Fiscal Year:	FY 2020	**Task Last Updated:**	FY 11/02/2020
PI Name:	Nelson, Gregory A. Ph.D.		
Project Title:	VNSCOR: Responses of the Nervous System to Chronic, Low Dose Charged Particle Irradiation		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HFBP**:Human Factors & Behavioral Performance (IRP Rev H)		
Human Research Program Risks:	(1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders (2) **Immune**:Risk of Adverse Health Event Due to Altered Immune Response (3) **Sensorimotor**:Risk of Altered Sensorimotor/Vestibular Function Impacting Critical Mission Tasks		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Zip Code:	92350-1700	**Congressional District:**	31
Comments:			
Project Type:	GROUND	**Solicitation / Funding Source:**	2016-2017 HERO NNJ16ZSA001N-SRHHC. Appendix E: Space Radiobiology and Human Health Countermeasures Topics
Start Date:	04/15/2018	**End Date:**	11/02/2022
No. of Post Docs:	2	**No. of PhD Degrees:**	
No. of PhD Candidates:	2	**No. of Master' Degrees:**	
No. of Master's Candidates:		**No. of Bachelor's Degrees:**	1
No. of Bachelor's Candidates:		**Monitoring Center:**	NASA JSC
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Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	2020 report: Dr. Roman Vlkolinsky has taken a new position and is no longer affiliated with the project.		
COI Name (Institution):	Hartman, Richard Ph.D. (Loma Linda University) Mao, Xiao Wen M.D. (Loma Linda University) Rosi, Susanna Ph.D. (University of California San Francisco) Wroe, Andrew Ph.D. (Loma Linda University)		
Grant/Contract No.:	80NSSC18K0785		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	[Ed. note Jan 2019: See also project, "VNSCOR: Mechanisms of Radiation-Induced Changes in Sustained Attention and Social Processing" (Principal Investigator-PI: Catherine Davis)] NELSON/DAVIS VIRTUAL NASA Specialized Center of Research (NSCOR): The project is a combined experimental campaign combined with "Mechanisms of Radiation-Induced Neurobehavioral Deficts (PI: Davis) (see above for official project title) to quantify responses for an interrelated set of central nervous system (CNS) outcome measures in mice to acute and protracted exposures to protons, simulated galactic cosmic rays and gamma rays. A definition phase review resulted in modifications to the original experimental plan to take advantage of new irradiation capabilities and to coordinate approaches with the Davis project. Funds became available for experimental work in the first quarter of FY 2019. The post definition phase project descriptions are provided below. Evidence has accumulated from animal studies that the central nervous system (CNS) undergoes deleterious changes after exposure to charged particle radiation such as protons and high atomic number atomic nuclei that are found in space as galactic cosmic rays and solar particle events. Observed changes include inflammation, oxidative stress, loss of neuron (dendrite) branches and connections (synapses), altered signaling molecules, altered electrical properties, loss of blood vessels, and impaired behavioral performance. If humans respond to charged particles in the same way as animals, then it is possible that deleterious changes may be sufficient to cause cognitive and other behavioral impairments that could compromise spaceflight missions and astronaut health. The current evidence is based primarily on short exposures to single radiation types. However, space radiation is a complex mixture of these particles and exposures accumulate gradually over the course of missions. It is well established in radiation biology that reduction of the dose rate can have a profound effect on the outcome. Therefore, to better simulate the space environment, we propose to expose adult mice to either protons or Gy mixtures of charged particles using the NASA/ Brookhaven National Laboratory (BNL)-developed 33-ion galactic cosmic ray simulation protocol (GCRsim). Then we will deliver the exposures over 4 weeks in 24 short exposures (fractions) compatible with particle accelerator operations. These results would be compared to results from acute exposures to establish the Dose Rate Effectiveness Factors (DREFs) which are needed for risk estimation for astronaut health. We predict that the high numbers (fluence) of protons will result in multiple traversals of cells within short times that may elicit interacting biological responses, whereas the lower fluence of higher charged ions will