Development of a Countermeasure to Enhance Sensorimotor Adaptation to Altered Gravity Levels

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Abstract— **Astronauts experience several gravitational transitions during their journey into space, and they must adapt their sensorimotor capabilities to perform their tasks safely and successfully. A decrement in orientation perception ability or motor skills during a critical mission phase such as landing or docking may lead to catastrophic consequences. The overall objective of this research effort is to investigate and quantify sensorimotor adaptation to altered gravity levels using a short-radius centrifuge. Individual differences, the effect of pre-training in a different gravity environment, and the effect of promethazine in reducing sensorimotor impairment and space motion sickness are of particular interest. The hypotheses are: (1) individual differences exist in the ability to adapt to altered gravity environments and these differences can be predicted for hypo-gravity by measuring adaptability in a hyper-gravity environment, (2) training in one altered gravity environment will improve sensorimotor adaptation in another altered gravity environment, and (3) promethazine will reduce motion sickness, but will have no influence on either basic vestibular perceptual function or sensorimotor adaptation. We are using two tasks to characterize performance decrements and subsequent adaptation that reduces errors: orientation perception and manual control. A series of experiments utilizing these tasks are being conducted on our short-radius centrifuge. For the perception task, subjects report their orientation during a series of roll tilts, while for manual control task, subjects attempt to null a pseudo-random roll tilt disturbance to keep themselves upright using a joystick. We describe preliminary results showing an initial disruption in ability to do both tasks in an altered gravity environment, followed by a learning process to reduce errors. We also tested whether promethazine impacts basic vestibular function by conducting a double-blind, within-subject study with 10 subjects, in which we compared vestibular perceptual thresholds measured with the administration of promethazine or a placebo. Results indicate that promethazine has little effect on perceptual thresholds. Since perceptual measurements can have some inherent measurement variability, we combined subject testing with Monte Carlo simulation tools we developed to evaluate how precisely adaptation rate can be measured. This approach allowed us to optimize experimental design to ensure that precise measures of adaptation rate will be determined. Experimental results show that subjects can, on average, report tilt with a precision of 2°. Simulations show that this corresponds to a coefficient of variation on adaptation time constant of around 20%.**

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1. INTRODUCTION

Human adaptation to altered gravity environments has been of concern from the earliest reports of space motion sickness, through the Apollo exploration era, and into current planning of exploration missions [1]. For example, the ability to perceive motion correctly is necessary for safe piloting of spacecraft. While the ability to perceive motion is initially disrupted when the magnitude of gravity changes, experience in new gravity levels causes errors to be reduced. Likewise, motion sickness is common when astronauts transition between gravity levels, but symptoms often subside, likely due to adaptation. Ideally, adaptation would occur more quickly so that errors cause fewer problems. Towards this goal, it is important to know if some people are faster adaptors than others. Likewise, it would be very helpful to have a method to train people to adapt faster.

This paper describes ongoing investigations that are part of a current National Space Biomedical Research Institute (NSBRI) funded project. It is being conducted by a collaboration of space flight investigators from MIT and the Massachusetts Eye and Ear Infirmary / Harvard, and takes a new approach that could lead to an effective, practical and acceptable protocol for pre-adapting astronauts to space flight. Using a centrifuge to add an "Artificial Gravity" centripetal acceleration, we are quantifying an individual's sensory adaptation capability and using it to predict and to minimize the consequences of movement in other gravity environments. In combination with appropriate use of a drug (promethazine), we are working towards the development of a new pre-flight adaptation protocol to minimize disorientation and motion sickness and to overcome disturbances in manual control. An important step in the development will be the determination of the benefit and risks associated with the use of promethazine in conjunction with adaptation training.

We begin by describing background on orientation perception and manual control in altered gravity environments in Section 2. Next, we describe our approach and planned countermeasures in Section 3. Sections 4, 5 and 6 provide select updates on experimental findings.

