Non-pharmaceutical motion sickness mitigation

NCT04859868

August 4, 2020

MAYO CLINIC

IRB Minimal Risk Protocol Template

General Study Information

Principal Investigator: Gaurav N. Pradhan, PhD (PI), Michael J. Cevette, PhD (co-PI)

Study Title: Non-pharmaceutical motion sickness mitigation

Protocol version number and date: Version 1 and August 4th 2020

Research Question and Aims

Hypothesis:
1. The efficacy of galvanic vestibular reduction to reduce motion sickness severity will depend on the timing and magnitude of the administration.
2. The functional task performance will decline with increasing levels of galvanic vestibular reduction.

Aims, purpose, or objectives:
Alterations in vestibular sensory processing following G-transitions lead to perceptual and motion sickness upon return to Earth's gravity. The use of a non-pharmaceutical mitigation for motion sickness will have several potential advantages over drug treatment options. First, the treatment would be effective immediately and for as long as needed without having to maintain therapeutic levels in the blood-stream. Second, the treatment level could be customized and continuously titrated during re-adaptation to minimize side effects while enhancing performance. Our project will validate a non-pharmaceutical tool using galvanic vestibular reduction (GVR) to better mitigate G-transitional induced motion sickness following symptom onset while customizing the treatment level to maximize crew performance.
Our first specific aim is to evaluate the effect of timing and magnitude on the administration of our nonpharmaceutical treatment to motion sickness. While we have previously demonstrated that our approach can mitigate motion sickness if introduced prior to the provocative stimuli, one of the goals of this study is to determine the efficacy if we administer the treatment following the onset of symptoms. Validating the efficacy following symptom onset would alleviate the need for certifying the device to be worn within the landing suit and greatly enhance flexibility to implement this treatment during recovery operations. Our first hypothesis is that efficacy of galvanic vestibular reduction to reduce motion sickness severity will depend on the timing and magnitude of the administration. We will test this hypothesis by exposing subjects to provocative Coriolis crosscoupling stimuli on a rotating chair using a repeated measures counter-balanced design to compare motion sickness severity across three treatment interventions: prior to stimulus (symptom) onset, following symptom onset, and placebo control. The GVR amplitude will be customized based on individual sensitivity. Symptom severity will be assessed using both subjective reports and objective autonomic measures (electrogastrography and cardiac interbeat intervals). We expect that the most effective administration will be GVR delivered prior to the onset of symptoms, but that it will continue to be more effective relative to placebo control even if delivered following symptom onset.

Our second specific aim is to evaluate the effect of GVR amplitude on functional fitness task performance. One disadvantage of pharmaceutical approaches is that increased drug dosage is often accompanied by sedative side

effects that impact functional ability. In order to leverage our non-pharmaceutical technique that allows continuous adjustments in "dosage" level throughout recovery, we must map changes in GVR level with functional performance. Our second hypothesis is that functional task performance will decline with increasing levels of galvanic vestibular reduction. We will test this hypothesis by measuring performance on a sensorimotor and cognitive test battery in steps ranging from 0mA (control) to the level of GVR thought to provide maximal motion sickness protection. The test battery, conducted on the same subjects as specific aim 1, will include dynamic posturography as well as other cognitive and flight simulator tasks. Sensitivity to galvanic stimulation will also be obtained for each subject and used to customize the GVR amplitude for the motion sickness testing in specific aim 1. The combined deliverable from both specific aims will be to validate the efficacy of GVR when customizing the stimulus level and introducing it following symptom onset, and to understand the effects of this non-pharmaceutical approach on crew performance on functional task performance.

Background (*Include relevant experience, gaps in current knowledge, preliminary data, etc*.):

The rationale of our approach rests on several key principles. First, the incidence and severity of motion sickness following G-transitions poses substantial risk to the deconditioned crew during landing and subsequent recovery operations. Second, there is a well-known relationship between bilateral vestibular loss and insusceptibility to motion sickness. Third, non-pharmaceutical approaches to motion sickness mitigation typical involve vestibular habituation or desensitization training with limited retention. Fourth, galvanic vestibular reduction provides a means to mitigate motion sickness following long-duration spaceflight without dependency on retention of preflight desensitization training.

