Risk of Acute and Late CNS Effects from Radiation Exposure – Evidence Report Review

Catherine M. Davis-Takacs

National Academies
Keck Center
Washington, DC

Introduction

- Report covers research across multiple labs, organisms, and over a span of several decades
- Areas of controversy covered
- Supports risk of CNS effects of radiation as problem for long duration spaceflight
- Gaps in knowledge are identified

How well is the risk understood?

- Acute (in-flight) and late risks to the CNS from galactic cosmic rays (GCR) and solar particle events (SPE) are concerns for human space exploration
  - In-flight: cognitive, behavioral, mood, and motor function changes
    - e.g., short term memory, learning, reaction time, fatigue, neuropsychological changes
  - Late: degenerative neurological disorders, premature aging
- Cell and animal models provide evidence base
  - Significant changes occur within NASA-relevant dose levels
- Data outlined demonstrate radiation-induced changes in:
  - Hippocampal neurogenesis
  - Persistent oxidative stress and neuroinflammation
  - Brain microvasculature
  - Dendritic branches and spines
  - Gene expression
  - Autophagy
  - Rodent tests of neurobehavioral/cognitive performance

How well is the risk understood?

- Limited by several factors:
  - No human epidemiological data on which to base risk estimation for CNS effects
    - Radiotherapy patients' cognitive deficits – high dose
    - Chernobyl and A-bomb survivors evidence for memory /cognitive impairments
      - Limited by dosimetry uncertainties/reporting issues
    - HZE and low-LET radiation not always similar
  - Operational significance of rodent behavioral decrements unclear
  - Lack of nonhuman primate studies with space radiation exposure

How well is the risk understood?

- Proton and HZE studies limited by:
  - Lack of dose protraction
    - Dose fractionation studies are on-going
  - Dose rates of animal studies
  - NSRL particle energies limited to 1 GeV/n
    - Upgrades to 1.5 GeV/n
  - Single ion/single energy experiments unlike complex mix of energies/particles in the space environment
    - NSRL GCR Simulation
  - Limited particle species investigated thus far
    - Fe, H, and Si

How well is the risk understood?

- Proton and HZE studies limited by:
  - Lack of interaction with other spaceflight factors:
    - Sleep deprivation, chronic sleep restriction
    - Fatigue
    - Acute stressors
    - Confinement/hostile environment
    - Microgravity

Major sources of disagreement

- Molecular changes apparent at early time points that appear to persist over time
- Variable behavioral changes
  - Differences in sex, strain, species, genotype, age at irradiation and/or testing
- Connection between cellular/molecular changes and clinically significant behavioral changes in operational performance unknown

Major sources of disagreement

- Dose responses both linear and non-linear
  - Opposing effects induced by different ions
  - No clear pattern for LET-dependent changes
- Low dose rate exposure vs. acute higher dose rate exposure at NSRL

Concern for spaceflight well-documented

- Data demonstrates significant changes in numerous cellular and molecular markers indicative of radiation-induced damage
  - Mimic aging and other neurodegenerative disease pathways
- Behavioral data demonstrates significant changes in many rodent studies thus far
- Yes, concern for spaceflight is well-documented

Are the named gaps most critical?

- Named gaps are critical areas
- Interaction of CNS effects of space radiation with other spaceflight factors known to impact cognition should be greater priority (currently CNS 8)
- Other gaps depend on known risk of CNS effects – countermeasures, risk estimates for acute and late effects, shielding
  - Could all be modified by interaction with other spaceflight factors

Are there additional gaps/aspects of existing gaps that are not addressed?

- Report provides an analysis of data representing various gaps for which a literature base exists
- Countermeasures, individual risk factors, synergistic effects of spaceflight mentioned and any existing data discussed
- No additional gaps

Address relevant interactions?

- Limited data for interactions, but data that exists is discussed
  - Immune system – known association of numerous neurological and neuropsychological disorders with inflammation[5]
    - Neuroinflammation data presented, but limited interaction with peripheral immune components[7-11]
    - Novel brain-immune system connections[6]
  - Cardiovascular –known association of vascular disease with depression[1-4]
  - Microbiome – NASA-supported investigations focus on astronaut health, but very few, if any, incorporate CNS endpoints

[1]Musselman et al., 1998
[2]Carney & Freedland, 2003
[3]Plante, 2005
[4]Ghoge et al., 2003
[5]Mosley, 2015
[6]Louveau et al., 2015
[7]Vlkolinsky et al., 2007
[8]Vlkolinsky et al., 2008
[9]Marquette et al., 2003
[10]Rabin et al., 2014

Recommendations

1. Provide at least one example of where adverse outcome pathway could start
   - Aging? Inflammation? AD AOP?
   - What is the “low hanging fruit” from NASA-supported studies to date?
     - Are there overlapping pathways/molecules from other areas (e.g., sleep, sensorimotor)?
     - Could tissue sharing enable these investigations?

Recommendations

2. Slightly more synthesis of behavioral data
   - Variability exists and quantifiable changes exist, but what are the themes?
     - Accelerated aging?
     - Acute memory impairment?
   - How do these behavioral tests relate to those taken by the astronauts?
   - This analysis might pair well with an AOP