2. SENSORIMOTOR ADAPTATION IN ALTERED GRAVITY ENVIRONMENTS

Sensorimotor function refers to neural responses in which a motor action is taken in response to a sensory input. In terms of the NASA Human Research Roadmap (humanresearchroadmap.nasa.gov) it also includes perception of sensory stimuli. Sensorimotor function is altered during gravitational transitions, such as those that occur during spaceflight. Related space motion sickness also occurs regularly during gravity transitions and impacts performance and operations. Astronauts must remain functional during the critical mission phases that occur during or temporally close to gravity transitions, particularly for vehicle control and landing tasks. Our project uses an experimental approach aimed at developing a combined pharmacological and pre-training countermeasure. Specifically, we are combining an anti-motion sickness drug (promethazine) and altered-gravity pre-training to reduce the severity of space motion sickness and sensorimotor impairment during gravitational transitions. Relevant to space piloting, we are using orientation perception and manual control as our primary measures of sensorimotor function. We have previously demonstrated errors in both of these tasks in altered gravity environments [2-4].

Sensorimotor adaptation to alterations in G forces has been studied largely in terms of a pilot's ability to continue to exercise control and avoid gray-out, blackout or spatial disorientation during "high-G" turns. (By "G" we refer to the net gravito-inertial force which includes the effects of gravity and all linear acceleration relative to inertial space). Aerospace applications range from fighter airplane maneuvers to spacecraft during liftoff or re-entry. The principal tool for hyper-G research has been the centrifuge. To change the G level, we use a centrifuge (Figure 1), which is capable of roll tilting subjects relative to the centripetal acceleration. Human adaptation to altered G-levels, identified as a critical research question in the Human Research Roadmap, is of particular concern when related to the ability to control a vehicle or walk on another planetary surface, or during a landing on the moon or another planet.

Adaptation refers to the process of altering a simple or complex perceptual or sensorimotor relationship in a purposeful manner – in order to achieve a goal or avoid a miscue. Closely associated with this is motion sickness, which results from the initially misaligned sensorimotor relationship, which eventually subsides as an individual adapts to the new relationship. G-adaptation, in particular, refers to the ability of an individual to appropriately change behavior when maneuvering in a gravitational field other than the usual 9.8 m/sec^2 we are accustomed to on Earth. Some specific examples were found in experiences in the Apollo and Space Shuttle programs. During the landing of the lunar module (LM), in addition to their reliance on attitude instruments and out-the-window scenes, astronauts were forced to make an adaptive re-interpretation of angular and linear acceleration stimuli to the vestibular system. A given vehicle pitch or roll angle in lunar gravity produced only 1/6 of the lateral acceleration experienced with that attitude during training on Earth. Once on the surface of the moon, even walking around and standing up required an adaptive response to altered gravity. When returning to Earth's gravity after a period in weightlessness yet another sensorimotor adaptation is required [5-9]. Despite the success of all the Space Shuttle landings, numerous cases of spatial disorientation of long or hard touchdowns have occurred [1, 10]. The oscillation in

Figure 1: The Massachusetts Eye and Ear Infirmary Eccentric Rotator Centrifuge

landing of the Space Shuttle STS-3 is an example in which the pitch-up apparently suddenly felt like a much larger angle and larger pitch rate after spaceflight. A pilot induced oscillation resulted [1].