Space motion sickness represents one of the greatest clinical challenges impacting crew activities during the first few days on orbit. While the inflight incidence has varied with different spacecraft, approximately 70% experience symptoms (Lackner and Dizio 2006) and one-third experience moderate to severe symptoms (Reschke et al. 2016). Symptoms generally last 2-3 days inflight, although symptoms may persist in a small number of people (Baker et al. 2008).
The intensity and incidence of other perceptual and sensorimotor signs and symptoms generally follow this same pattern of intersubject variability. Inflight motion sickness has been reasonably treated by limiting early crew activities and the use of intramuscular promethazine, although the sedative side effects of promethazine have been more problematic on the ground (Bagian and Ward 1994). Re-entry motion sickness has now become a greater issue following long-duration missions. Even with pharmaceutical interventions recent studies report that most, if not all crewmembers experience some level of symptoms following 6-month duration ISS missions (Reschke et al. 2017). Water landings are expected to exacerbate this problem. The incidence and severity of motion sickness has serious implications for the deconditioned crew to perform critical operational tasks (Wood et al. 2019). Of 23 participants in the field testing, only 57% were able to complete all tasks, 26% were only able to partially complete the tasks and 17% were unable to complete any tasks.

The role of vestibular input in the neural basis for motion sickness has been well established (Cohen et al. 2019). While there are many factors that contribute to interindividual differences in susceptibility (Golding 2006), it has also been known for some time that individuals with bilateral vestibular loss are insusceptible to motion sickness (Graybiel and Johnson 1963; Yates et al. 1998). Although susceptibility to other forms of terrestrial motion sickness stressors may not be predictive of G-transitional induced motion sickness (Lackner and Dizio 2006), it is still reasonable to presume that suppressing vestibular function would help reduce post-

landing motion sickness. In support of this, it has been our personal experience working with astronauts during our field tests and Shuttle landings that motion sickness severity is associated with hypersensitivity to head movements (Reschke et al. 2016).

Most non-pharmaceutical approaches to motion sickness mitigation involve some type of training. Cowings et al (2018) recently demonstrated improvement with autogenic feedback training, although subjects in this study were required to undergo a 2 hr refresher training prior to each provocative test. Vestibular habituation or desensitization training has been very effective in aviation, generally relying on the desensitization to one provocative motion transferring to the operational environment (Cheung and Hofer 2005). Although the success rate ranges between 50-85%, the retention of this training in the absence of exposure has not been clearly established beyond a few months (Samuel and Tal 2015). The Russian cosmonauts rely on a systematic preflight desensitization training program (Bryanov et al. 1975; Matsnev et al. 1983). While the effectiveness of this program for inflight mitigation may result in reduced symptoms early inflight, the incidence and severity of motion sickness cosmonauts experienced during our field tests clearly suggest that retention through spaceflights of six-month duration is not effective in mitigating post-landing symptoms. Several authors have noted that one consequence of the cosmonaut desensitization program is an alteration of vestibular reflexes that may be dysfunctional for operational tasking (Wetzig et al. 1993; Clement et al. 2007).

The advantage of our galvanic vestibular reduction approach over other non-pharmaceutical approaches is that it does not require training or have issues with retention. We have previously employed galvanic vestibular stimulation (GVS) to reduce the sensory conflict associated with simulators, essentially providing virtual head signals to match the moving visual field, which we refer to as oculo-vestibular recoupling (Cevette et al. 2012). In exploring its use as a vestibular prosthesis, Peterka (2012) provided GVS bilateral cancellation-type feedback to sway motion to remove the ability of a subject with normal vestibular function to use vestibular information for balance control. Minor and Goldberg (1991) had previously noted that galvanic anodal (inhibitory) currents, when delivered bilaterally, results in a reversible ablation of irregular afferents. Irregular afferents are important for encoding self-motion, and Oman and Cullen (2014) have speculated “sensory conflict” neurons may exist in “reafference” neural processing associated with active motion. Galvanic vestibular reduction may therefore be attempted through either a cancellation-type feedback of actual motion (Peterka 2012) or by delivering bilateral inhibitory signals provided independent of sensing actual motion (Minor and Goldberg 1991). In our recent implementation of GVR through DoD funded work, we measured a reduction in motion sickness symptoms and changes in electrogastrography in the GVR treatment group relative to controls (Cevette et al. 2014b). In this paradigm, the subject’s only external visual cues were presented through a virtual window where both the window and subject were misaligned with the vehicle direction. The nature of this sensory conflict is similar to capsule motion during water landings where passive motion is present without stable Earth horizontal visual cues.

