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Understanding the Impact of Chronic Low-Dose, Low Energy, Proton Radiation on Systemic Inflammation and Anxiety-Like Behaviors in Mice

Paula Nolte
Hope College

Victoria Parker
Hope College

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Paula Nolte, Victoria Parker, Phillip D. Rivera

Hope College Biology Department, Hope College, Holland, MI.

Abstract

A major component of NASA's 2018 strategic plan was to send astronauts to and beyond our lunar orbit within the next couple of decades. A risk to mission success is an astronauts' exposure to galactic cosmic radiation (GCR), a mixture of chronic low-dose, high-energy, high-charge ion particles (HZE). Previous high-energy radiation proton studies show lasting inflammation in the eye in humans treated for uveal melanomas. In mice, HZE particles also showed deficits in cardiac physiology, brain electrophysiology, and memory. Of particular interest to long-term mission success are low-dose, low-energy protons due to their high abundance in the space environment. Given the detrimental physiological and cognitive impact on humans and rodents after high-energy proton studies and a lack of low-energy proton studies on skin and inflammation, knowledge of how inflammation might respond to chronic low-dose, low-energy proton radiation is warranted. In our experiment, mice were put into a 50mL conical tube; half were irradiated using the Hope College Pelletron accelerator at a low-dose (~2 mGy/wk) of protons. After 10 weeks, half the irradiated mice and half the non-irradiated mice were euthanized for molecular studies. Levels of inflammatory cytokines like tumor necrosis factor, which are associated with increased depression, bipolar disorder and schizophrenia were assessed. The other half underwent behavioral tests that looked at stress behaviors. Therefore, the proposed study aimed to test the hypothesis that chronic low-dose, low-energy proton radiation negatively impacts mental health due to lasting systemic inflammation. Future directions are to examine HZE particles (e.g. Fe, Si, and C) at Brookhaven National Laboratories in Long Island, NY, to compare chronic low-dose particles and high-energy low-dose protons which will help future NASA missions to and beyond lunar orbit.

Introduction

Fig 1. The interior of the SpaceX capsule. Astronauts are exposed to radiation within the spacecraft, although some shielding does occur.

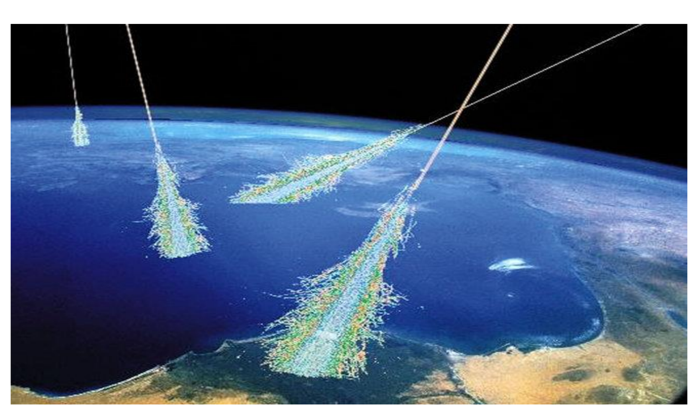


Fig 2. Spallation patterns of Galactic Cosmic Radiation hitting the Earth's atmosphere.

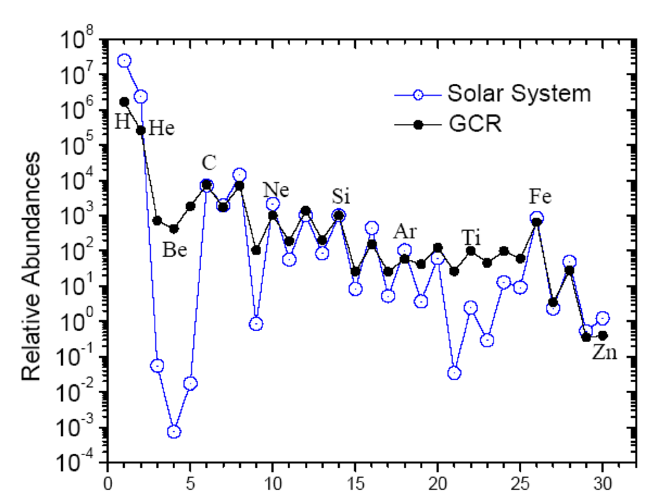


Fig 3. Elemental composition of Galactic Cosmic Radiation (GCR) and solar radiation. Hydrogen (protons) are the primary component of both types.

