Title: Sensorimotor Impairment from a New Analog of Spaceflight-altered Neurovestibular Cues

Running Title: A New Spaceflight Analog for Sensorimotor Impairment

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Keywords –Vestibular system – Spatial orientation – Balance – Locomotion – Internal model

Call for Papers: Advances in Vestibular Research: A Tribute to Bernard Cohen, MD

ABSTRACT

Exposure to microgravity during spaceflight causes central reinterpretations of orientation sensory cues in astronauts, leading to sensorimotor impairment upon return to Earth. Currently there is no ground-based analog for the neurovestibular system relevant to spaceflight. Here we propose such an analog, which we term the "wheelchair head immobilization paradigm" (WHIP). The subject lays on their side on a bed fixed to a modified electric wheelchair, with their head restrained by a custom facemask. WHIP prevents any head tilt relative to gravity which normally produces coupled stimulation to the otoliths and semicircular canals, but does not occur in microgravity. Decoupled stimulation is produced through translation and rotation on the wheelchair by the subject using a joystick. Following 12 hours of WHIP exposure, subjects systematically felt illusory sensations of self-motion when making head tilts and had significant decrements in balance and locomotion function using tasks similar to those assessed in astronauts post-spaceflight. These effects were not observed in our control groups without head-restraint, suggesting the altered neurovestibular stimulation patterns experienced in WHIP lead to relevant central reinterpretations. We conclude by discussing the findings in light of post-spaceflight sensorimotor impairment, WHIP's uses beyond a spaceflight analog, limitations, and future work.

NEW AND NOTEWORTHY

We propose, implement, and demonstrate the feasibility of a new analog for spaceflight-altered neurovestibular stimulation. Following extended exposure to the analog, we found subjects reported illusory self-motion perception. Further, they demonstrated decrements in balance and locomotion, using similar tasks as have been used to assess astronaut sensorimotor performance post-spaceflight.

INTRODUCTION

Humans must interpret sensory information, such as visual, vestibular, and proprioceptive cues, to produce appropriate motor control responses for everyday sensorimotor tasks like balance and locomotion. However, sensorimotor impairment may occur either i) in individuals that have experienced trauma (Minor, 1998), aging (Bermúdez Rey et al., 2016) or other dysfunction (sensory, cognitive, and/or motor) (Merfeld et al., 2010), or ii) healthy individuals that are exposed to an altered environment such as spaceflight (Paloski et al., 2008; Shelhamer, 2015). In the latter case (Clark et al., 2015b) individuals have fully functioning sensory and motor capabilities, but inappropriately interpret sensory cues yielding impaired motor responses. This interpretation of sensory cues is closely associated to the concept of *internal models* – neural systems that replicate the behavior/dynamics of physical systems, see (Tin & Poon, 2005) for a review – which appear to be involved with spatial orientation perception (Angelaki et al., 1999, 2004; Merfeld et al., 1999). Presumably the central nervous system (CNS) has developed internal models appropriate for the sensory motion stimulation experienced here on Earth (Cullen, 2012; Merfeld et al., 1993). The continual reinforcement of our Earth environment helps maintain these internal models (Wolpert et al., 1998), yielding typically excellent perception of orientation (Bortolami et al., 2006) and associated sensorimotor performance. However, when the environment changes dramatically, such as for an astronaut in microgravity, these internal models become inappropriate. This may cause the internal models to degrade (Merfeld, 2003), be adjusted for the new environment (Parker et al., 1985; Young et al., 1984), and/or drive the creation of entirely new internal models (Imamizu et al., 2000; Wolpert et al., 1998). To better understand the dynamics of sensorimotor internal models and the associated performance decrements, here we develop and assess a novel ground-based analog of spaceflight-altered processing of neurovestibular cues.

The neurovestibular/sensorimotor response to spaceflight is thoroughly reviewed elsewhere (Clark, 2019; Paloski et al., 2008; Wood et al., 2011). To summarize, upon entering microgravity, the majority of astronauts experience space motion sickness (Lackner & DiZio, 2006) and disorientation (Paloski et al., 2008), presumably due to the altered and unexpected graviceptor stimulation. Fortunately, all astronauts to date have suitably adapted to the microgravity environment. This adaptation process appears to begin immediately and, at least overtly, be completed within a few days (Shelhamer, 2015). However, the vestibular adaptations while in microgravity produce impairment upon return to Earth (or presumably another gravity-rich environment, such as the moon or Mars). This includes postural (Wood et al., 2015) and locomotion deficits (Mulavara et al., 2018), misperceptions of spatial orientation (Clément & Wood, 2014), altered eye movements (Clément, 1998), manual control decrements (Merfeld, 1996), motion sickness (Lackner & DiZio, 2006), and ataxia (Paloski et al., 1993).