3. COUNTERMEASURES FOR ERRORS IN ORIENTATION PERCEPTION AND CONTROL

We are using a *new approach* herein, combining pre-training in an altered gravity environment with a pharmacological countermeasure to reduce motion sickness associated with gravitational transitions. Adaptation to an altered gravity environment requires an update to the cerebellar internal model (i.e. a neural implementation of physical laws or dynamics), which provides cancelling efferent copy information to the otolith vestibular-only (VO) neurons [11]. Specifically, in altered gravity the internal model must relearn the relationship between head tilt and otolith cues, which are modified in different gravity environments. We hypothesize that an individual's speed and effectiveness in making this internal model adaptation is a personal trait. As anecdotally observed in microgravity exposure, some individuals excel at this reinterpretation and have minimal symptoms, while others struggle. Further, we propose that through pre-training this personal trait of internal model adaptability can be temporarily enhanced. While other pre-training protocols have had limited success, many of these have aimed simply at increasing an individual's emetic threshold for motion sickness through exposure to different non-gravity related sensory-rearrangement environments. We are pre-training *directly in* an altered gravity environment. Specifically, we hypothesize that with practice the subject's internal model can learn to adapt efference copy outflow to a new gravitational environment more rapidly, thereby reducing sensory conflict. During first exposure, prior to adaptation, sensory conflict is inevitable and motion sickness may ensue. To reduce motion sickness symptoms we are using an anti-motion sickness drug promethazine, hypothesizing that its application will minimize the symptoms but not impair sensorimotor adaptation.

We are measuring orientation perception and manual control to characterize sensorimotor impairment during g-adaptation and subjective reports for motion sickness intensity. We have previously validated these measures in related preflight/postflight Shuttle/Spacelab mission testing [12] and ground-based studies [2-4, 13]. We are using hyper-G and hypo-G, as provided by a centrifuge, as our altered gravity test-bed. We believe that the measures of subjective spatial orientation (e.g. *perception*) and *manual control* performance are of greatest use for quantifying the adaptability to altered gravity. These measures have the most direct application to human performance in the space environment. Specifically, these two tasks are essential to pilot control of a space vehicle. We are using these measures to test the following hypotheses:

1. Individual differences exist in the ability to adapt to altered gravity environments and these differences can be predicted by measuring adaptability in one altered gravity environment.
2. Pre-adaptation training in one altered gravity environment will improve sensorimotor adaptation in another altered gravity environment.
3. Promethazine will reduce motion sickness, but will have no influence on either basic vestibular perceptual function or sensorimotor adaptation to altered gravity environments.

4. ORIENTATION PERCEPTION AND MANUAL CONTROL RESULTS

Orientation perception

In the orientation perception task, we characterize the initial errors subjects make in reporting their orientation in altered gravity, followed by their adaptation to improve their reporting. The altered gravity environment is provided by the horizontal, centripetal acceleration, directed along the subject's z-axis during centrifugation, as measure at the head level, which we refer to as "G_z." Since orientation is altered relative to the centripetal acceleration and orthogonal to gravity, gravity provides no salient task cue. A baseline measurement is initially conducted in 1 G_z. Following that, subjects experience altered gravity. In each G_z level, subjects experience approximately 48 brief tilts to angles between -28 degrees and +28 degrees, relative to the centripetal acceleration direction. The protocol

