Fiscal Year:	FY 2023	**Task Last Updated:**	FY 01/03/2023
PI Name:	Wood, Scott J. Ph.D.		
Project Title:	Optimizing the Combination of Intranasal Scopolamine and Sensory Augmentation to Mitigate G-Transition Induced Motion Sickness and Enhance Sensorimotor Performance		
Division Name:	Human Research		
Program/Discipline:			
Program/Discipline--Element/Subdiscipline:			
Joint Agency Name:		**TechPort:**	No
Human Research Program Elements:	(1) **HHC**:Human Health Countermeasures		
Human Research Program Risks:	(1) **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		
PI Email:	scott.j.wood@nasa.gov	**Fax:**	FY
PI Organization Type:	NASA CENTER	**Phone:**	(281) 483-6329
Organization Name:	NASA Johnson Space Center		
PI Address 1:	2101 NASA Parkway		
PI Address 2:	Mail code SD2		
PI Web Page:			
City:	Houston	**State:**	TX
Zip Code:	77058	**Congressional District:**	36
Comments:	NOTE: PI returned to NASA JSC in January 2017. PI was at Azusa Pacific University from August 2013 – January 2017; prior to August 2013, PI was at NASA JSC.		
Project Type:	GROUND	**Solicitation / Funding Source:**	2019-2020 HERO 80JSC019N0001-HHCBPSR, OMNIBUS2: Human Health Countermeasures, Behavioral Performance, and Space Radiation-Appendix C; Omnibus2-Appendix D
Start Date:	01/01/2021	**End Date:**	03/01/2024
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:	Stenger, Michael	**Contact Phone:**	281-483-1311
Contact Email:	michael.b.stenger@nasa.gov		
Flight Program:			
Flight Assignment:			
Key Personnel Changes/Previous PI:	December 2022 report: None		
COI Name (Institution):	Daniels, Vernie M.S. (KBR/NASA Johnson Space Center) Reschke, Millard Ph.D. (NASA Johnson Space Center)		
Grant/Contract No.:	Internal Project		
Performance Goal No.:			
Performance Goal Text:			