References:

Bagian JP, Ward DF (1994) A retrospective study of promethazine and its failure to produce the expected incidence of sedation during space flight. J Clin Pharmacol 34:649-651

Baker ES, Barratt MR, Wear ML (2008) Human responses to space flight. In: Barratt MR, Pool SL (eds) Principles of Clinical Medicine for Space Flight. Springer, New York, NY, pp 27-57

Bos JE, Damala D, Lewis C, Ganguly A, Turan O (2007) Susceptibility to seasickness. Ergonomics 50:890-901 doi: 10.1080/00140130701245512

Bryanov, II, Matsnev EI, Yakovleva IY (1975) Otorhinolaryngological problems in medical support of space flights. Acta Astronaut 2:217-223 doi: 10.1016/0094-5765(75)90092-2
Cevette MJ, Pradhan GN, Cocco D, Crowell MD, Galea AM, Bartlett J, Stepanek J (2014a) Electrogastrographic and autonomic responses during oculovestibular recoupling in flight simulation. Aviat Space Environ Med 85:15-24 doi: 10.3357/asem.3673.2014
Cevette MJ, Stepanek J, Cocco D, et al. (2012) Oculo-vestibular recoupling using galvanic vestibular stimulation to mitigate simulator sickness. Aviat Space Environ Med 83:549- 555 doi: 10.3357/asem.3239.2012
Cevette MJ, Stepanek J, Galea AM (2014b) Galvanic vestbular stmulation system and method of use for simulation, directional cueing, and alleviating motion-related sickness. Patent: US 8,718,796 B2, USA
Cheung B, Hofer K (2002) Lack of gender difference in motion sickness induced by vestibular Coriolis cross-coupling. J Vestib Res 12:191-200
Cheung B, Hofer K (2005) Desensitization to strong vestibular stimuli improves tolerance to simulated aircraft motion. Aviat Space Environ Med 76:1099-1104
Clement G, Deguine O, Bourg M, Pavy-LeTraon A (2007) Effects of vestibular training on motion sickness, nystagmus, and subjective vertical. J Vestib Res 17:227-237
Cohen B, Dai M, Yakushin SB, Cho C (2019) The neural basis of motion sickness. J Neurophysiol 121:973-982 doi: 10.1152/jn.00674.2018
Cowings PS, Toscano WB, Reschke MF, Tsehay A (2018) Psychophysiological assessment and correction of spatial disorientation during simulated Orion spacecraft re-entry. Int J Psychophysiol 131:102-112 doi: 10.1016/j.ijpsycho.2018.03.001
Fisher LD, Van Belle G (1993) Biostatistics: A Methodology for the Health Sciences. John Wiley & Sons, Inc., New York
Gianaros PJ, Muth ER, Mordkoff JT, Levine ME, Stern RM (2001) A questionnaire for the assessment of the multiple dimensions of motion sickness. Aviat Space Environ Med 72:115-119
Golding JF (2006) Motion sickness susceptibility. Auton Neurosci 129:67-76 doi: 10.1016/j.autneu.2006.07.019
Graybiel A, Johnson WH (1963) A comparison of the symptomatology experienced by healthy persons and subjects with loss of labyrinthine function when exposed to unusual patterns of centripetal force in a counter-rotating room. Ann Otol Rhinol Laryngol 72:357-373
Graybiel A, Wood CD, Miller EF, Cramer DB (1968) Diagnostic criteria for grading the severity of acute motion sickness. Aerosp Med 39:453-455
Lackner JR, Dizio P (2006) Space motion sickness. Exp Brain Res 175:377-399 doi: 10.1007/s00221-006-0697-y
Matsnev EI, Yakovleva IY, Tarasov IK, Alekseev VN, Kornilova LN, Mateev AD, Gorgiladze GI (1983) Space motion sickness: phenomenology, countermeasures, and mechanisms. Aviat Space Environ Med 54:312-317
Minor LB, Goldberg JM (1991) Vestibular-nerve inputs to the vestibulo-ocular reflex: a functional-ablation study in the squirrel monkey. Journal of Neuroscience 11:1636-1648
Oman CM, Cullen KE (2014) Brainstem processing of vestibular sensory exafference: implications for motion sickness etiology. Exp Brain Res 232:2483-2492 doi: 10.1007/s00221-014-3973-2
Oman CM, Lichtenberg BK, Money KE, McCoy RK (1986) M.I.T./Canadian vestibular experiments on the Spacelab-1 mission: 4. Space motion sickness: symptoms, stimuli, and predictability. Exp Brain Res 64:316-334
Peterka RJ (2012) Use of galvanic vestibular feedback for a balance prosthesis. Conf Proc IEEE Eng Med Biol Soc 2012:6137-6140 doi: 10.1109/EMBC.2012.6347394
Pradhan GN, Cevette MJ, Stepanek J, Brookler KH (2019) Oculo-cognitive addition testing. Patent: US 0259291 A1, USA

