Fiscal Year:	FY 2021	**Task Last Updated:**	FY 10/14/2020
PI Name:	Britten, Richard Ph.D.		
Project Title:	Hadron-induced Impairment of Executive Function: Role of Perturbed Neurotransmission and the Exacerbating Impact of Sleep Deprivation		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:	HUMAN RESEARCH--Radiation health		
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **SR**:Space Radiation		
Human Research Program Risks:	(1) **BMed**:Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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City:	Norfolk	**State:**	VA
Zip Code:	23507-1607	**Congressional District:**	3
Comments:			
Project Type:	Ground	**Solicitation / Funding Source:**	2013-14 HERO NNJ13ZSA002N-NSCOR Radiation
Start Date:	12/02/2015	**End Date:**	05/01/2022
No. of Post Docs:	0	**No. of PhD Degrees:**	0
No. of PhD Candidates:	0	**No. of Master' Degrees:**	0
No. of Master's Candidates:	0	**No. of Bachelor's Degrees:**	0
No. of Bachelor's Candidates:	0	**Monitoring Center:**	NASA JSC
Contact Monitor:	Zawaski, Janice	**Contact Phone:**	
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Flight Program:			
Flight Assignment:	NOTE: End date changed to 5/01/2022 per NSSC info (Ed., 11/30/20) NOTE: End date changed to 12/31/2020 per NSSC info (Ed., 11/12/19) Ed. NOTE (April 2016): Proposal modified from original NSCOR proposal, per Space Radiation Element; not an NSCOR project		
Key Personnel Changes/Previous PI:	October 2020 report: Dr. Hargsoon Yoon from Norfolk State University has been added as CoInvestigator to help develop the neural network cohesiveness studies.		
COI Name (Institution):	Sanford, Larry Ph.D. (Eastern Virginia Medical School) Wellman, Laurie Ph.D. (Easterm Virginia Medical School) Yoon, Hargsoon Ph.D. (Norfolk State University)		
Grant/Contract No.:	NNX16AC40G		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	The proposed studies will address multiple issues of concern to NASA. The proposed studies will generate data on the likelihood that GCR (galactic cosmic radiation) exposure will result in the impairment of neurocognitive (Executive Function) tasks that will be absolutely vital for the successful completion of a deep-space mission, under conditions that are more representative of the actual mission (when individuals are suffering from perturbed sleep). These studies will be conducted in a rat model that is relatively unique in that the rats are exercised regularly, and are preselected for a high level of executive function performance (high cognitive reserved) prior to space radiation exposure. Such a model system more closely resembles the physical and cognitive reserve of astronauts, and addresses a key operational issue of whether space radiation exposure will impact previously imprinted cognitive skills. Specifically, these studies will determine the impact that mission-relevant doses of space radiation (Z<15 single ion exposures, in addition to the multi-ion GCRSim) have on advanced executive functions, specifically Attentional Set Shifting (ATSET) and creative problem solving (UCFlex). This data can be used to address Risk of Adverse Cognitive or Behavioral Conditions and Psychiatric Disorders Bmed Gap 102 [previously central nervous system (CNS) Gap 2], and determine the likelihood of Astronauts being able to successfully conduct neurocognitive (problem-solving) tasks. This study will also determine whether the incidence and/or severity of executive function impairments would be altered by exposure to another frequent flight stressor, insufficient sleep [Bmed-107 and Bmed-108, formerly (CNS Gap 8)]. A key component of these studies is an assessment of inter-individual susceptibility to develop deficits in these two cognitive processes following space radiation exposure (with or without the additional sleep stressor). Such data can be used (by others) to determine the best approach to develop a population Threshold Dose for dose risk estimations [Bmed-102 and Bmed-107, formerly (CNS Gap 3)]. [Ed. note October 2020: Human Research Program (HRP) gaps have changed with Integrated Research Plan Rev L such that gaps listed previously have been merged into newer gaps, as noted] Initially, three hypotheses were tested by the studies covered by this grant. 1. Sleep perturbation reduces the ability of rats to perform executive functions, and will be especially pronounced in space radiation (SR)-irradiated rats. 2. Sleep perturbation alters the sensitivity of the brain to develop SR-induced cognitive impairment. 3. SR irradiation alters Delta and Theta wave activity (EEG), and that these SR-induced changes in EEG activity are the underlying cause of the impairment of executive function performance. In 2019, we received supplemental funding (an HRP-IWS Graduate Fellowship) to develop the technical capability to simultaneously assess neural activity in multiple brain regions (neural network activity) of rats that are actively engaged in cognitive flexibility tasks, and how sleep fragmentation impacts neural network cohesiveness. In 2020, we received further supplemental funding (an HRP-IWS Graduate Fellowship) to establish whether sleep fragmentation exacerbates SR-induced deficits in fine motor skills.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	The newly developed capability of measuring neural network functionality when rodents are under cognitive loading will allow more detailed work on establishing the basis for chemo- and beamo-brain in cancer patients.
