOURNAL OF RADIATION BIOLOGY
<https://doi.org/10.1080/09553002.2019.1694190>

Neutron Radiation

The rats were exposed to neutrons for 15.9–18.3 h/day, N.30), total neutron dose: 18 cGy

Sleep Fragmentation Chamber (Lafayette Instrument Co., Lafayette, IN)



Sleep Fragmentation

Rats placed in Sleep Fragmentation chamber, Active/Sleep (Dark/Light), Sweep time 2 mins, Allows dozing but not deep (REM) sleep.

SD – Simple Discrimination
CD – Compound Discrimination
CDR – Compound Discrimination Reversal
IDS – Intra Dimensional Shift
IDR – Intra Dimension Reversal
EDS – Extra Dimensional Shift
EDR – Extra Dimensional Reversal

1. Under rested wakefulness conditions, no significant effect of Si or low dose neutron radiation:-
2. After sleep fragmentation rats showed a significant increase in the ATRC :
 - for the IDR, and EDS stages of the ATSET test after Si radiation
 - for the IDR stage of the ATSET test after low dose neutron radiation
 - IDR deficits are not typically induced after SR exposure



Future HRP Brain Health & Countermeasure Projects



Adaptive Training Variable Practice

- Mars Adaptive TRaining-Integrative Knowledge System (MATRIKS)

PI: **A. Stahn/C. Jones**, University of Pennsylvania

Approach:

- 6-DOF docking simulation trainer
https://taskbook.nasaprs.com/tbp/index.cfm?action=public_query_taskbook_content&TASKID=15661

- Multi-Environment Virtual Training for Long Duration Exploration Missions

PI: **Anderson**, University of Colorado Boulder

Approach:

- Multi-environment VR training for Entry/landing/descent; Habitat maintenance; EVA
https://taskbook.nasaprs.com/tbp/index.cfm?action=public_query_taskbook_content&TASKID=14612

- A Haptic Sensory Supplement to Optimize In-Flight Adaptive Training for Human Control of Spacecraft Robotic Arms

PI: **Robinson S.**, University of California San Diego

Approach:

- Augment ROBoT training via haptic and visual feedback
https://taskbook.nasaprs.com/tbp/index.cfm?action=public_query_taskbook_content&TASKID=14631



JOURNAL ABOUT ARTICLES RESEARCH TOPICS FOR AUTHORS EDITORIAL BOARD ARTICLE ALERTS

< Articles

THIS ARTICLE IS PART OF THE RESEARCH TOPIC
Brains in Space: Effects of Spaceflight on the Human Brain and Beha

HYPOTHESIS AND THEORY article

FUTURE RESEARCH DIRECTIONS TO IDENTIFY RISKS AND MITIGATION STRATEGIES FOR NEUROSTRUCTURAL, OCULAR, AND BEHAVIORAL CHANGES INDUCED BY HUMAN SPACEFLIGHT A NASA-ESA Expert Group Consensus Report

Provisionally accepted

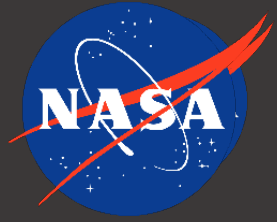
The final version of the article will be published here soon pending final quality checks

Notify me

Mathias Basner¹, **Peter Zu Eulenburg**², **Rachael D. Seidler**³, **Alexander C. Stahn**¹, **Claudia Stern**^{4*} and **Floris L. Wuyts**^{5, 6}