Reschke MF, Clément GR, Thorson SL, et al. (2016) Neurology. In: Nicogossian AE, Williams RS, Huntoon CL, Doarn CR, Polk JD, Schneider VS (eds) Space Physiology and Medicine, 4th edn. Springer, New York, NY, pp 245-282
Reschke MF, Good EF, Clément GR (2017) Neurovestibular symptoms in astronauts immediately after space shuttle and international space station missions. OTO Open 1 doi: 10.1177/2473974x17738767
Samuel O, Tal D (2015) Airsickness: Etiology, Treatment, and Clinical Importance-A Review. Mil Med 180:1135-1139 doi: 10.7205/MILMED-D-14-00315
Wetzig J, Hofstetter-Degen K, von Baumgarten R (1993) Responses to eccentric rotation in two space-bound subjects. Clin Investig 71:757-760
Wood SJ, Paloski WH, Clark JB (2015) Assessing sensorimotor function following ISS with computerized dynamic posturography. Aerosp Med Hum Perform 86:A45-53 doi: 10.3357/AMHP.EC07.2015
Wood SJ, Reschke MF, Rader AM, Rosenberg MJ, Tomilovskaya ES, Kozlovskaia IB (2019) Gtransition induced motion sickness: Implications for deconditioned crew following long duration spaceflight. Scientific Reports (in preparation)
Yates BJ, Miller AD, Lucot JB (1998) Physiological basis and pharmacology of motion sickness: an update. Brain Res Bull 47:395-406 doi: 10.1016/s0361-9230(98)00092-6

Study Design and Methods

Methods: *Describe in lay terms, completely detailing the research activities that will be conducted by Mayo Clinic staff under this protocol*.

Consent: Consent forms include typical notifications of the sponsor and purpose of the study, identification of any risks in the minimal-risk protocol, discussion of privacy dimensions of the study and description of the amount and compensation structure schedule. We brief participants of their right to opt out of the study at any time and for any reason. We include consent forms in the attached draft IRB that are patterned after similar forms used in other persistent sensor wear studies the Mayo team has conducted.

Compensation: Enumeration of $300 is proposed to fairly reimburse participants for the time involved.

Protocol:
Participants will attend four sessions of the experiment on four separate days. The first/initial session will be required to establish galvanic vestibular sensitivity measures to customize the GVR level, and to characterize performance on a sensorimotor-cognitive test battery as a function of GVR stimulus level. In the next three sessions, we will test the efficacy of GVR to mitigate motion sickness by comparing conditions across three separate counterbalanced sessions: administration from the onset of testing, at a midpoint of testing, and placebo control. Each session will be conducted on four separate days at least two days apart so that there is no influence on each other. Using a repeated measures design, we will compare motion sickness symptom onset, severity and recovery during standardized motion sickness testing using a rotatory chair.

Equipment: The motion sickness experiments will be conducted using our GyroStim Multi-Axis Rotating Chair (used in the previous IRB approved project – IRB # 19-003257) located in Aerospace Medicine and Vestibular Research Lab at Mayo Clinic Arizona (Figure 1A). Subjects will be restrained in a chair but free to bend their head forward to elicit Coriolis cross-coupling stimuli. Subjects will be tested with their eyes closed. Galvanic

vestibular reduction will be delivered using a proprietary system developed at the Mayo clinic laboratory. This utilizes a two-channel commercial galvanic stimulator (Good Vibrations Engineering Ltd, King City, ON; used in the previous IRB approved projects – IRB # 19-003257, 18-005564, 14-003906, 11-007718, 09-003815) with custom software. The GVR system consists of the four electrodes (two behind each ear). The stimulator can bidirectionally deliver the electrical stimulation and receive information about the amplitude delivered accounting for skin impedance. In addition to motion sickness reporting, we also propose to quantify the magnitude of the motion perception during the Coriolis cross-coupling protocol using a multidimensional joystick (Figure 1B, Logitech® FreedomTM 2.4; used in the previous IRB approved projects – IRB # 19-003257, 18-005564). Before the start of the experiment, participants will be trained to use joystick in cyclic sideways left/right, forward/backward and twist counterclockwise/ clockwise for the perceived roll, pitch and yaw motions respectively. The perceived motion inputs from the joystick will be recorded by the custom software program named AVATAR which will also display the animation of 3D graphical human figure based on joystick inputs (Figure 1C).