result in rare independent events. DREFs > 1 are predicted for protons and DREFs ~1 are predicted for high Z particles. We will also compare the "protracted" exposures of charged particle mixtures to gamma rays to determine whether they have equivalent dose effects or are more effective. The relative biological effectiveness factor (RBEs) will be derived. These RBEs are utilized in predicting densely ionizing radiation effects in humans for whom only gamma ray and X-ray data are available with the assumption that the ratios obtained in animal models are realistic surrogates for humans. For this project, mice will be irradiated with a broad energy spectrum of protons in acute and protracted (12 fractions over 4 weeks) exposures at a dose of 0.5 Gy and sham controls; acute and protracted (24 fractions over 4 weeks) exposures to 0.25 and 0.5 Gy of charged particles (33 ion GCR simulation); and acute and protracted (24 fractions over 4 weeks) exposures to 0.75 and 2.0 Gy of 137-Cs gamma rays. All proposed work will use wild type mice and will be performed under Institutional Animal Care and Use Committee (IACUC) approved protocols in AAALAC-certified facilities at Loma Linda University (LLU), the University of California (UCSF), and Brookhaven National Laboratory (BNL). For all three specific aims the species is Mus musculus, strain C57Bl/6J. Ages are 5 - 6 months at acquisition and the beginning of irradiation procedures. We will test both male and female animals as their responses are not identical and the astronaut population is of mixed gender. Scheduled sacrifices are at 30-45 days and 90-110 days post-irradiation. For each of the exposure regimens we will conduct a battery of behavior tests, explore task-driven neuronal pathway activation patterns using c-fos imaging, quantify changes in selected gene expression patterns, and quantify selected biomarkers and the structure of the tissue using state of the art biochemical, histochemical, and microscopy methods. This will allow us to identify the underlying physiological changes most sensitive to dose rate and radiation quality and how they combine to produce behaviors that are adaptive or maladaptive. All outcome measures will be quantified in males and a subset of measures will be quantifies in females The Covid-19 pandemic disrupted the 2020 BNL experimental campaign resulting in a 1-year delay in implementing GCR exposures. Therefore, during this period, exploratory studies of interactions between proton radiation and chronic mild stress were initiated to model interactions between multiple spaceflight stressors (e.g. altered gravity, isolation and confinement, sleep disruption) and radiation. Together the data generated by the project will enhance NASA's ability to translate animal assessments of CNS (central nervous system) structure and function to humans, and to update risk estimates based on single radiation species, high dose rate irradiation protocols, to higher fidelity space-like exposures of charged particle mixtures delivered at dose rates approaching those observed in space.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The primary research impact to NASA is in estimation of potential adverse cognitive and behavioral effects of exposures to space radiation on long (e.g., 3-year Mars missions) deep space missions where exposures are of a chronic nature and are comprised of complex mixtures of charged particles dominated by protons. Such adverse effects could affect in-mission performance as well as post mission health of crew members. The experimental plan uses radiation fields and exposure conditions scaled to the life span of the experimental animal model. On Earth, the principal benefits will be for estimation of health risks to humans from charged particles in the environment (e.g., Radon alpha particles) and potential side effects of particle-based radiotherapy (e.g., proton and carbon beams) which requires pre-clinical animal studies. The current task will provide insight into adverse effects on normal brain tissue from proton exposures similar to those expected for normal tissues outside tumor treatment volumes in head & neck and brain tumor treatment scenarios. Low dose rate exposures to protons as well as 33-ion GCRsim radiation fields with substantial proton and helium components will inform risk estimates for the general population due to Radon exposures and for first responders to radiological accidents (e.g., Fukushima, Chernobyl).