When returning to Earth, a ground support team is typically able to prevent astronaut sensorimotor impairment having an operational impact on mission success. However, sensorimotor impairment may have catastrophic impacts on future moon or Mars landings where astronauts may have a more active piloting role and will not have a ground support team to assist after landing, at least initially (Clark, 2019; Paloski et al., 2008). To date, numerous potential countermeasures have been proposed, including artificial gravity (Bretl et al., 2019; Clément, 2015; Clément et al., 2015; Clément & Bukley, 2007; Young, 1999), sensorimotor training or rehabilitation (Bloomberg et al., 2015; Clark et al., 2015a; Harm & Parker, 1993), or using mechanical or electric orientation-reference devices (Galvan-Garza, 2016; Mulavara et al., 2015; Rupert, 2000). Yet, to date none have been systematically evaluated in astronauts exposed to microgravity, and thus have not transitioned to operational use.

Here on Earth, gravito-inertial acceleration (GIA) stimulation is the combination of gravity and linear acceleration. GIA, which is transduced by the otolith organs of the vestibular system (Fernandez & Goldberg, 1976), must be disambiguated by the CNS to distinguish between head tilts (gravity) and translation (linear acceleration) (Merfeld et al., 1999). This motivated the otolith tilt-translation reinterpretation (OTTR) hypothesis (Parker et al., 1985; Young et al., 1984), which suggests that because "stimulation from gravity is absent during orbital flight, interpretation of otolith responses as tilt is meaningless" (Young et al., 1984). Instead "[otolith signals] are centrally reinterpreted, for example, to represent linear acceleration rather than tilt" (Parker et al., 1985). This is supported by astronauts reporting illusory perceptions of translation when making head tilts post-spaceflight (Clément & Wood, 2014; Parker et al., 1985; Reschke & Parker, 1987). An alternate (though potentially complementary) hypothesis, the rotation otolith tilt-translation reinterpretation (ROTTR) hypothesis (Merfeld, 2003), emphasizes the importance of rotational cues, such as those transduced by the semicircular canals of the vestibular system (Fernandez & Goldberg, 1971). When making head tilts, the normally tightly coupled stimulation of graviceptors (e.g., otoliths) and rotation sensors (e.g., semicircular canals) becomes uncoupled in microgravity. This is suggested to cause "deterioration in the ability of the [CNS] to use rotational cues to help accurately estimate the relative orientation of gravity ('tilt'). Changes in the ability to estimate gravity then influence the ability…to estimate linear acceleration ('translation')" (Merfeld, 2003). ROTTR would explain illusory translation perceptions, but also altered tilt perception, post-spaceflight (Clément, 1998; Clément & Wood, 2014). While the evidence is reviewed elsewhere (Clark, 2019), there is currently not a well-accepted conceptual understanding of the neurovestibular reinterpretation that occurs in microgravity.

Spaceflight investigations of sensorimotor/neurovestibular impairment are limited by a relatively small number of astronauts flying and returning infrequently. The small N makes it difficult to systematically assess countermeasures, capture inter-individual differences, and validate a conceptual understanding of CNS reinterpretations. Further, it is difficult to perform assessments *immediately* post-landing due to operational constraints (e.g., landing in remote locations). This has focused scientific measures to a Field Test occurring approximately one hour following landing (Reschke et al., 2019; Tomilovskaya et al., 2014), while systematic laboratory measures are often delayed a day or more post-landing (Reschke & Clément, 2018b). As readaptation to Earth gravity begins immediately and occurs rapidly (Carriot et al., 2015), these delays likely prevent quantifying the most severe sensorimotor impairments (Paloski et al., 2008) that occur during operationally demanding periods such as piloted landing or emergency vehicle egress. Alternatively, a ground-based analog for spaceflight-altered central processing of neurovestibular cues would overcome these constraints and limitations by enabling testing *numerous* subjects *immediately* after simulated microgravity exposure.

Deconditioning of other physiological systems (e.g., musculoskeletal or cardiovascular) is often studied using long duration exposure to head down tilt bed rest as a ground-based analog (Hargens & Vico, 2016). While bed rest has been used to investigate sensorimotor changes (Clément et al., 2015; Mulavara et al., 2018), it is important to note that gravity stimulation to the vestibular system (and other graviceptors) is not removed in bed rest. Bed rest instead could be considered a lower extremity motor coordination disuse analog for the sensorimotor system, specifically not replicating the neurovestibular alterations of spaceflight. Parabolic flight can replicate the neurovestibular stimulation of microgravity, but only for very short durations (20-30 seconds) (Karmali & Shelhamer, 2008) that are too brief to induce central reinterpretations.