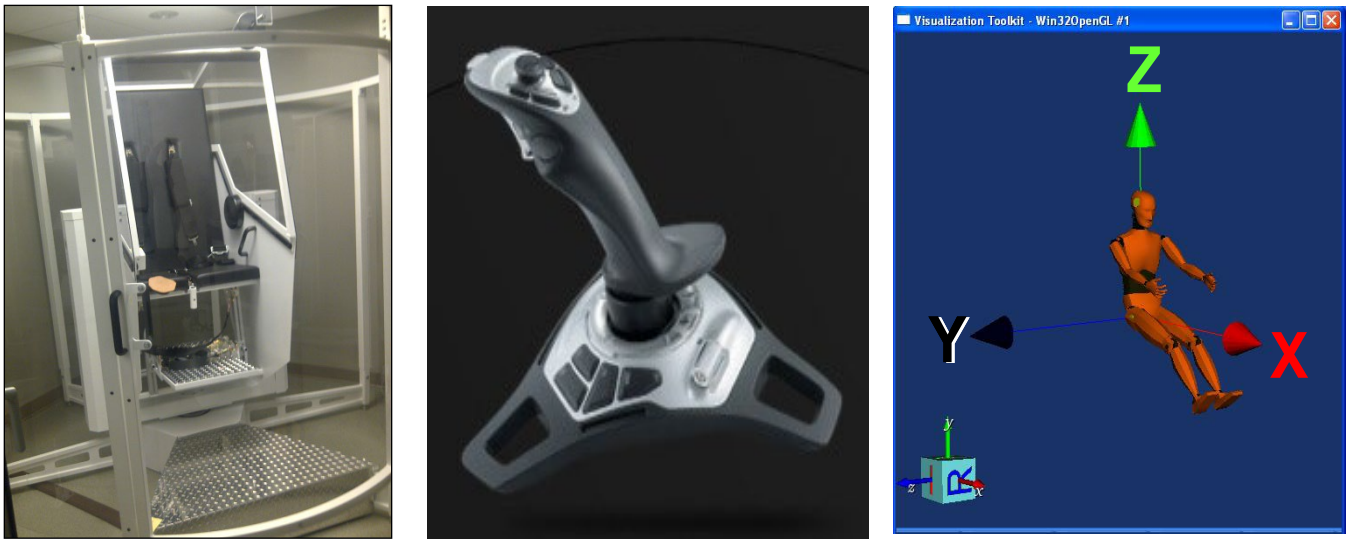

Figure 1: A. Aerostim Multi-Axis Rotating Chair, Ultrathera Technologies, B. 360° Wireless Joystick, Logitech® FreedomTM 2.4; C. AVATAR software that display the animation of 3D graphical human figure based on joystick inputs

Motion sickness test paradigm: At the beginning of each motion sickness session, the rotator will be accelerated (10 deg/sec/sec) to a constant velocity up to 120 deg/sec for up to 60 sec to allow the per-rotatory sensations to decay. The direction of rotation will be alternated each session and counterbalanced across subjects. Head

movements will be cued every 10 sec, alternating between pitch forward (chin resting on chest) and pitch backward (head upright). This timing allows for subjects to use the joystick to record motion perception associated with each pitch forward and backward movement. There will be a short pause following each set of 9 forward/backward movements (3 min) to review symptoms with the subject, although motion sickness symptoms will be obtained throughout the test protocol using verbal reports. Subject will continue making head movements until the motion sickness endpoint (moderate nausea) or the maximum number of paired forward/backward head movements (90) has been reached.