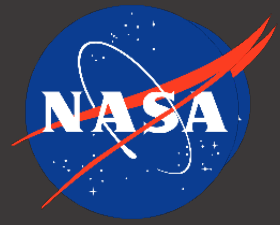
Team Acknowledgement



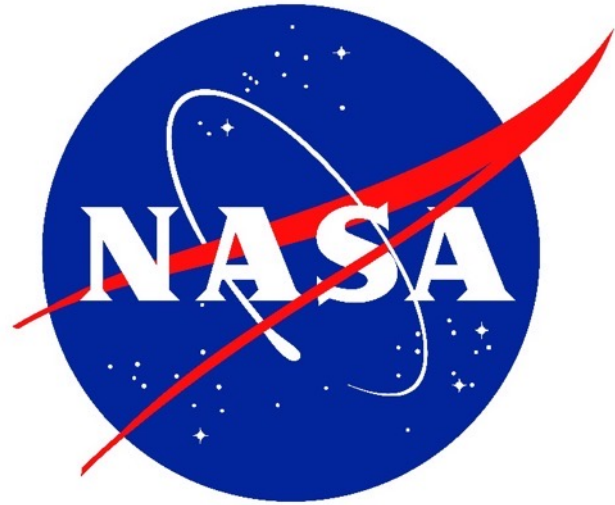
- Jacob J Bloomberg, NASA (Retired)
- Scott Wood, Sensorimotor Discipline Scientist, NASA
- Igor Kofman, Neuroscience Laboratory, KBR
- Yiri De Dios, Neuroscience Laboratory, KBR
- Nicole Gadd, Neuroscience Laboratory, KBR
- Millard Reschke, NASA (Retired)
- Alexandra Whitmire, HFBP Element Scientist, NASA
- Kerry George, Scientist, KBR
- Gregory Nelson, Space Radiation CNS Discipline Scientist, NASA
- Thomas J Williams, NASA (Retired)
- Vivian Mao, Loma Linda University School of Medicine
- Richard Britten, Eastern Virginia Medical School
- Christopher Jones & David Dinges, Upenn



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- Rachael Seidler, University of Florida, Gainesville, FL, USA
- Patricia Reuter-Lorenz, University of Michigan, Ann Arbor, Michigan, USA
- Ofer Pasternak, Harvard Medical School, Boston, MA 02115, USA
- Roy Riascos, The University of Texas Health Science Center, Houston, Texas, USA
- Vincent Koppelmans, University of Utah, Salt Lake City, UT, USA
- Jessica Lee, German Aerospace Center, Cologne, Germany
- Heather McGregor, University of Florida, Gainesville, FL, USA
- Kathleen Hupfeld, University of Florida, Gainesville, FL, USA
- Grant Tays, University of Florida, Gainesville, FL, USA
- Ana Salazar, University of Florida, Gainesville, FL, USA
- Sutton Richmond, University of Florida, Gainesville, FL, USA



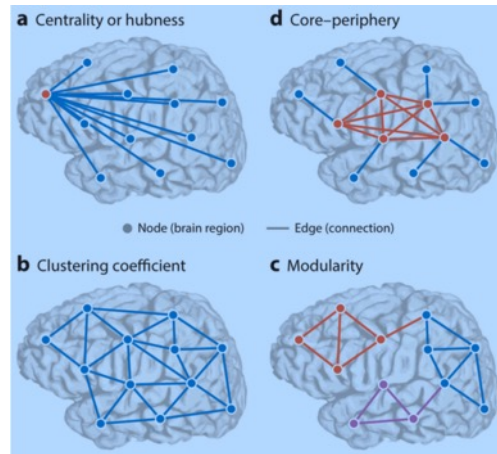
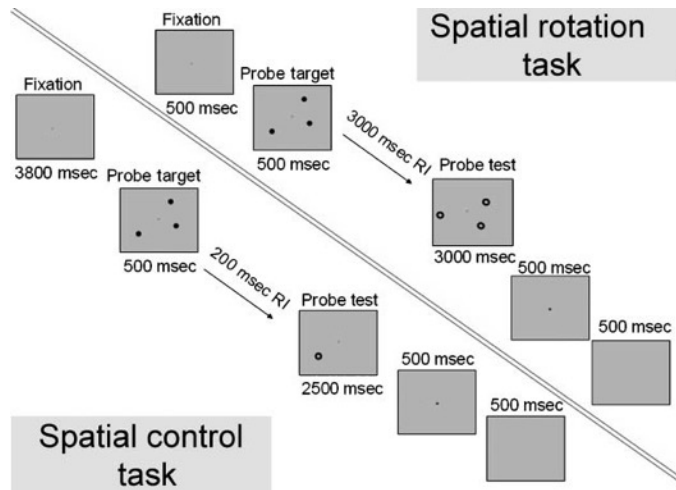