Task Description:	Motion sickness represents one of the greatest clinical challenges impacting crew activities during and following g-transitions. Shorter duration missions involving new commercial vehicles and/or Artemis lunar missions will require continued emphasis on motion sickness countermeasures for early inflight prevention and treatment. The higher incidence of re-entry motion sickness following longer duration spaceflights coupled with the challenges associated with capsule egress during water landings also impose greater risks for crew recovery operations. Our overall goal is to characterize the effectiveness of motion sickness countermeasures to improve inflight and postflight recovery for future space travelers on these various platforms. We are conducting both controlled laboratory experiments of specific countermeasures during capsule wave motion simulation and conducting field testing in operational environments to characterize the incidence of motion sickness during various mission phases, and the efficacy of motion sickness countermeasures, if any, are utilized. The aims of our laboratory studies include evaluation of intranasal scopolamine and sensory augmentation to mitigate motion sickness and enhance crew performance. The intranasal form of scopolamine has the advantage of rapid bioavailability (i.e., therapeutic plasma concentration) with minimal side effects. This formulation allows crewmembers to self-medicate in a suited environment either before or after the onset of symptoms. Water landings may involve provocative wave motion during which crewmembers are deprived of a stable Earth reference inside the crew capsule. Sensory augmentation, e.g., vibrotactile feedback of Earth vertical, has been effective as a spatial awareness and balance aid with vestibular impairment. We hypothesize that both intranasal scopolamine and sensory augmentation of Earth vertical, either administered separately or combined, will be effective to mitigate motion sickness and improve task performance. The initial pilot ground study involved validation of a wave motion stressor to induce sickness, and evaluation of sensory augmentation in this simulated wave motion environment. A multi-degree of freedom platform with the subject seated in an enclosed cabin mockup was utilized to simulate the provocative capsule motion during water landings. Performance on a series of functional tasks (tilt motion tracking with and without a paced auditory serial addition test (PASAT) dual-task, eye-head-hand target acquisition, psychomotor vigilance test) was measured pre, during, after capsule wave motion. The capsule motion consisted of three 15 min periods of combined pseudorandom pitch, roll and heave that continued until the subject reached a motion sickness endpoint representing severe malaise on the Pensacola Diagnostic Index (up to 45 min maximum duration). The first study aim (1a) focused on prevention of motion sickness using intranasal scopolamine using a double-blinded repeated measures design in 30 subjects. Intranasal scopolamine was provided by Defender Pharmaceuticals, Inc. (DPI-386 Nasal Gel, referred to as Inscop) self-administered by a nasal pump (Aptar Pharma) that delivers 0.4 mg dose (0.2 mg / nostril). Motion sickness symptom onset, severity, and recovery were compared across treatment and placebo control sessions counterbalanced across subjects and separated by at least one week. The bioavailability of scopolamine for each session will be estimated from plasma concentrations obtained every 15 min. Cognition (psychomotor vigilance task) and subjective reports of drug side effects were obtained. Based on the pilot study, operational performance was assessed during the capsule wave motion using tilt motion tracking and a tablet-based eye-hand target acquisition task. The second part of this laboratory aim (1b) will be to evaluate sensory augmentation with and without intranasal scopolamine to prevent motion sickness during simulated capsule wave motion. For specific aim 2, a laboratory-based study will be used to evaluate the efficacy of intranasal scopolamine to provide treatment (“rescue”) of symptoms following motion sickness onset during simulated capsule wave motion. We are currently evaluating utilizing the advanced capsule wave motion capabilities of the Disorientation Research Device (aka Kraken) at the Naval Medical Research Unit – Dayton for aim 1B and/or aim 2. Specific aim 3 will evaluate the feasibility and efficacy of administering the intranasal scopolamine in operational field settings using both astronaut and ground-control subjects that are exposed to provocative motion as part of their assigned duties. For the ground-control subjects, these may involve a number of operational environments including motion simulations (e.g., high-g profile simulations during centrifugation), parabolic flights and/or Orion capsule recovery operations at sea. For the astronaut participants, we are recruiting from free-flier missions (e.g., Polaris Dawn), and both Private Astronaut Missions (PAM) and United States Orbital Segment (USOS) crewmembers assigned to the missions to the International Space Station (ISS). Astronaut participants may choose to test Inscop during provocative preflight training exercises (e.g., centrifugation), and can choose to take the medication prophylactically to prevent symptoms or after symptom onset to treat motion sickness during the launch and/or landing mission phases. Both ground-control and astronaut participants will be required to test the medication during a training session to monitor for adverse side effects. Participants will complete a short debrief questionnaire to capture motion sickness symptoms, side effects, and feasibility comments each time they take the medication. We will also include astronaut “control” subjects who do not take Inscop to comment on motion sickness severity within the initial early inflight and postflight periods, what countermeasures they did use and rate their effectiveness. While this study aim is not blinded, the inclusion of both active and control subjects will provide a more complete characterization of the impacts of motion sickness on crew activities during and following g-transitions, and the effectiveness of motion sickness countermeasures to improve inflight and postflight recovery. In addition, we are conducting a retrospective review of medical records from both the Shuttle and ISS programs to include a more comprehensive characterization of the motion sickness risks during missions with different vehicles and mission durations.
Rationale for HRP Directed Research:	
Research Impact/Earth Benefits:	Intranasal scopolamine provides crewmembers with the ability to self-administer medication for prevention and/or treatment of motion sickness during critical mission phases, including launch, landing, and recovery operations. The rapid bioavailability, minimal side effects, and ability to self-administer real-time dosage adjustments make this an ideal formulation for other operational environments that involve provocative motion, e.g., military pararescue and emergency medicine, as well as entertainment platforms, e.g., boating and virtual reality. Sensory augmentation using vibrotactile feedback of body position has shown promise as an effective rehabilitation tool for vestibular disorders and piloting aid. The combination of non-pharmaceutical approaches like sensory augmentation with intranasal scopolamine has the benefit to mitigate motion sickness and enhance crew performance over a variety of spaceflight and earth-based motion platforms.