Galvanic Vestibular Reduction (GVR) application: We will use a repeated measures design to compare motion sickness severity for each subject across the three treatment interventions: prior to stimulus onset, following symptom onset, and placebo control. For each session, the participant will be instrumented for GVR prior to rotation. The amplitude (up to 2.5 mA) will be customized based on individual sensitivity (see below). The order of the three sessions will be counter-balanced across subjects. For the "*prior to*" session, the GVR will be initiated just prior to the chair motion. For the "*midpoint*" session, the GVR will be initiated following 4 of 10 sets of movements or the onset of slight nausea, whichever occurs first. For the "*control*" session, the subject will be instrumented without turning on the GVR throughout the testing.

Motion sickness recordings: Objective measures of sickness will be obtained using electrogastrography (EGG) methodology that we've employed successfully in previous motion sickness studies (Cevette et al. 2014a) (IRB # 18-005564, 14-003906). The EGG measurements will require seated baseline reading for approximately 20 mins prior to rotation. We propose up to three alternate methods for subjective reporting (to be finalized during pilot testing). First, an acute score will be derived using the Pensacola diagnostic criteria introduced by Graybiel et al. (1968). Using this scale, the subjective intensity of eight different modalities of symptoms and signs are reported on a "slight/moderate/severe" basis, and then numerically to arrive at a weighted "malaise index". We will also obtain a subjective magnitude estimation score using a scale 0-20, with 20 indicating vomiting (Oman et al. 1986). And finally, participants will be asked to quantify motion sickness severity along multiple dimensions (e.g., gastrointestinal, central, and peripheral symptoms, Gianaros et al. 2001) using a multi-point scale for each.

Sensorimotor and cognitive test battery: Our second specific aim is to evaluate the effect of GVR amplitude on functional fitness task performance. This aim is important to understand how crewmembers could titrate their GVR amplitude to retain motion sickness benefits while optimizing functional performance. For this aim, the same subjects participating in the motion sickness tests will undergo the test battery while exposed to GVR in multiple steps ranging from 0mA (control) to the level of GVR thought to provide maximal motion sickness protection. The sensorimotor test battery will include (1) dynamic posturography, (2) Timed up and go (TUG) test (3) flight simulator performance and (4) an oculo-cognitive addition test. The posture measurements will be obtained using a Bertec platform with the similar protocol used during postflight medical crew testing (Wood et al. 2015). Bertec Portable Essential's dual-balance plate balance system used for dynamic posturography is clinically used in Mayo Clinic Arizona, to test balance. For this test we will use the sensory organization test with more reliance on the vestibular system (eyes closed on unstable surface). Similarly, TUG test is clinically used in Mayo Clinic Arizona to assess an individual's functional balance. It requires appropriate static and dynamic balance system integration. TUG provides a measure of functional balance integration not provided from standing balance tasks. The flight simulator performance will use a Lockheed Martin developed Prepare3D flight simulation environment adapted to VR environment (Oculus Rift). This entire system was used in the previous IRB approved project – IRB # 18-005564. It provides simulator immersion and visuomotor

function during flight. The primary task during the flight simulation will be to fly through the "ring target". The cognitive test will include Mayo's proprietary Ocular Cognitive Addition Test (OCAT, Pradhan et al. 2019) which requires subjects to look for numbers on a screen and add these numbers together. The OCAT test includes eye-tracking to measure cognitive and oculomotor performance measures (used in previous IRB approved projects – IRB # 18-005564, 18-004184, 19-004883, 16-007938). Each test will be repeated for up to GVR amplitudes (including 0mA control) presented in random order. OCAT will be conducted on a 14-inch tablet with an integrated eye-tracking sensor (EyeOn – EyeTech Digital Systems). We expect performance to decline with increasing GVR amplitude.

Galvanic vestibular sensitivity: We will compare motion perception at different GVR amplitudes using a similar rotator protocol as described above for the motion sickness testing. Motion perception will be quantified using the joystick. The GVR amplitudes (same range as above) will be presented in random order. Assuming a saturation effect, we will select the lowest GVR level that reduces motion perception as the amplitude for the motion sickness testing above.

