Fiscal Year:	FY 2021	**Task Last Updated:**	FY 01/25/2021
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Project Title:	Brain-Related Assessments for Investigating the Neurophysiology of SANS (BRAIN-SANS)		
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Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
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Human Research Program Risks:	(1) **SANS**:Risk of Spaceflight Associated Neuro-ocular Syndrome (SANS)		
Space Biology Element:	None		
Space Biology Cross-Element Discipline:	None		
Space Biology Special Category:	None		
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Project Type:	GROUND	**Solicitation / Funding Source:**	2018-2019 HERO 80JSC018N0001-SANS: Spaceflight Associated Neuro-ocular Syndrome Countermeasures. Appendix C
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Task Description:	Spaceflight Associated Neuro-ocular Syndrome (SANS) remains an important and unmitigated risk to long-duration spaceflight. Current hypotheses suggest that the lack of gravity leads to fluid shifting towards the head, resulting in congestion and/or elevated pressures in the cranial, vascular, and/or lymphatic compartments. NASA is proposing to conduct 30-day head-down tilt (HDT) experiments to test SANS countermeasures at the :envihab facility in Cologne, Germany. We propose to provide numerous key measurements in support of these planned 30-day missions. We will focus in particular on providing a toolkit for detailed neurophysiological and fluid shift assessment and monitoring suitable for measuring both SANS- and countermeasure-related changes. These tools will be designed to complement the standard ocular measures used for SANS diagnosis and monitoring (e.g., optical coherence tomography (OCT), ocular ultrasound (US), fundoscopy, visual acuity). Our proposed measures will include: • Relative intracranial pressure (ICP) measurements via distortion product otoacoustic emissions (distortion product otoacoustic emissions: DPOAE). • Blood volume shifts along the body axis via near-infrared spectroscopy (NIRS). • Intracranial blood inflow and outflow, via internal jugular vein (IJV) and carotid artery (CA) ultrasound cross-sectional imaging and Doppler. • Cerebral pulsatility assessment, per our parabolic flight and SPACE-COT (Studying Physiological and Anatomical Cerebral Effects of CO2 and Tilt) :envihab NIRS study. • Blood pressure at the level of the head via local, cuffless superficial temporal artery tonometry. • Sagittal sinus blood volume imaging and monitoring using diffuse optical tomography (DOT). • Cerebral edema assessment based on H2O concentration imaging, similar to that used in our previous altitude sickness studies. • Cerebral electrical activity, via electroencephalogram (EEG) measurements. • Dynamic cerebral autoregulation (CAR) assessment during countermeasure (CM) challenges, which can be derived from the NIRS signals used in the above measurements. Our tools will be made fully compatible with the planned SANS countermeasures, as well as with those of other teams proposing specific CMs. Along with the measures, we will provide the necessary expertise and analysis to quantify physiological changes associated with SANS countermeasures deployed during the 30-day HDT campaigns at :envihab. Our specific aims are as follows: Aim 1: Develop an integrated collection of hardware to support multiple simultaneous, continuous brain monitoring/imaging capabilities, and ensure the hardware and measurements are fully compatible with all countermeasures deployed during the :envihab missions. Aim 2: Characterize and quantify individual subjects' physiological responses to each planned condition, including comparative assessment of SANS countermeasures. Aim 3: Relate neurophysiological changes over the 30-day HDT—both with and without SANS-CMs—to cognitive and operational performance, sleep, mood, and ocular measures. This will include the Cognition battery, psychological/mood surveys, and a suite of ocular measures (OCT, fundoscopy). We will obtain as many measures as possible through data sharing and investigate the relationship of our neurophysiological measures to each of these outcome assessments. Jointly, the planned measures and Aims will enable NASA to quantitatively evaluate and compare the (neuro)physiological changes and fluid shifts associated with HDT and SANS countermeasures.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Our work will involve developing a detailed toolbox of measures for assessing brain physiology. These technologies will be compatible with the planned SANS countermeasures, and hence could be deployed in multiple other settings on Earth, ranging from intensive care units to exercise settings. The detailed and simultaneous monitoring of numerous cerebral physiology variables is expected to provide new insights into how the brain responds to various types of interventions. As such, the data could provide insights into how the body--and brain in particular--responds to pre-syncope, bedrest, exercise, fluid shifts, B-complex supplementation, and sequestration of blood in the extremities. All of these have implications in medicine here on Earth.