Task Progress:	Astronauts on the mission to Mars will be exposed to Space Radiation (SR) and most will experience problems with their sleep patterns. Inadequate sleep is well known to adversely impact performance in multiple cognitive tasks, including problem solving. Data from our laboratory, and others, have shown that mission-relevant SR doses reduces problem solving ability in 30-50% of rats. This project will determine whether sleep perturbation alters the incidence and/or severity of SR-induced problem solving impairments. Over the last two years, studies were conducted that determined whether SR-exposed male rats differ in their problem solving ability following sleep perturbation compared to non-irradiated rats subjected to the same sleep stress. Irradiated rats with apparently normal problem solving performance (in the attentional set shifting (ATSET) assay), and unirradiated rats, were thus subjected to sleep perturbation and reassessed for ATSET performance the following day. Sleep perturbation resulted in 10% of the sham rats performing badly in all stages of the ATSET test, with the exception of the IDS stage where 30% of the sham rats performed badly. In contrast, sleep perturbation resulted in 40-50% of the irradiated rats under-performing in the IDS, IDR, EDS, and EDR stages of the test, despite them previously having good performance when not sleep deprived. Importantly set shifting performance (IDS, IDR, EDS, and EDR stages) performance has rarely been shown to be impacted by SR. The same observations were made in male rats exposed to 5 cGy 600 MeV/n 28Si ions (Britten et al., 2020) and to 18 cGy of 252Cf-generated neutrons delivered over 6 months (Britten et al., 2019). This “unmasking” of latent ASTET deficit suggest that the true impact of SR on cognitive impairment (and possibly other processes) may not be fully evident in normally rested rats. A worrying aspect of these studies is that sleep perturbation appears to have a bigger impact on ATSET performance in irradiated rats than in non-irradiated rats. This raises the possibility that irradiated individuals may have a generalized issue in task performance (even sensorimotor based tasks) under sub-optimal sleep conditions. Over the last year our studies have evolved to expand the scope of investigation to include female rats and to assess whether sleep fragmentation would exacerbate any cognitive impairment induced by the simulated GCR beam. While some progress has been made in these areas, the COVID-related shutdown at Eastern Virginia Medical School (EVMS) drastically reduced the amount of data that could be generated from the batch of prescreened rats that were irradiated at NASA Space Radiation Laboratory (NSRL) in the Fall of 2019, while the COVID-related shutdown of Brookhaven National Laboratory (BNL)/NSRL in April 2020 prevented that cohort of prescreened (male and female) rats being irradiated. The data we were able to generate does show that female rats are susceptible to SR-induced impairments in ATSET performance. This is in stark contrast to some mouse studies that suggest that GCR exposure did not impact Novel Object Recognition memory in female mice but that male mice had severely impaired performance. Our data does indicate that there are some stages within the ATSET test where males show bigger performance decrements than females, but there are others (specifically the Compound Discrimination stage) where 3-fold more females than males

	have severe performance decrements. The very limited data on the exacerbating impact of sleep perturbation on ATSET performance in GCR exposed rats suggests that qualitatively there is the same “unmasking” of latent deficits by sleep fragmentation as we have observed with other ions in males, and possibly in female rats. However, further data is needed before a definitive conclusion can be made on this matter. There were some major technological advances in our studies that are assessing the exacerbating impact of sleep fragmentation and/or SR on neural network cohesion while the rats are actively performing executive functions. Six sham and 6 He-exposed rats were implanted with electrodes after returning from NSRL and local field potential (LFP) readings were obtained from 2 sham and 3 He-exposed rats while they performed in our newly developed Associative Recognition Memory Interference Touchscreen (ARM-IT) test. We have shown that it is possible (using a wireless back-pack transmitter) to get concurrent LFP recordings from nodes (Hpc, amygdala, mPFC) within the cortico-limbic (CLN) network in rats under cognitive loading, and to perform cross correlation analysis to assess functional connectivity between these nodes. We also developed the technical capability to generate electronic time stamps from the touchscreen apparatus (when specific events occurred) and incorporate these as part of the LFP output signals. Using such time stamps it is now possible to accurately assess the functional connectivity between nodes when the rats are performing specific responses within the ARM-IT task. For example, this “electronic mind” can establish the LFP signature from 3 brain regions when the rat “notices” that the “target” is activated on the touchscreen and just prior to pressing the correct or incorrect “target.” These studies were curtailed when EVMS (and Norfolk State University-- who are responsible for the LFP data analysis) operations were shut down in April 2020 in response to the COVID pandemic. Similarly, our proposed plans to assess the impact of sleep fragmentation on the incidence and severity of SR-induced impairment of fine motor skills were also suspended with the shutdown of operations at NSRL in April 2020.
Bibliography Type:	Description: (Last Updated: 05/16/2025)
Abstracts for Journals and Proceedings	Britten RA, Fesshaye A. "Space radiation-induced neurocognitive impairment: hidden figures revealed by sleep perturbation." 2020 NASA Human Research Program Investigators’ Workshop, Galveston, TX, January 27-30, 2020. Abstracts. 2020 NASA Human Research Program Investigators’ Workshop, Galveston, TX, January 27-30, 2020. , Jan-2020
Articles in Peer-reviewed Journals	Britten RA, Fesshaye A, Duncan VD, Wellman LL, Sanford LD. "Sleep fragmentation exacerbates executive function impairments induced by low doses of Si ions." Radiat Res. 2020 Aug 1;194(2):116-23. https://doi.org/10.1667/RADE-20-00080.1 ; PMID: 32845991 , Aug-2020
Articles in Peer-reviewed Journals	Britten RA, Duncan VD, Fesshaye A, Wellman LL, Fallgren CM, Sanford LD. "Sleep fragmentation exacerbates executive function impairments induced by protracted low dose rate neutron exposure." Int J Radiat Biol. 2019 Dec 6:1-11. Published online: 06 Dec 2019. https://doi.org/10.1080/09553002.2019.1694190 ; PMID: 31724895 , Dec-2019