Risk Title: Risk of Acute (In-flight) and Late Central Nervous System Effects from Radiation Exposure

National Academies' workshop on NASA's evidence reports

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Risk Statement

Given that the crew members are exposed to radiation from the space environment, there is the possibility that they will develop CNS damage leading to acute (in-flight) and/or late changes in cognition, motor function, behavior and mood, and/or neurological disorders.

Description of Central Nervous System Risks of Concern to NASA

- Acute CNS risks include: altered cognitive function, reduced motor function, and behavioral changes, all of which compromise missions.

- Late CNS risks are possible neurological disorders such as Alzheimer's disease, dementia, or premature aging. The effect of the protracted exposure of the CNS to the low dose-rate (< 50 mGy/h) of protons, HZE particles, and neutrons of the relevant energies for doses up to 2 Gy is of concern.

Space Radiation Environment

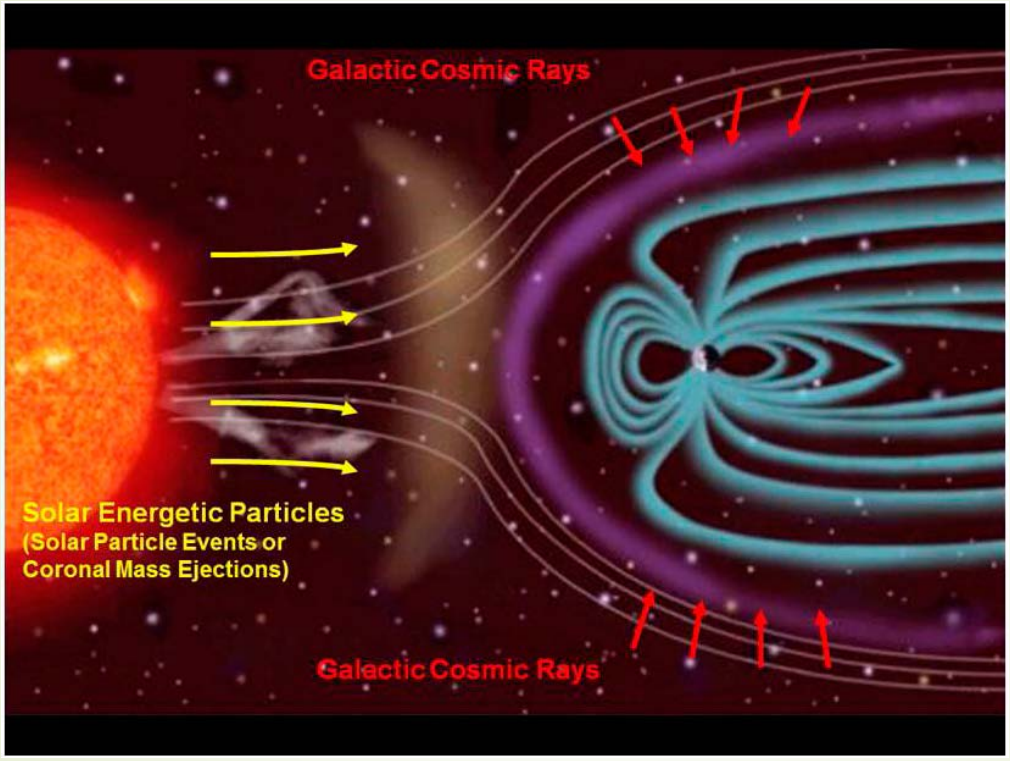
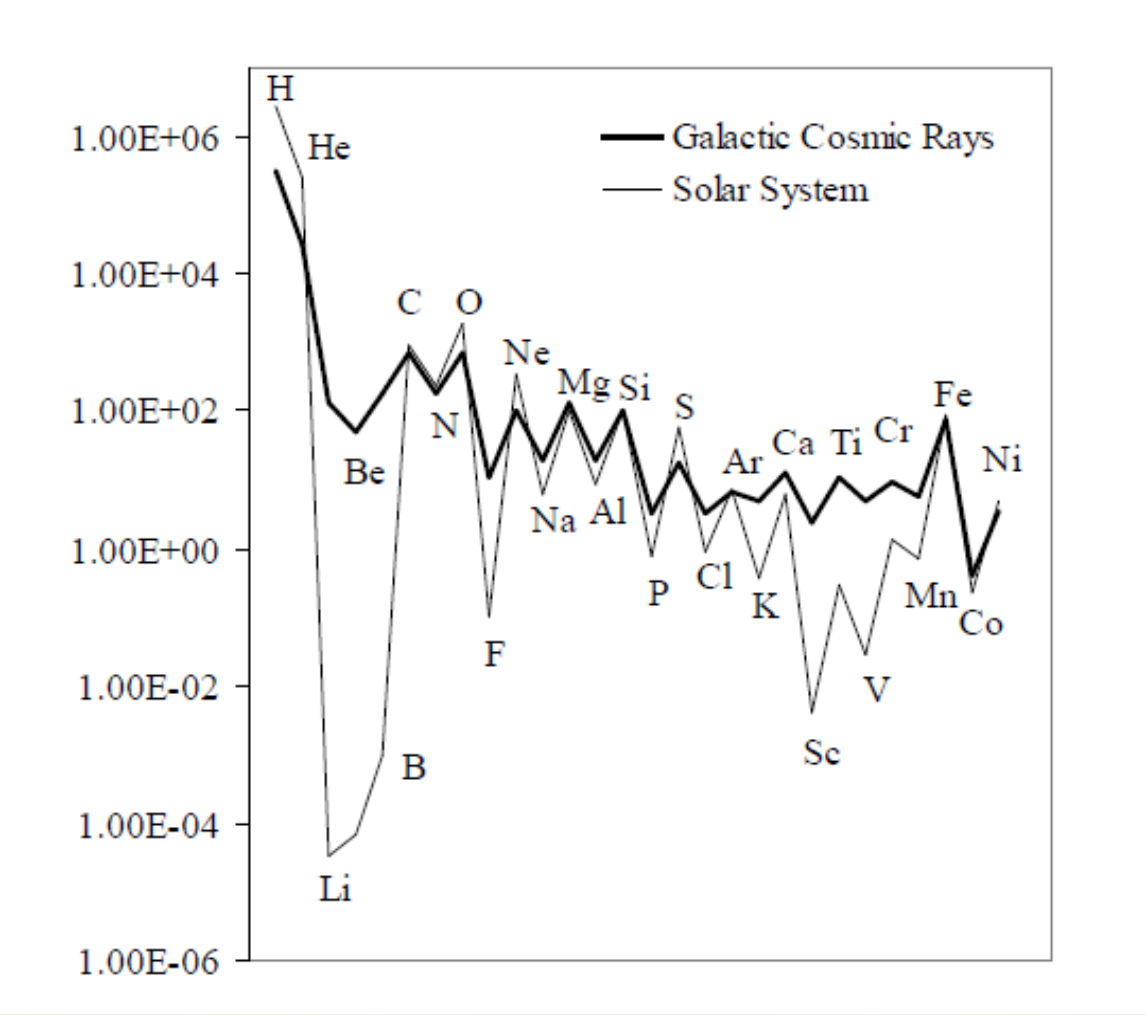


Figure courtesy of NASA/JPL-Caltech.

Current Mars design reference mission exposure: 0.25 Gy - 0.5 Gy from GCR with shielded SPE exposures on the order of 0.15 to 0.5 Gy to internal body organs within a typically shielded spacecraft.