Task Progress:

Aim 1 Pilot Study: This past year, we completed a pilot study (1) to validate a capsule wave motion simulation as a platform to evaluate motion sickness countermeasures and (2) to evaluate a sensory augmentation belt providing vibrotactile feedback of gravitational upright. Ten healthy subjects were exposed to complex wave motion on a six-degree-of-freedom platform that included pitch, roll and heave at provocative stimulus frequencies (0.1-0.25 Hz) while seated in an illuminated cabin deprived of external visual cues. Subjects reported acute symptoms for up to three consecutive 15-minute trials or until they reached a motion sickness endpoint of 8 pts on the Pensacola Diagnostic Index (PDI). Subjects also reported Subjective Discomfort Ratings on a 0-20 scale, where 20 represents vomiting, similar to previous Field Tests. Five subjects were randomly assigned to the Sensory Augmentation (SA) group, while the other five served as controls (CN group). Based on a Motion Sickness Susceptibility Questionnaire, the two groups had similar motion sickness histories (susceptibility percentile ranking of CN group = 27.5 ± 63.6 in the CN group versus 27.5 ± 37 in the SA group, median ± IQR). The vibrotactile feedback consisted of a single array of 8 electromechanical tactors positioned around the torso on an adjustable belt (Engineering Acoustics, Inc.) that utilized an integrated inertial measurement unit (IMU) to indicate the direction of upright (e.g., subject's back tactor on during forward tilt). During each wave motion trial, subjects performed a battery of four different tasks: tracking Earth vertical using a joystick with and without a secondary task (Paced Auditory Serial Addition Test), an eye-hand target acquisition task on a cabin-fixed tablet, and the psychomotor vigilance test (PVT). The eye-hand task was similar to that used in the recent Field Tests (PI: Reschke), except that the tablet was cabin fixed, so the subjects were required to extend their dominant hand to a target external to themselves. The PVT utilized the same software as included in Spaceflight Standard Measures cognition test battery.
All ten subjects reported varying levels of motion sickness with 6 of 10 reaching a symptom endpoint. The PDI and SDR, motion sickness scores, were highly correlated (Spearman's rho = 0.70, $p<0.001$). This was important since we are using the simpler 0-20 SDR scale in our field testing. Interestingly, subjects anecdotally reported that engagement in some tasks (e.g., joystick tracking) was less provocative than others. During the first block, the cabin-fixed target acquisition task appeared to be more provocative, especially for the control group. Sensory augmentation appeared to delay symptom onset, with 2 of 5 reaching an endpoint within the first 15-minute trial in the CN group versus none in the SA group (PDI after 15 min = 6.0 ± 2.5 in the CN group versus 3.4 ± 2.5 in the SA group, mean ±std). For the purposes of statistical comparison and plotting across timepoints, the highest symptom value was carried forward for subjects who reached a motion sickness endpoint. Independent samples of Mann-Whitney U tests indicated the SDR symptom score was significantly lower for the SA group at minute 10 ($U=2.5$, $p=0.032$) and remained lower through the remainder of the initial 15-minute block.

In addition to delaying motion sickness onset, sensory augmentation also improved performance on the joystick tracking task at lower stimulus frequencies (0.1 Hz in roll and 0.2 Hz in pitch). While the magnitude of the tilt motion was cued by pulsing the tactors more during greater amplitudes of tilt, this was of limited value based on anecdotal reports. During the pilot testing, this task was repeated with a dual task involving paced auditory serial addition test. There were no differences in performance detected with the dual task in this pilot study. Both CN and SA groups maintained a consistent level of performance on the eye-hand target acquisition and PVT throughout the baseline (no motion) and wave motion periods. Our pilot study results validated that the simulated capsule wave motion paradigm provides an effective motion stressor and is currently being used to investigate the effects of intranasal scopolamine to prevent motion sickness. Sensory augmentation using vibrotactile feedback appears to improve spatial awareness and delay symptom onset during complex passive motion. One advantage of this portable belt design is that it incorporates all tactor drive and IMU circuitry and, therefore could continue to be worn by crewmembers and serve as a balance aid during egress and ambulation with recovery operations. These results from this pilot study will be presented at the 2023 Investigators' Workshop (Bollinger et al., 2023).