Research Question

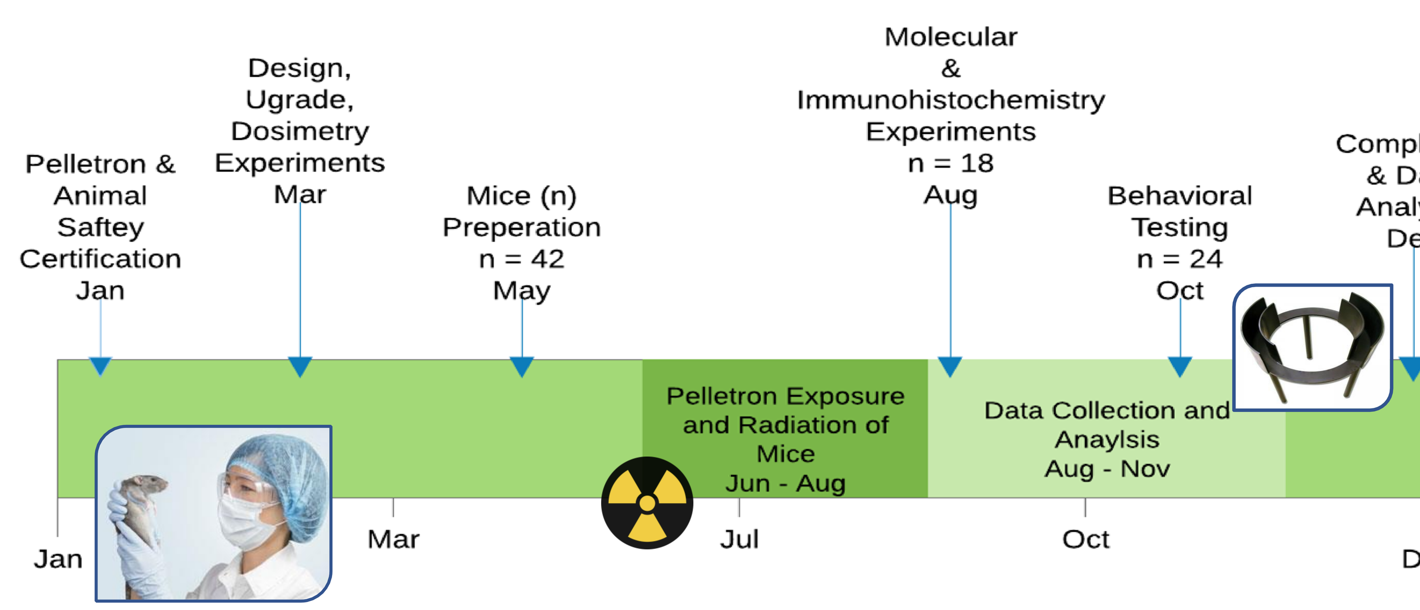
How does chronic, low-dose, low-energy proton radiation impact mental health and behavior of mice?

Technical Design

Fig 4. Amazing scientists in front of the pelletron accelerator in the Hope College physics department. It will emulate galactic cosmic radiation.

Fig 5. The chamber at the end of the line on the pelletron will scatter the proton beam to deliver radiation to the mice.

Graphical Methods



Hypothesis:

Chronic low-dose, low-energy proton radiation negatively impacts mental health due to lasting systemic inflammation.

Treatment Groups

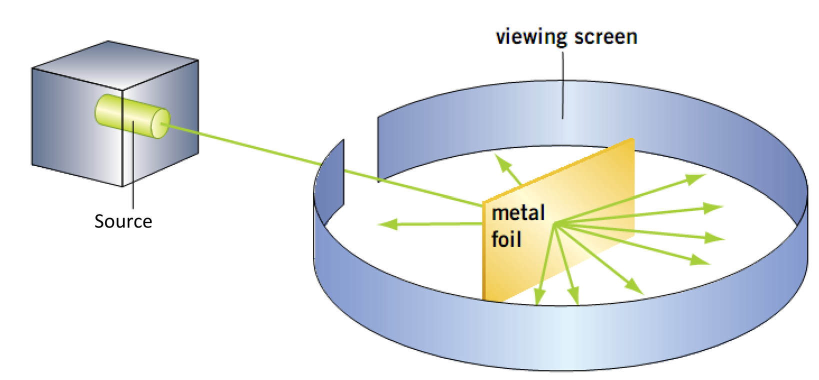
1. No irradiation (IRR), no constraint
2. No IRR, constraint (Fig.6)
3. IRR, constraint