Functional Connectivity During Task Performance and associations with Card Rotation task

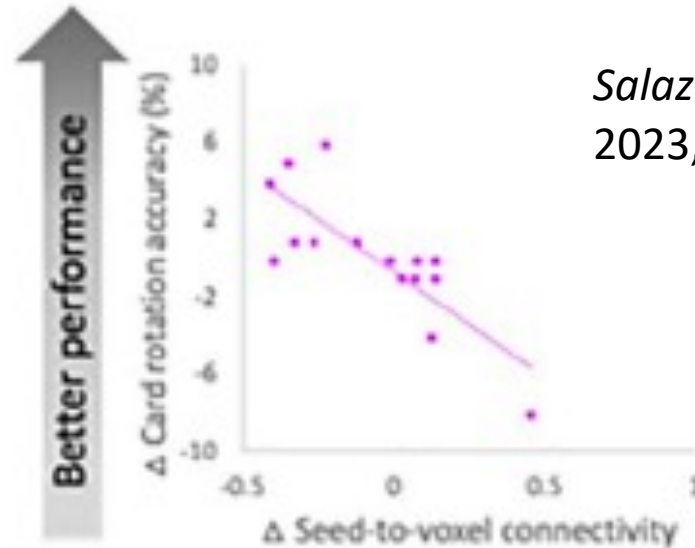


Short Term Working Memory – Brain mapping during mental rotation

Decoupling functional connectivity between Left Middle Occipital Gyrus and Left Supramarginal Gyrus improved Card Rotation Accuracy

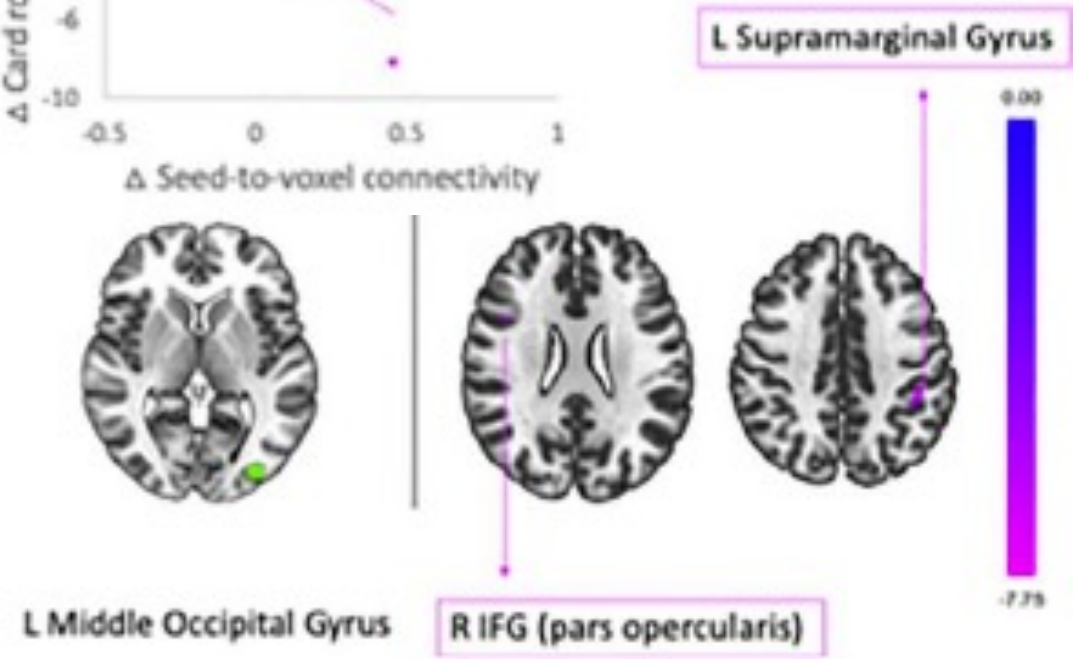
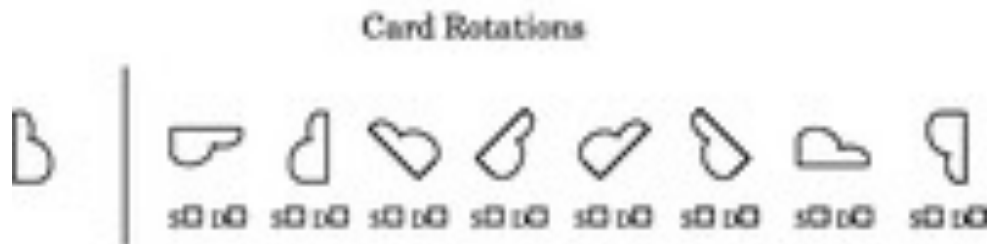