GCR Abundance in Free Space



Nat. Res. Council (2008) Managing Space Radiation Risk in the New Era of Space Exploration

What was Known

Risk Ratings and Dispositions per Design Reference Mission (DRM) Category

DRM Categories	Mission Duration	Operations		Long-Term Health	
		LxC	Risk Disposition *	LxC	Risk Disposition *
Low Earth Orbit	6 months	Not Available	*Not Applicable*	Not Available	*Not Applicable*
	1 year	Not Available	*Not Applicable*	Not Available	*Not Applicable*
Deep Space Sortie	1 month	Not Available	*Not Applicable*	Not Available	*Not Applicable*
Lunar Visit/ Habitation	6 months	Not Available	*Not Applicable*	Not Available	*Not Applicable*
Deep Space Journey/Habitation	1 year	Not Available	*Not Applicable*	Not Available	*Not Applicable*
Planetary	3 years	**To Be Determined**	*Not Applicable*	**To Be Determined**	*Not Applicable*

Problems: There are currently no common standards for defining "significant" cognitive/performance impairments, and late degenerative conditions are usually detectable only when they reach clinical thresholds.

Unique Properties of CNS

- The cell nuclei may not necessarily be the most important target volumes.
- Multiple cells occupy the same target volumes.
- Much of the initial damage to CNS tissue will be delivered to complex interconnected cell processes intimately associated with the microenvironment.
- Connectivity patterns and extended domains of cells may amplify the physiological effects and extend the range of responses from microns to millimeters.
- Interpretations of CNS radiation responses should not rely on simple target theory analyses based on cell nuclei.

The nature of radiation-induced CNS damage leading to functional and cognitive effects is significantly different from cellular damage leading to cancer.

Gaps

- ✓ CNS - 1: What are significant adverse changes in CNS performance in the context and time scale of space flight operations? How is significance defined, and which neuropsychological domains are affected?
- ✓ CNS - 2: Does space radiation exposure elicit key events in adverse outcome pathways associated with neurological diseases? What are the key events or hallmarks, their time sequence and their associated biomarkers?
- ✓ CNS - 3: How does individual susceptibility including hereditary pre-disposition (e.g. Alzheimer's, Parkinson's, apoE allele) and prior CNS injury (e.g. concussion, chronic inflammation or other) alter significant CNS risks? Does individual susceptibility modify possible threshold doses for these risks in a significant way?

CNS - 4: What are the most effective biomedical or dietary countermeasures to mitigate CNS risks? By what mechanisms are the countermeasures likely to work?

CNS - 5: How can new knowledge and data from molecular, cellular, tissue and animal models of acute CNS adverse changes or clinical human data, including altered motor and cognitive function and behavioral changes be used to estimate acute CNS risks to astronauts from GCR and SPE?

CNS - 6: How can new knowledge and data from molecular, cellular, tissue and animal models of late CNS risks or clinical human data be used to estimate late CNS risks to astronauts from GCR and SPE?

CNS - 7: What are the best shielding approaches to protect against CNS risks, and are shielding approaches for CNS and cancer risks synergistic?

CNS - 8: Are there significant CNS risks from combined space radiation and other physiological or space flight factors, e.g., psychological (isolation and confinement), altered gravity (micro-gravity), stress, sleep deficiency, altered circadian rhythms, hypercapnea, altered immune, endocrine and metabolic function, or other?

Evidence Reports

- Review of human data. Doses are higher for these radiotherapy patients than would be experienced by astronauts in the space environment.
- Review of space flight issues. First, the lengths of past missions are relatively short and the population sizes of astronauts are small. Second, when astronauts are traveling in LEO, they are partially protected by the magnetic field and the solid body of the Earth, which together reduce the GCR dose-rate by about two-thirds from its free space values.
- Ground-based radiobiology studies in behavior, neurogenics, neurochemistry, neuroinflammation, and electrophysiology.