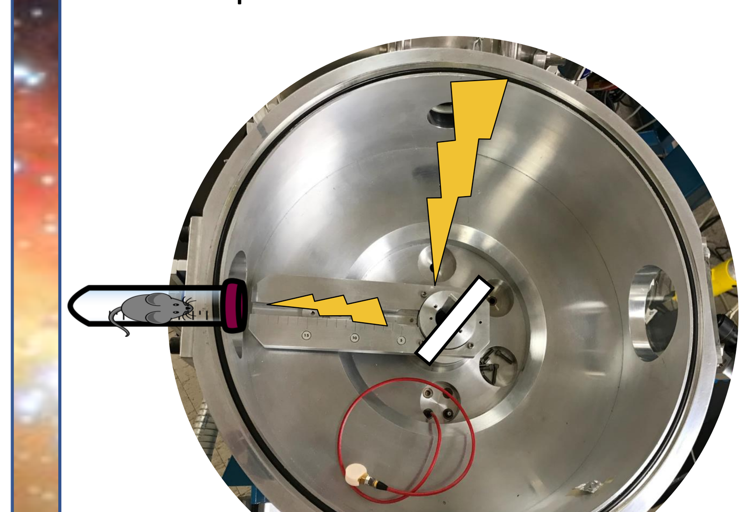
Fig 6. Mice with constraint will be placed inside a conical tube as shown above. However, constraint also induces stress, so one treatment group will not have constraint

Pelletron Modifications

Rutherford Scattering

Protons hit the shielding of the space capsule and scatter, which will decrease the amount of total protons and decreases the energy of the protons.



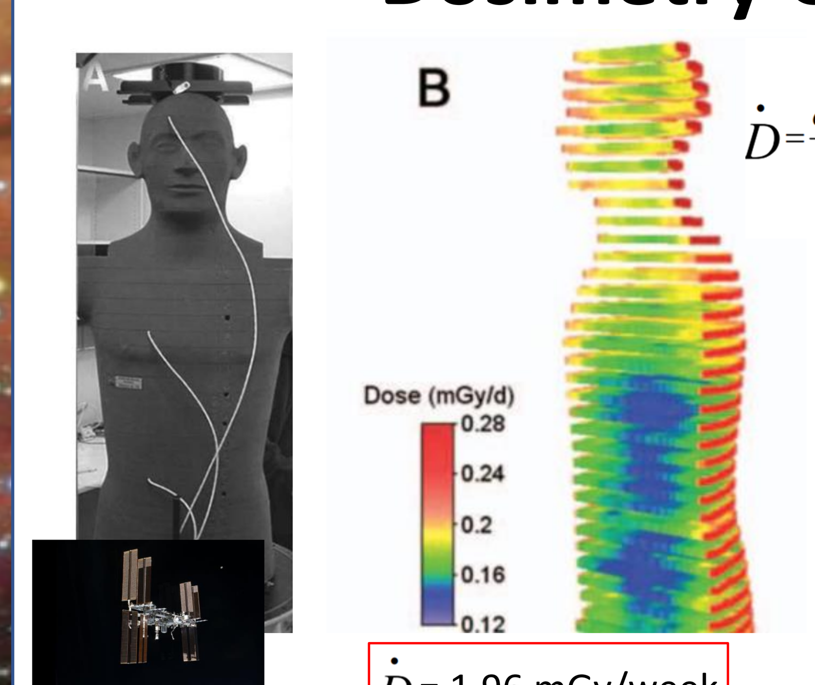


Technical Design

Proton beam from the pelletron will strike a thin gold sheet in the chamber, and scatter. In this design, Rutherford scattering recreates astronauts' experience in space, allowing for a way to mimic proton radiation observed in the ISS.

Fig 7. Protons hit gold sheet to scatter and strike a chamber containing the mouse at 45°.