	PROJECT OVERVIEW Background Spaceflight associated neuro-ocular syndrome (SANS) is an unsolved risk for astronauts on long duration missions. When diagnosed from Frisen grade papilledema on fundoscopy, some 10 of 68 astronauts have exhibited SANS, although related ocular findings are more common (e.g., acquired hyperopia, globe flattening, choroidal folds, retinal fiber nerve layer thickening). Unexpectedly, SANS signs do not always spontaneously resolve upon return to Earth gravity. While the cause of SANS is unknown, the hyperopia, globe flattening, and choroidal folds—coupled with typically normal or slightly elevated intra-ocular pressure (IOP)—suggests that intracranial pressure (ICP) may be elevated as compared to average Earth levels. Various pathophysiological mechanisms have been proposed for SANS, with a particular suspicion regarding cephalad fluid shifts. SANS Countermeasures Most hypotheses regarding SANS involve headward fluid shifts as a factor, and various proposed SANS countermeasures (CMs)—including lower-body negative pressure (LBNP), veno-constrictive thigh cuffs (VTC), inspiratory resistance threshold devices (ITD), and artificial gravity (AG) all involve "mechanical" redistribution of body fluids away from the head. Understanding the relative benefits of each CM calls for assessments of perfusion and fluid flow into, within, and out of the cranium not only for potentially assessing and monitoring SANS, but also to help quantify and compare the effect sizes of various CMs.

Task Progress:	SANS-CM Study at German Aerospace Center's (DLR) Envihab Facility To address the lack of SANS CMs, NASA has negotiated a plan with the German Aerospace Center's :envihab facility to conduct 30-day head-down tilt (HDT) bedrest studies—the SANS-CM study. This effort has evolved to include 6 study arms: 1. 6o HDT bedrest alone (Reference); 2. 6o HDT bedrest plus two 3-hour periods seated upright (Seated CM); 3. 6o HDT bedrest plus 16 hours seated control (Control); 4. 6o HDT bedrest plus two 3-hour periods of LBNP (LBNP CM); 5. 6o HDT bedrest plus a B-complex vitamin supplement (Vit-B CM); 6. 6o HDT bedrest plus two ~1-hour periods of exercise plus VTC (Exercise CM). Each arm will consist of n=12 subjects, and different investigators will be involved in different portions of the overall SANS-CM study. BRAIN-SANS Contribution.This BRAIN-SANS project seeks to provide a wide range of brain-related measures for all subjects in all study arms. These include changes in (i) intracranial pressure (ICP), (ii) blood flow in/out of the brain, (iii) cerebral blood flow, (iv) brain perfusion and oxygenation, (v) blood distribution along the body axis, (vi) intracranial pulsatility, (vii) sagittal sinus imaging of potential, (viii) intracranial water concentration, (ix) functional brain activation, (x) electrical brain activity, as well as (xi) cognitive performance data (Cognition). We also plan to compare these measures with measures from other groups including ocular measures, mood and sleep, 1-carbon single nucleotide polymorphisms, and MRI. ACHIEVEMENTS IN YEAR 1 By the end of the 1st year of this project, we will have completed the following major tasks: Institutional Review Board (IRB) approval: Massachusetts General Hospital (MGH) granted Cede Review status to NASA on July 3, 2020. The NASA IRB granted full approval on Dec 8, 2020. Integration of BRAIN-SANS with all study arms and other investigators: This involved increasing the scope from 3 study arms to 6 study arms, coordinating with other SANS-CM investigators for data sharing, and adjusting our measurement timeline based on feasibility, hardware, and personnel constraints. Completion of Aim 1, development of the toolbox for multi-modal brain assessment: We assembled the required hardware and completed the needed customizations, configuration, and donning plans to achieve our measurement goals (see BRAIN-SANS Contribution, above). These measurements will be made during both rest and pre/during/post-countermeasure deployment. Experimental preparations: We have all hardware ready for shipping to DLR, when that is warranted based on COVID-19 restrictions. We have assembled manuals for all devices to be used. We have also developed detailed protocols for DLR :envihab personnel to facilitate making the BRAIN-SANS measurements, as well as all training materials for virtual training of DLR personnel. During the training process, we expect that further optimizations will be made to the experimental protocol details—adding, removing, or modifying procedural steps to ensure more accurate, reliable, and thorough data collection from the study. This process will also continue into the early part of grant year 2 as the first SANS-CM Mission approaches. Ideally, further optimization can be completed in-person in the July-August 2021 timeframe. SUMMARY Despite challenges bought on by COVID-19 since the beginning of our funding, we have met all deadlines and achieved all required integration. We are thus on-track to conduct our component of the SANS-CM study as soon as it can feasibly be initiated.
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