A complete experimental methodology to be conducted in this protocol is shown the tables below:

Visit 1	Duration (mins)
Consent form	
Balance Performance (Dynamic Posturography): *Device: Bertec Portable Essential's dual-balance plate balance system (https://www.bertec.com/bertec-balance-advantage-systems)* Quantify dose-response for the following GVR amplitudes: Standing Eyes Open – 0mA (baseline), 1.25mA, 1.5mA, 1.75mA, and 2mA Standing Eyes Closed - 0mA (baseline), 1.25mA, 1.5mA, 1.75mA, and 2mA	10
Timed up and go (TUG): The test will be performed for each GVR amplitudes: 0mA (baseline), 1.25mA, 1.5mA, 1.75mA and 2mA Method: • The patient starts in a seated position • The patient stands up upon on command: walks 4 meters, turns around, walks back to the chair and sits down.	10

• An obstacle (foam block 30 cm height) will be positioned between the chair and the 4m turning point, and the patient will be required to step over this obstacle twice, once on the way toward the turning point and again on the return back. • The time stops when the patient is seated.	
Cognitive Performance *Device: Oculo-Cognitive Addition Test (OCAT):* 0mA (baseline), 1.75mA (GVR)	5
Galvanic Vestibular Sensitivity: *Device: Gyrostim Rotating Chair and Joystick* The chair will be rotated for up to 60 seconds with an acceleration of 10 deg/s/s to a constant velocity up to 120 deg/sec and deceleration of 10 deg/s/s to a complete stop. 5 trials of rotations will be tested for each GVR amplitudes: 0mA (baseline), 1.25mA, 1.5mA, 1.75mA and 2mA The GVR will be turned on before each corresponding rotation. 1 minute washout period after each rotation. Motion perception (i.e., yaw) will be measured using the joystick for each rotation. Decide the lowest GVR amplitude that reduced motion perception, say ***R mA.***	20

Table I – First/Initial session i.e. First Visit

Visit 2/3/4 – Prior Session/Mid-point Session/Control Session	Duration (mins)
Baseline End-tidal CO2 (EtCO2) is measured.	<1
Devices: Gyrostim Rotating Chair and Joystick ***Prior Session:*** MAXIMUM number of sets: 10 Each set duration: 6-7 mins	60-70

During each set: 1. GVR will be turned on at ***R mA.*** 2. The chair will be rotated with an acceleration of 10 deg/s/s to a constant velocity up to 120 deg/sec. 3. Head movements will be cued every 10 seconds, alternating between pitch forward (chin resting to chest) and pitch backward (head upright). There will be a total of 9 forward and 9 backward movements (3 mins). 4. Motion perception (Coriolis illusion) will be measured using the joystick. 5. The chair and GVR will be paused for 2 minutes. 6. Motion sickness questionnaire score (Pensacola diagnostic criteria and Oman's subjective magnitude estimation score 0-20) will be recorded. ***Midpoint Session:*** MAXIMUM number of sets: 10 Each set duration: 6-7 mins During each set: 1. For first **four** sets, GVR will not be turned on**.** From fifth to maximum set, GVR will be turned on at ***R mA.*** 2. The chair will be rotated with an acceleration of 10 deg/s/s to a constant velocity up to 120 deg/sec. 3. Head movements will be cued every 10 seconds, alternating between pitch forward (chin resting to chest) and pitch backward (head upright). There will be a total of 9 forward and 9 backward movements (3 mins). 4. Motion perception (Coriolis illusion) will be measured using the joystick. 5. The chair and GVR will be paused for 2 minutes. 6. Motion sickness questionnaire responses (Pensacola diagnostic criteria and Oman's subjective magnitude estimation score 0-20) will be recorded. ***Control Session:*** MAXIMUM number of sets: 10 Each set duration: 6-7 mins During each set:	

1. GVR will be not be turned. 2. The chair will be rotated with an acceleration of 10 deg/s/s to a constant velocity up to 120 deg/sec. 3. Head movements will be cued every 10 seconds, alternating between pitch forward (chin resting to chest) and pitch backward (head upright). There will be a total of 9 forward and 9 backward movements (3 mins). 4. Motion perception (Coriolis illusion) will be measured using the joystick. 5. The chair and GVR will be paused for 2 minutes. 6. Motion sickness questionnaire responses (Pensacola diagnostic criteria and Oman's subjective magnitude estimation score 0-20) will be recorded.	
Post- EtCO2 is measured. Motion Sickness Questionnaire responses (gastrointestinal, central and peripheral symptoms on VAS: 0-10) will be recorded after the end of session.	2

Table II – Next three sessions (Prior, Mid-point, and Control Sessions)

Subject Information

Target accrual is the proposed total number of subjects to be included in this study at Mayo Clinic. A "Subject" may include medical records, images, or specimens generated at Mayo Clinic and/or received from external sources.