Task Progress:	To date, two proton irradiation campaigns have been conducted and provided biological replicates for measurements. Future experiments will examine simulated GCR spectra for which protons are the main component. A battery of 15 behavioral tests assessed cognitive, affective, and sensorimotor performance in both male (1, 3, & 9 months post IR) and female mice (3 months post IR). 9-month measurements in males were not originally planned but resulted from Covid-19 related restrictions on animal care facility access. In cases where 0.5 Gy proton exposure resulted in altered behavioral parameters, the percent change from sham values ranged up to 74% and the magnitude of change from fractionated exposures often exceeded that for acute exposures. This included: Y-maze, elevated plus maze, light-dark box, open field exploration, novel object and novel place recognition, sociability and social recognition, modified balance beam, tail suspension, and forced swim tests. Fractionated exposures were notably more effective for step-through passive avoidance. Defensive marble burying, grip strength, water maze, and accelerating rotarod coordination behaviors were not significantly affected by irradiation and animals maintained good learning ability in training phases. To assess neuronal network function, expression of the immediate early gene c-fos was measured in selected brain regions of male mice at 3 months post IR. 90 min after completion of the 24-hour recall phase of passive avoidance testing mice were sacrificed and brain tissue prepared for counts of cells expressing c-fos. Regions of interest (ROI) used for cell counting included: orbitofrontal cortex, cingulate cortex, hippocampus, caudate putamen, thalamic and hypothalamic nuclei, amygdala, and cerebellum. Passive avoidance testing elicited strong gene expression in all of these regions compared to home cage controls. Prior radiation exposure resulted in altered c-fos expression reflecting changes in behaviorally driven network activity. Percent changes in c-fos(+) cell number in ROIs of irradiated animals compared to shams were typically of the order 50% and the ratios of change (acute vs fractionated treatment samples) were typically 1.1 to 1.8. Three regions showed notable differences in expression levels as a function of treatment: hippocampus CA1 & CA3 fields and cerebellum granular layers. c-fos imaging is currently in progress for a second behavioral “task,” tail suspension, which is expected to drive neuronal pathways associated with anxiety and depression-like behaviors. To determine which molecular markers and signaling pathways underlie outcomes of the treatment conditions we used NanoString® technology to profile mRNA expression at 3 months post irradiation of male mice in orbitofrontal cortex, hippocampus, and cerebellum. Five replicate brain regions were used for each treatment condition (sham, acute, fractionated). A set of 760 genes from the nCounter® Mouse Neuropathology panel for 23 fundamental pathways were examined and were characterized according to annotations for: structural integrity, metabolism, neuroinflammation, neuron-glia interaction, plasticity & aging, and neurotransmission. Expression patterns varied with radiation dose rate and brain region. In hippocampus, pathway activation was generally similar for fractionated vs acute expression while in frontal cortex fractionated exposure differed substantially from either sham or acute exposures. Pathways involving activated microglia, growth factors and trophins, nerve structure as well as endothelial cells were the most affected by dose rate and region. During the Covid-19 driven delay in the use of BNL irradiation facilities we have initiated exploratory experiments using the chronic mild stress (CMS) model to simulate combined stressors experienced during space flight. This well-vetted model will deliver mild stress over a 4-week period to simulate the set of non-radiation space flight stressors and measure selected outcome measures as described above. Then the CMS regimen will be combined with a 0.5 Gy proton exposure to characterize interactions of the combined stresses. Characterization of the dose rate effects by a simple parameter like DREF is problematic for CNS outcome measures which are deterministic and exhibit non-linear dose responses. Behavioral outcome measures reflect complex interactions of motivation, sensory and motor function, emotional status, etc. and outcome parameter values reflect the balance between conflicting behavioral drives such as anxiety and curiosity. Thus, deviations from the control values can be positive or negative reflecting an altered but stable new state not necessarily interpretable as detrimental. Non-DREF methods for comparing dose rate effects will be considered as the study progresses. To date, presentations of experimental finding have been made to the 2019 and 2020 annual meetings of the Radiation Research Society and to the 2020 NASA Human Research Program (HRP) Investigators’ Working Group. Publications on proton-irradiations conducted in 2019 – 2020 are in preparation.
Bibliography Type:	Description: (Last Updated: 03/13/2024)
Abstracts for Journals and Proceedings	Nelson G, Jones T, Stanbouly S, Tolan B, Wroe A, Hartman R. "Effects of Dose Rate on Responses of the Brain to Charged Particles." 65th Annual Meeting of the Radiation Research Society, San Diego, CA, November 3-6, 2019. Westin Gaslamp Hotel 11/3-6/2019 65th Annual Meeting of the Radiation Research Society, San Diego, CA, November 3-6, 2019. Poster # PS8-33. , Nov-2019
Abstracts for Journals and Proceedings	Nelson G, Jones T, Stanbouly S, Tolan B, Wroe A, Rosi S, Grue K, Hartman R. "Dose rate effects of protons on mouse central nervous system." 66th Annual Meeting of Radiation Research Society, Virtual Meeting, October 18-21, 2020. 66th Annual Meeting of Radiation Research Society, Virtual Meeting, October 18-21, 2020. Poster # PS9-06. , Oct-2020
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