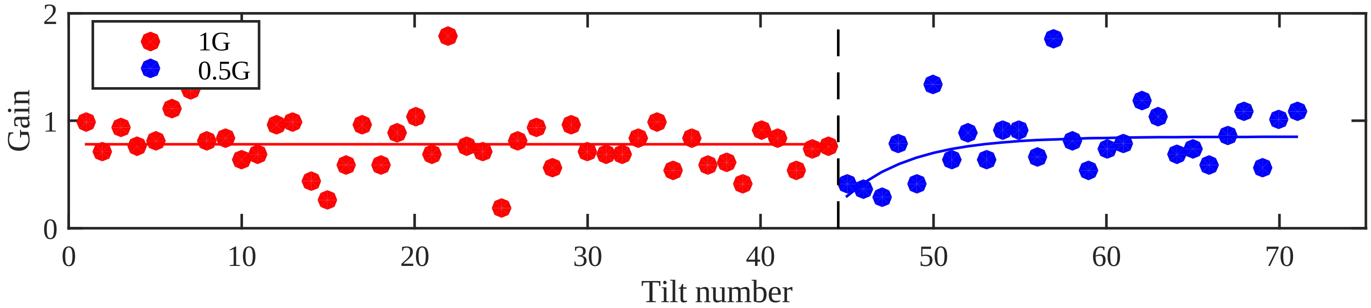

Figure 2: Orientation perception in an altered gravity environment, demonstrating disruption and adaptation (one subject). Each symbol represents one report in which the subject is tilted, and has to report his/her tilt by aligning a bar with their perception of vertical. The gain is calculated by dividing the subject's reported tilt by the actual tilt of the subject. A gain of 1 indicates that subjects correctly perceive their tilt angle. The abscissa is measurement response number. Red indicate 1 G_z responses. Blue indicate hypo-gravity responses (0.5 G_z). Note the large underestimation of tilt initially in hypo-gravity, followed by the gradual return back to a gain similar to that in 1 G_z.

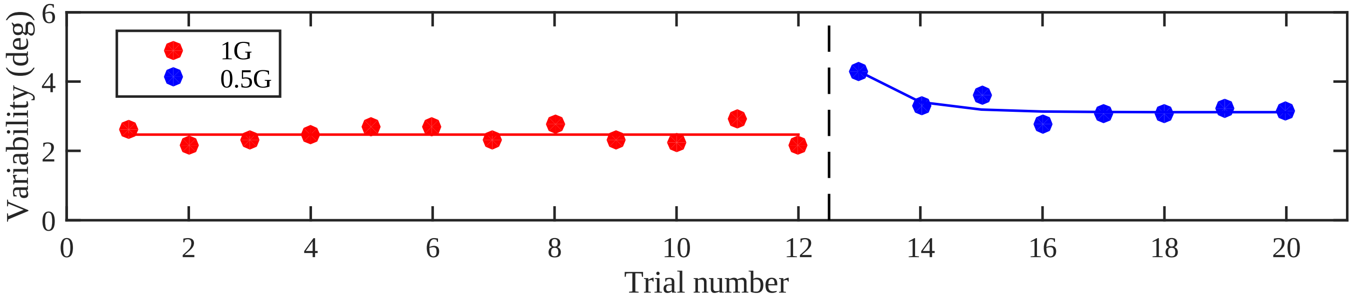

Figure 3: Manual control in an altered gravity environment, demonstrating disruption and adaptation (one subject). Each symbol represents one segment of time in which the subject is randomly moved and has to use a joystick to keep the chair and their body upright. The Variability (degrees) is calculated as the standard deviation of the chair's position from upright. The abscissa is trial number. Red indicates 1 G_z responses. Blue indicate hypo-gravity responses (0.5 G_z). Note the large increase in variability initially in hypo-gravity, followed by the gradual return back to a variability similar to that in 1 G_z.

requires approximately one hour. After each tilt, subjects are presented with an illuminated bar on a computer screen, and they are asked to rotate the bar, using two buttons, to align the bar with their perceived upright. Subjects are able to do this task quite precisely.

An example of the disruption in orientation judgment, followed by adaptation, for one subject is shown in Figure 2. The data are fit well with an exponential curve. Note that not all subjects experience this initial disruption, highlighting the individual differences found between subjects.

Manual Control

As with the orientation perception task, in the manual control task we characterize the initial increase in errors subjects make in controlling their orientation in altered gravity, followed by their adaptation to improve their manual control. A baseline measurement is initially conducted in 1 G_z. Following that, subjects experience altered gravity. In each case, the subject's task is to use a joystick to control a motorized chair so that the tilt position of their body is upright relative to the centripetal acceleration. To increase the difficulty of the task, subjects experience a random disturbance of their tilt position, which they are required to null to bring their body back towards upright. This lasts approximately thirty minutes. Subjects were able to do this task quite precisely.

As an example of the reduction in manual control ability, followed by adaptive improvement, data for one subject is shown in Figure 3. The data are fit well with an exponential curve. Note that not all subjects experience this initial disruption, highlighting the individual differences found between subjects.