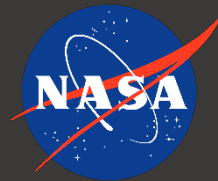
functional connectivity



Salazar et al., *Cerebral Cortex*, 2023, **33**, 2641–2654

Card Rotation – a paper and pencil test, 120 presentations, rotate 2-dimensional shapes to match



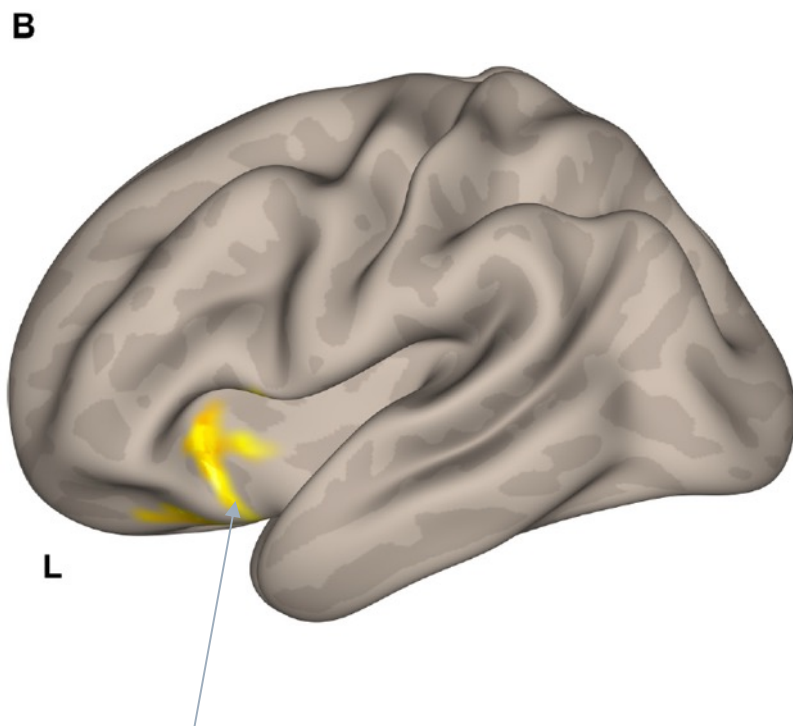


Spaceflight Neuroplasticity – Task based

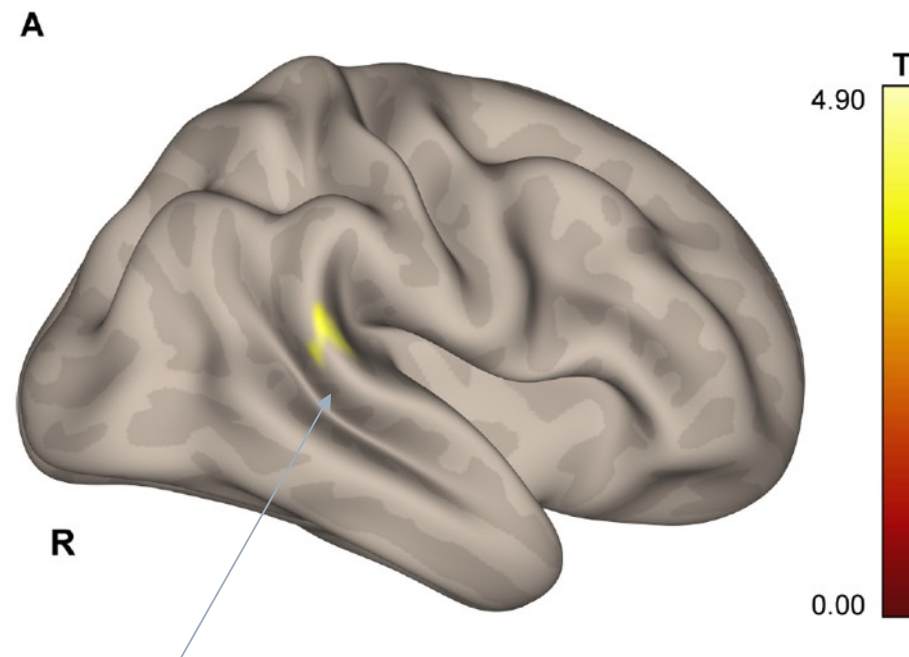
functional connectivity modifications

- The severity of space motion sickness symptoms correlated with a measure of connectivity between the right supramarginal gyrus and the left anterior insula.
- Down weighting of vestibular signals, upweighting of other sensory information

Pechenkova E, et al., 2021 Frontiers Physiology



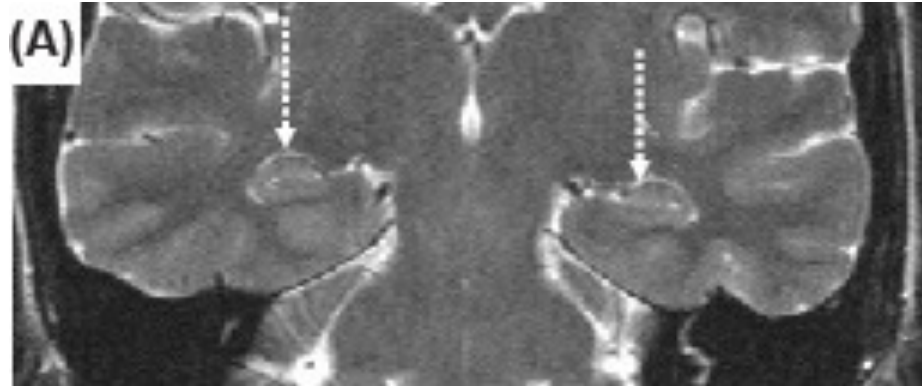