Aim 1a Lab Study: Plans for our laboratory testing were highlighted during the 2022 Investigators' Workshop (Beltran et al., 2022). Due to delays in testing related to COVID, and based on the pilot study results described above, we elected to limit our initial Aim 1 laboratory data collection to a comparison of intranasal scopolamine (0.4 mg) and placebo control conditions using a repeated measures double-blinded design, postponing the combination of Inscop and sensory augmentation. We completed data collection on all thirty subjects during two sessions, each separated by at least one week. The joystick used during the pilot testing exhibited differential spring resistance and therefore was replaced with a hand-held board using an IMU to measure roll and pitch movements. The subject instruction was modified to maintain the board level, i.e., parallel to the perceived horizon (Clément et al., 2002), thus accomplishing a similar spatial tracking task. The dual tasking was also omitted in favor of increasing the duration of the joystick tracing task. Otherwise, all of the functional tasks were identical to the pilot testing. Data processing is ongoing at this time while the study remains blinded.

Plasma concentrations of scopolamine will be measured by a modified liquid chromatography with a tandem mass spectrometry (LC-MS/MS) method similar to that reported previously (Wu et al., 2015). During this past year, Dr. Wang has been standing up this refined methodology in the Nutritional Biochemistry laboratory using a LC-MS/MS process published by Waters Corporation to complete this analysis. Importantly, the previous internal standard (Hyoscyamine) has been replaced with a stable isotope-labeled scopolamine-d3 (Swaminathan et al., 2019). This improved the analytical range to 25 to 5000 pg/mL with correlation coefficients =0.99. The previous lower limit of quantitation of scopolamine was 50 pg/mL using the previous standard. Unfortunately, the plasma concentration analysis has been delayed due to repairs needed for the LC-MS/MS equipment. The repairs were completed at the end of the year and should be completed during FY23.

The Interagency Agreement with the Naval Medical Research Unit – Dayton (NAMRU-D) was approved this past year and includes the use of the DRD Kraken for simulated wave motion. We anticipate Aim 1b and/or Aim 2 to be conducted following the implementation of this motion with increased heave motion.

Aim 3 Field Testing: During this past year, the initial field test results on the first private commercial orbital flight were highlighted during the 2022 Investigators' Workshop (Ericson et al., 2022). Two of four crewmembers utilized intranasal scopolamine effectively mitigated immediate symptoms of nausea and was easily self-administered by crewmembers with minimal training and did not impede flight operations by requiring unscheduled suit doffing or medical equipment access. Three ground-control subjects were also tested during the National Aerospace Training and Research (NASTAR) g-profile training with similar results. The augmentation for additional astronauts and retrospective analysis was processed, and four crewmembers of the SpaceX Polaris Dawn mission were recruited. This implementation will require all participants to record motion sickness history, including those that choose not to take Inscop. The Select for Flight process for United States Operational Segment (USOS) crewmembers was submitted for out-of-board approval, and we anticipate recruiting additional crewmembers in the near future. The retrospective data

	mining was initiated with the Life Sciences Data Archive to summarize the medical records from Shuttle and the International Space Station (ISS). These results will be published in a new edition of Principles of Clinical Medicine for Space Flight. A review of the existing data was provided this year at a motion sickness conference in Caen, France (Wood et al., 2022).
Bibliography Type:	Description: (Last Updated: 04/29/2024)
Abstracts for Journals and Proceedings	Beltran NE, Bollinger AM, Duplechin R, Wang Z, Daniels VR, Reschke MF, Wood SJ. "Optimizing the combination of intranasal scopolamine and sensory augmentation to mitigate g-transition induced motion sickness and enhance sensorimotor performance" 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. Abstracts, 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. , Feb-2022
Abstracts for Journals and Proceedings	Ericson I, Mateus J, Menon AS, Wood SJ "Examining the use of intranasal scopolamine in commercial spaceflight" 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. Abstracts, 2022 NASA Human Research Program Investigators' Workshop, Virtual, February 7-10, 2022. , Feb-2022
Abstracts for Journals and Proceedings	Wood SJ, Clément GR, Reschke MR "Motion sickness induced by g-transitions during spaceflight" Motion Sickness: Theories, Models and Empirical Evidence; Caen, France, June 7, 2022 msw.sciencesconf.org/resource/page/id/5 , Jun-2022