5. MONTE CARLO APPROACH TO EXPERIMENTAL DESIGN FOR ADAPTATION STUDIES

Many studies require a precise measure of the rate of adaptation of behavioral or neural responses. Usually this is done with an exponential fit, and adaptation rate is characterized by an "adaptation time constant". However, measurement variability on individual reports can reduce the quality of this fit, especially if adaptation is rapid relative to the number of measurements made. Proper experimental design can improve the precision of adaptation fit parameters. We used a Monte Carlo simulation approach to design our experiments, in which we explored a large parameter space of subject measurement error, length of experiment, and length of individual trials. Monte Carlo simulations were run in Matlab, using 1000 repetitions for each set of conditions.

When we assumed a measurement precision for each subject of 2 degrees, we found that the estimated adaptation time constant would have a coefficient of variation of just over 20% if the subject's time constant was close to the value for which we designed the experiment and six measurements were made (Figure 4). Thus, this provided a good estimate of time constant. However, if the actual time constant were much different from the one for which we designed, or a shorter experiment was conducted, the coefficient of variation can be large enough to make successful results difficult to obtain.

These large differences in CV depending on the conditions used demonstrates the importance of careful experiment design in adaptation experiments, and highlights the importance of our tool.

6. MOTION SICKNESS DRUGS HAVE LITTLE IMPACT ON ORIENTATION PERCEPTION

Motion sickness drugs (e.g. promethazine) are routinely administered during spaceflight and during high-performance jet flight. However, it is unknown whether these drugs also interfere with motion sensation. Dai [14] found no effect of promethazine on VOR gain, time constant or adaptation in humans in a double blind, crossover study. To build on this study, we investigated motion perception with an oral dose of 25 mg of promethazine in humans in a double blind, crossover study. We measured vestibular perceptual motion thresholds, in which we measured the motion amplitude for which subjects could reliably recognize motion direction. Vestibular perceptual thresholds are a