left orbitofrontal cortex, insula & operculum



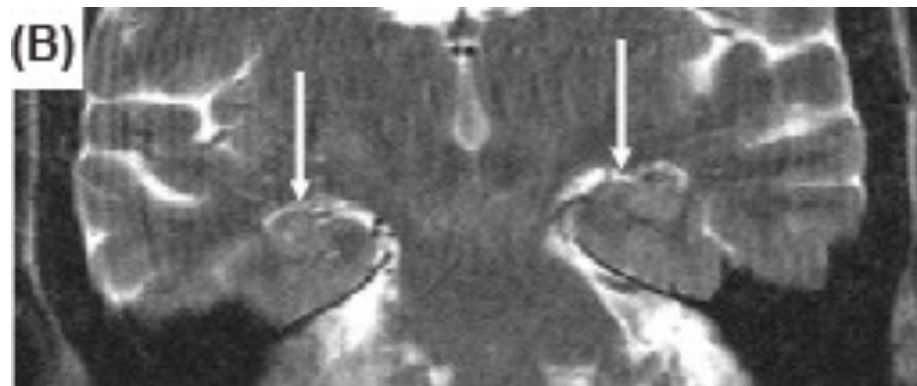
right posterior supramarginal gyrus & Left anterior Insula

Vestibular loss and spatial memory

Control Subject



BVL Patient



- Patients (n = 10) with acquired chronic bilateral vestibular loss (BVL) develop a significant selective atrophy of the hippocampus (16.9% decrease relative to controls)
- The same patients exhibited significant spatial memory and navigation deficits that closely matched the pattern of hippocampus atrophy (Brandt et al., 2005)



Biomarkers of Brain Changes



- Biomarkers include behavioral, physiological and biological indicators
- multi-modal approaches assessing longitudinal changes may be more reliable and discriminating