Target accrual: 40 participants

Subject population (children, adults, groups): Healthy adults with normal vestibular function

Inclusion Criteria: For our purposes, participants must be able to consent to participate themselves and be 21 to 55 years of age and must be able to attend in-person sessions at the Mayo Aerospace Medicine and Vestibular Research Laboratory in Scottsdale, AZ. No racial/ethnic groups will be excluded, although all participants must be fluent speakers of English.

Exclusion Criteria: History of vestibular disease, migraine, or significant balance disorder; traumatic brain injury, recent middle ear infection or recent motion sickness (within 72 hrs), history of severe motion sensitivity, women who are pregnant.

Biospecimens

Collection of blood samples. When multiple groups are involved copy and paste the appropriate section below for example repeat section b when drawing blood from children and adults with cancer.

a. **From healthy, non-pregnant, adult subjects who weigh at least 110 pounds**. For a minimal risk application, the amount of blood drawn from these subjects may not exceed 550ml in an 8 week period and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

b. **From other adults and children considering age, weight, and health of subject.** For a minimal risk application, the amount of blood drawn from these subjects may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period, and collection may not occur more frequently than 2 times per week.
   Volume per blood draw: _____ml
   Frequency of blood draw (e.g. single draw, time(s) per week, per year, etc.) _____

Prospective collection of biological specimens other than blood: _____

Review of medical records, images, specimens

Check all that apply (data includes medical records, images, specimens).

☐ Only data that exists before the IRB submission date will be collected.

Date Range for Specimens and/or Review of Medical Records:
Examples: *01/01/1999 through 12/31/2015*, or all records through *mm/dd/yyyy*.

Note: The Date Range must include the period for collection of baseline data, as well as follow-up data, if applicable.

☐ The study involves data that exist at the time of IRB submission **and** data that will be generated after IRB submission. Include this activity in the Methods section.
Examples

- The study plans to conduct a retrospective chart review and ask subjects to complete a questionnaire.
- The study plans to include subjects previously diagnosed with a specific disease and add newly diagnosed subjects in the future.

☐ The study will use data that have been collected under another IRB protocol. Include in the Methods section and enter the IRB number from which the research material will be obtained. *When appropriate, note when subjects have provided consent for future use of their data and/or specimens as described in this protocol*.

Enter one IRB number per line, add more lines as needed

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

☐ Data ☐ Specimens ☐ Data & Specimens _____

Data Analysis

Power analyses may not be appropriate if this is a feasibility or pilot study, but end-point analysis plans are always appropriate even if only exploratory. Provide all information requested below, or provide justification if not including all of the information.

Data Analysis Plan:
We hypothesize that efficacy of galvanic vestibular reduction to reduce motion sickness severity will depend on the timing of the administration, being more effective when administered prior to stimulus (symptom) onset. For specific aim 1 we will use repeated measures ANOVA to examine changes in symptom severity, test duration (terminated at moderate nausea), and recovery to baseline across three levels: prior to stimulus (symptom) onset, following symptom onset, and placebo control. For specific aim 2 we hypothesize that functional task performance will decline with increasing levels of galvanic vestibular reduction amplitude. We will use repeated measures ANOVA to examine changes in cognitive performance, dynamic posturography, and dual tracking performance across up to 5 levels of GVR amplitude. Sample size estimates are based on: (1) the expected variability (s2) in the response parameters, (2) the alpha (a, type I) error level, or probability of incorrectly concluding there is an effect when responses are equivalent, (3) the magnitude of the effects to be detected between the means (μ1, μ2), and (4) the certainty (statistical power, 1- b) with which the effect is to be detected. Sample sizes can be calculated based on the expected standardized differences (Δ) between conditions (Fisher and Van Belle 1993).

Power Statement:
Standardized mean differences of 0.75 will be considered operationally relevant effect sizes for this comparison based our previous motion sickness mitigation protocols using the oculovestibular recoupling methodology

(Cevette et al. 2012). Based on the equation above, we will have 80% statistical power to detect standardized mean differences (two-sided tests) of 0.75 with an alpha error level of 0.05 with a sample of 16 subjects. A target of at least 30 subjects is requested to account for incomplete data sets.

Endpoints
Primary: Our project will deliver a non-pharmaceutical countermeasure approach using galvanic vestibular reduction (GVR) that can be customized to mitigate G-transitional induced motion sickness while optimizing sensorimotor and cognitive performance.