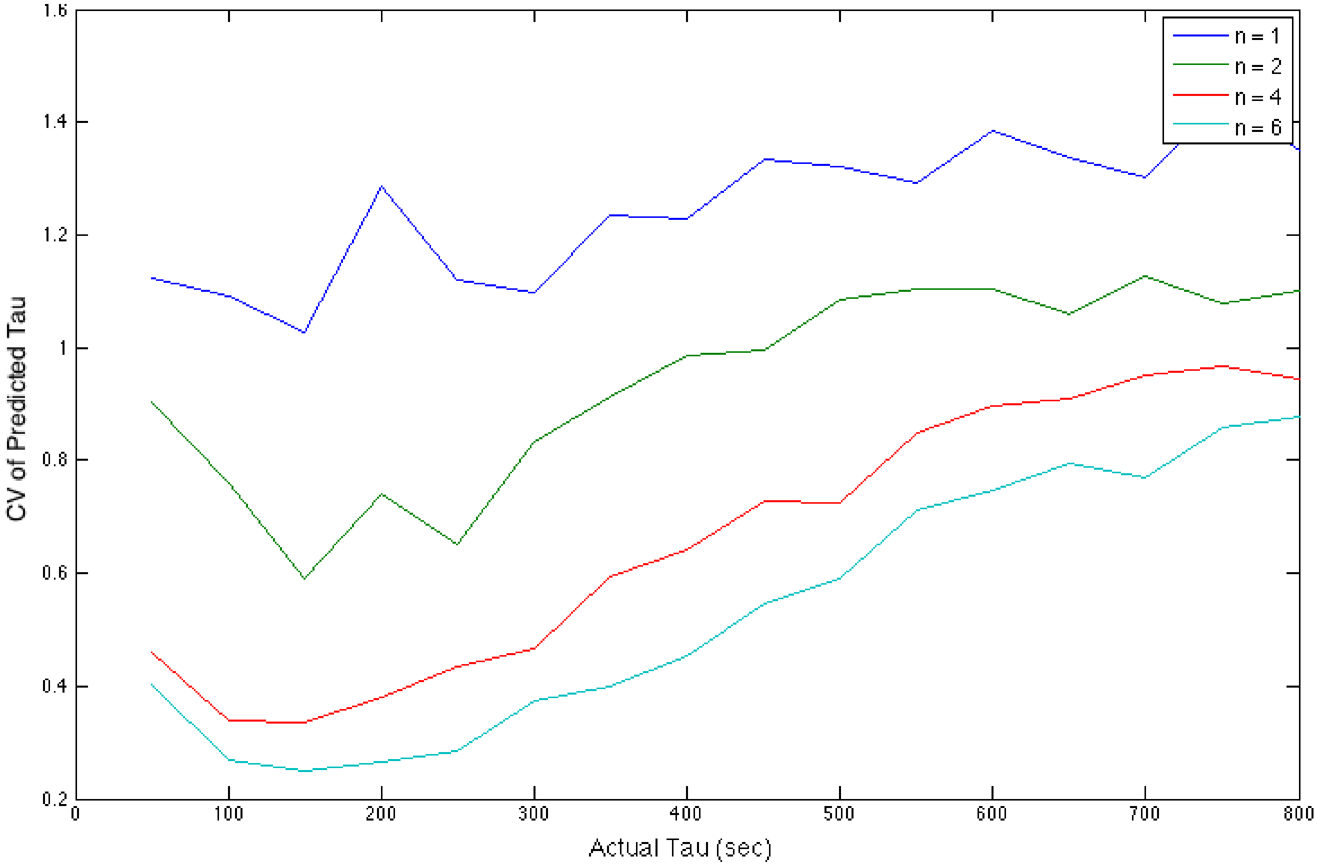

Figure 4: Monte Carlo simulation results showing how precisely time constant (tau) can be estimated based on the number of measurement repetitions (n) and the actual underlying time constant (actual tau). CV=Coefficient of variation.

robust and reliable methodology for studying basic vestibular function [15-17]. Ten subjects participated in two testing sessions each (25 mg promethazine and placebo) with the order of the tests counterbalanced. Tests were separated by at least four days to ensure any residual drug effects had dissipated. Subjects sat on a chair on top of a MOOG 6DOF2000E platform, which moved them in various directions. The smallest motion amplitude that can be correctly distinguished was determined by moving subjects in random directions (e.g. yaw left vs. yaw right, or translate left vs. translate right) at adaptively changing amplitudes. After each trial subjects indicate the direction of their perceived motion by pressing a button in their left or right hand. We measured thresholds for three types of stimuli: 1) upright yaw rotation, 2) upright inter-aural (Y) translation, and 3) upright roll tilt. Motion stimuli consisted of a single cycle of sinusoidal acceleration, with a frequency of 0.2 Hz for roll tilt and 1 Hz for yaw and Y translation [15-17]. Subjects had the opportunity to train for a few trials to ensure they felt they understood the task. Thresholds were determined from responses using standard psychophysical methodologies. A preliminary analysis found that there was little difference between thresholds with promethazine and placebo, and the difference was not statistically significant (two-way, repeated-measures ANOVA, p=0.18).

7. SUMMARY

We are using a *new approach* herein, combining pre-training in an altered gravity environment with a pharmacological countermeasure to reduce motion sickness associated with gravitational transitions. We tested the ability of subjects to adapt both orientation perception and manual control performance. Our preliminary analysis demonstrate performance decrements in both immediately after a change in G level, followed by adaptation to bring performance closer to the 1 G baseline. In addition, our preliminary analysis suggest that the anti-motion sickness drug promethazine has little effect on vestibular perception.

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REFERENCES

[1] W. H. Paloski, C. M. Oman, J. J. Bloomberg, M. F. Reschke, S. J. Wood, D. L. Harm, *et al.*, "Risk of sensory-motor performance failures affecting vehicle

control during space missions: a review of the evidence," *Journal of Gravitational Physiology,* vol. 15, 2008.