Dosimetry Calculations



Berger et. al 2013

$\dot{D}$ = 1.96 mGy/week

$$\dot{D} = \frac{\dot{\varphi} A(-dE/dx)\Delta x}{\rho A \Delta x} = \dot{\varphi}\left(-\frac{dE}{\rho dx}\right)$$

$\dot{D}$ = dose rate

$\dot{\varphi}$ = fluence rate ($cm^{-2} s^{-1}$)

ρ= density

A = area

$\dot{\varphi}$ = 43.9 protons/cm^2

$\left(-\frac{dE}{\rho dx}\right)$ = Range from 328 to 621 MeV/ g/cm^2

$\dot{D}$ = Range from 262 to 138 uGy/min

$\dot{D}$ = Range from 1.834 to 0.966 mGy/week

Behavior Studies

Marble Burying (MB)

Mouse behavior examined: compulsive behaviors, anxiety

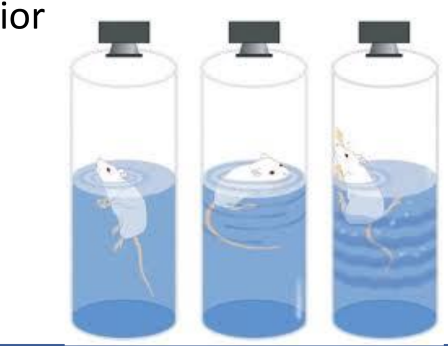
Open Field (OF)

Mouse behavior examined: activity, anxiety

Elevated Zero Maze(EZM)

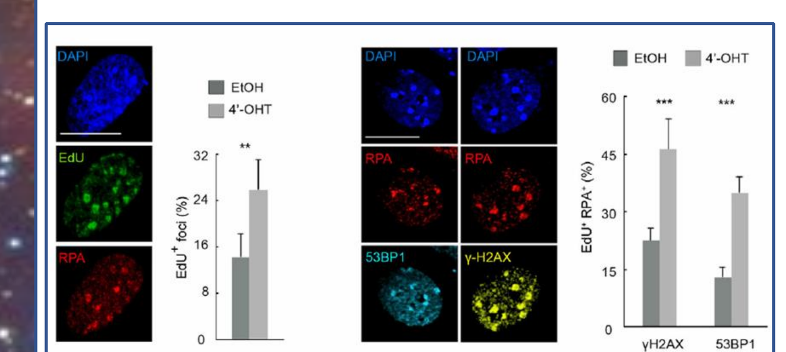
Mouse behavior examined: anxiety

Forced Swim Test (FST)



Mouse behavior examined: depressive-like behaviors

Molecular Studies

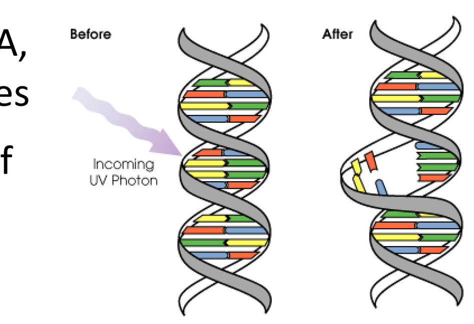


Bravo et. al 2015.

Figure 8. The molecular tests used in this experiment regarding histones and DNA synthesis are the same types of molecular studies our project would do; therefore, these results would be similar to what we expect. Increased coloration is increased protein concentration.

Radiation causes breaks in DNA, disrupting normal cell processes

Experiment will assess levels of three proteins associated with DNA damage:



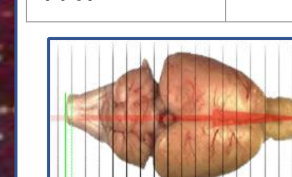
Protein	Function
53BP1	Repairs double strand breaks in DNA
g-H2AX	Repairs single strand breaks in DNA
TNF	Immune cytokine

Expected Results

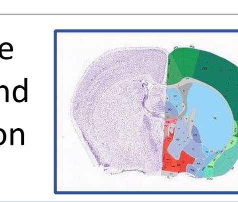
Molecular Tests

(relative to control)

Protein	Irradiation w/ constraint	No irradiation w/ constraint
53BP1	+++	+
g-H2AX	+++	+
TNF	+++	+



Whole mouse brain (left) and a brain section (right).



Behavioral Tests

(relative to control)

Behavior Test	Response	IRR w/ constraint	No IRR w/ constraint
MB	Anxiety	+++	+
	Compulsive behaviors	+++	+
OF	Anxiety	+++	+
	Activity	+++	+
EZM	Anxiety	+++	+
FST	Depressive behaviors	+++	+

Future Directions

- Examine high energy particles (HZE) at Brookhaven National Laboratories in Long Island, New York, to compare chronic low-energy low-dose particles and high-energy low-dose protons which will help future understanding of radiation on NASA mission success.
- Look to assess telomere length as a part of aging in response to radiation

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Acknowledgments

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