Key observations on the effects of space radiation in cell, tissue and animal models

Charged Particle Radiation Results in:

- Substantial reduction in neurogenesis (<0.5Gy)
- Persistent reductions in neuron arborization and synapse number (<0.25Gy)
- Significant increase of oxidative stress in neuronal precursor cells (<10 cGy)
- Gradual loss of endothelial cells and capillaries (0.5Gy)
- Disrupted vascular perfusion and blood brain barrier function (0.5Gy)
- Increase in activation of newly-born but not mature microglia
- Reduction in fluid diffusion along white matter fiber tracts
- Mutations in transgenes with tissue & dose specific structure
- Adhesion molecule, cytokine and growth factor gene expression changes (<0.5Gy)
- Changes in synaptic function (plasticity) leading to hyperexcitability
- Electrophysiological changes in LTP model of memory
- Decreased latency to AD-associated pathology
- Deficits in hippocampus-dependent neurocognitive tasks (≤0.1Gy)

Overall, the evidence points to significant alterations in behavioral, neurogenic, neurochemical, inflammatory, and electrophysiological changes to the CNS elicited by space-like radiation fields generated by accelerators. However, experimental endpoints show complex response with dose and time dependence. Different ions show common, unique or opposite responses, and we do not yet know if these changes rise to the level of operational or clinical significance in humans.

The major disagreement in the literature pertaining to radiation risk of CNS

- Threshold dose
- Dose response-linear or complex (U shape)
- Time of the tissue collection
- Age at exposure
- Radiation quality, and dose-rate effects
- Genetic susceptibility to CNS risk
- Animal behavior studies: data are not consistent
- Active debate regarding the relative importance of vasculature or glia as the primary determinant of CNS injury

More research is required and better methods for assessing the CNS damage have to be developed before CNS risk can be estimated.

Recommendations

- Simulating the space radiation environment -low dose thresholds, dose-rate and radiation quality effects (including possible synergistic interactions of particles of different radiation qualities). Threshold dose effects at lower doses (<0.5 Gy) has not yet been carried out to a sufficient extent.
- Appropriate animal models: extent small animal to larger size of animal for extrapolation to human. An approach has not been discovered to extrapolate existing observations to possible not only cognitive changes, but emotional, social performance (attention) degradation, or late CNS effects in astronauts.
- Mechanisms and major risk pathways, with integrated “omics” tool are not well-characterized.
- individual sensitivity (genetic, epigenetic, previous injury, age, sex/gender, etc.)
- Synergistic effects of radiation combined with spaceflight environment stressors (High pCO2 and fluid shifts, microgravity, environmental constraints, emotional stress)

Standardized experimental radiation protocol (dose/dose rate, radiation type and energy), so the data can be more comparable among investigators with their endpoints.

Potential New Gaps for CNS Risks

- What mixed radiation types, including protons, helium and heavier nuclei, are sufficient to adequately simulate the biological and health consequences of GCR across risk areas?
- How to integrate data across many biology scales for CNS endpoints?
- What are the most effective computer models to develop risk projection of the CNS from space radiation for risk assessment?
- How can system biology approaches with new technologies: three-dimensional multiple cell and organ cultures, integrated “omics” (genomics, proteomics, metabolomics) and innovated brain imaging be used to estimate acute CNS risks to astronauts from GCR and SPE?

Relevant Interactions among Risks

- Evidence reports discussed relevant interactions with risk of adverse cognitive or behavioral condition. However, potential interaction with other risks, especially potential interaction with cardiovascular risk, risk of performance errors due to sleep loss, circadian desynchronization, fatigue, and risk due to altered immune response should be explored.

- Discussion on interaction or synergistic effects of radiation with other spaceflight environment stressors should be expanded.

Conclusions

- Evidence reports well documented and summarized up-to-date research data that do suggest that space radiation can produce neurological and behavioral effects at dose as low as 0.1-0.25Gy; therefore, it is possible that mission operations will be impacted.
- The cited references for the topic covered in the report were comprehensive. However, more of the most recent literature needed to be added.
- Reliable projections for CNS risks from space radiation exposure cannot be made at this time.