[2] T. K. Clark, M. C. Newman, C. M. Oman, D. M. Merfeld, and L. R. Young, "Human Perceptual Overestimation of Whole-Body Roll Tilt in Hyper-Gravity," *Journal of Neurophysiology,* vol. 113, pp. 2062-77, 2015.

[3] T. K. Clark, M. C. Newman, C. M. Oman, D. M. Merfeld, and L. R. Young, "Modeling Human Perception of Orientation in Altered Gravity," *Frontiers in Systems Neuroscience,* vol. 9, 2015.

[4] T. K. Clark, M. C. Newman, D. M. Merfeld, C. M. Oman, and L. R. Young, "Human Manual Control Performance in Hyper-Gravity," *Experimental Brain Research,* vol. 233, pp. 1409-1420, 2015.

[5] D. M. Merfeld, "Rotation otolith tilt-translation reinterpretation (ROTTR) hypothesis: A new hypothesis to explain neurovestibular spaceflight adaptation," *Journal of Vestibular Research-Equilibrium & Orientation,* vol. 13, pp. 309-320, 2003.

[6] C. M. Oman, "Neurovestibular Adaptation to Spaceflight: Research Progress," *Journal of Vestibular Research,* vol. 12, pp. 201-203, 2002.

[7] M. F. Reschke, J. J. Bloomberg, D. L. Harm, and W. H. Paloski, "Space-Flight and Neurovestibular Adaptation," *Journal of Clinical Pharmacology,* vol. 34, pp. 609-617, Jun 1994.

[8] D. L. Harm, M. F. Reschke, and D. E. Parker, "Visual-Vestibular Integration Motion Perception Reporting (DSO 604 OI-1)," 1999.

[9] D. E. Parker, M. F. Reschke, A. P. Arrott, J. L. Homick, and B. K. Lichtenberg, "Otolith Tilt-Translation Reinterpretation Following Prolonged Weightlessness - Implications for Preflight Training," *Aviation Space and Environmental Medicine,* vol. 56, pp. 601-606, 1985.

[10] R. McCluskey, J. B. Clark, and P. Stepaniak, "Correlation of Space Shuttle Landing Performance with Cardiovascular and Neurological Dysfunction Resulting from Spaceflight," NASA, Houston, TX2001.

[11] J. Carriot, M. Jamali, and K. E. Cullen, "Rapid adaptation of multisensory integration in vestibular pathways," *Front Syst Neurosci,* vol. 9, p. 59, 2015.

[12] D. M. Merfeld, "Effect of spaceflight on ability to sense and control roll tilt: Human neurovestibular studies on SLS-2," *Journal of Applied Physiology,* vol. 81, pp. 50-57, Jul 1996.

[13] E. L. Brown, H. Hecht, and L. R. Young, "Sensorimotor Aspects of High-Speed Artificial Gravity: I. Sensory Conflict in Vestibular Adaptation," *Journal of Vestibular Research,* vol. 12, pp. 271-282, 2002.

[14] M. Dai, M. Kunin, T. Raphan, and B. Cohen, "The relation of motion sickness to the spatial–temporal properties of velocity storage," *Exp Brain Res,* pp. 173-189, 2002.

[15] L. Grabherr, K. Nicoucar, F. W. Mast, and D. M. Merfeld, "Vestibular thresholds for yaw rotation about an earth-vertical axis as a function of frequency," *Experimental Brain Research,* vol. 186, pp. 677-681, Apr 2008.

[16] Y. Valko, R. F. Lewis, A. J. Priesol, and D. M. Merfeld, "Vestibular Labyrinth Contributions to Human Whole-Body Motion Discrimination," *Journal of Neuroscience,* vol. 32, pp. 13537-13542, Sep 26 2012.

[17] F. Karmali, K. Lim, and D. M. Merfeld, "Visual and vestibular perceptual thresholds each demonstrate better precision at specific frequencies and also exhibit optimal integration," *J. Neurophysiol,* vol. 111, pp. 2393-2403, 6/15/2014 2014.

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