Here, we propose a novel ground-based approach to produce sustained replication of the neurovestibular cues experienced in microgravity, in a single plane by restraining the head to keep gravity out of the plane of interest (Figure 1). Translation and rotation stimulation, typically experienced in microgravity, is produced through the base of a motorized wheelchair attached to a recumbent bed that persons lie on during exposure. To demonstrate feasibility and perform preliminary validation, we assess sensorimotor functional performance (spatial orientation perception, balance, and locomotion) before and immediately following extended exposure to what we term the "wheelchair head immobilization paradigm" (WHIP). Additionally, we assess a control condition in which the subject has similar experiences, but the head is left unrestrained to avoid controlled manipulation of neurovestibular cues. Finally, we assess an additional control group called the "Baseline" condition for quantifying general population performance on our specific sensorimotor test battery, without any exposure to the WHIP device. While here we focus on WHIP as an analog for spaceflight-altered central processing of neurovestibular cues, the paradigm may be relevant to better understanding neurovestibular/sensorimotor adaptations to other altered environments or individuals with pathology-based balance impairments (Wood et al., 2011).

METHODS

Neurovestibular Cues

On Earth and in microgravity, as depicted in Figure 1, the otolith organs experience a shear force (*sf*) in response to head linear acceleration (*a*) (panels A, C). However, only on Earth (or another planetary body) in the presence of gravity (*g*) can a head tilt also elicit an afferent response from the otolith organs (panel B). This highlights the importance of semicircular canal stimulation in response to angular rotations/tilts (ω) for disambiguating cues from the otolith organs in a gravity environment (panel B). In a microgravity environment (panels C, D) these two sensory pathways become uncoupled such that astronaut head tilts do not have the typical combination of canal and otolith stimulation. Rather, they are not subjected to the tilt-translation ambiguity as all otolith stimulation is due to head translation (linear acceleration, *a*).

FIGURE 1 PLACEMENT (Neurovestibular Cues & WHIP Device)

Although we cannot remove the vestibular sensation of gravity here on the ground, it is possible to decouple tilt and rotational cues similar to microgravity, in a single plane. By having subjects lie on their sides (lateral-recumbent) on a bed capable of Earth-vertical rotation and fore-aft translation, as seen in Figure 1, they can experience normal accelerations (panel E) *and* rotation stimulation in the sagittal plane without concurrent tilt stimulation (panel F). Specifically, subject's heads are fixed relative to the device to prevent out-of-plane head tilts that would elicit coupled vestibular stimulation, and their interaural axis is aligned with the rotational axis of the bed (panels G-I). Desired motion inputs are provided through a joystick allowing for "active" (i.e., subject controlling their own motion) rotations and translations, which may be essential to induce adaptation (Carriot et al., 2013; Roy & Cullen, 2001). The WHIP paradigm has the following critical similarities to microgravity: 1) Most notably, WHIP prevents the vestibular organs from experiencing normal, coupled rotation and tilt stimulation relative to gravity for an extended period of time; 2) through active wheelchair motion, WHIP allows for normal x-axis (naso-osccipital) translation, and 3) normal rotation stimulation without concurrent tilt stimulation (i.e., otolith) in the sagittal plane (i.e., pitch; nodding head 'yes'). 4) Finally, WHIP removes the tonic loading of gravity on the otoliths in the z-axis (rostrocaudal) as is normally experienced on Earth during erect posture.

Device Hardware

Our prototype WHIP device (Figure 1, Panel I) consisted of a steel cart mounted to the base of a commercial-off-the-shelf electric wheelchair device and a Tempur-Pedic© memory foam mattress. WHIP subjects had their head fixed in the facemask to a countered foam block supported by an aluminum and steel frame that could be adjusted to align each subject's inter-aural axis with the center of rotation of the wheelchair. The height of the frame (y-axis) could also be adjusted throughout the test for subject comfort.

Not pictured in Figure 1 were bed extensions that could be added during idle periods for lower leg comfort, and an inertial measurement unit (IMU) fixed to the facemask either directly above the right ear on the facemask (for WHIP subjects) or mounted on the underside of the table (for Control subjects). The IMU was used to quantify the motions – linear accelerations and angular velocities – experienced as well as inadvertent out-of-plane head tilts made by WHIP-subjects due to slight flexibility of the facemask. Approximately 95% of WHIP accelerations experienced at the head fell under 0.18 G's (1.8 m/s^2) in the x-axis (naso-osccipital, fore-aft wheelchair translation), 0.12 G's (1.2 m/s^2) in the z-axis (rostrocaudal, produced via combined wheelchair rotation and translation yielding centripetal acceleration at the head location), but were as high as 0.5 G's. Similarly, 95% of y-axis rotation (pitch, sagittal plane) angular velocities were less than 81 °/s, but peaked near 100 °/s. The peak forward linear velocity was 1.76 m/s. Even when the subject attempted, only small out-of-plane head tilt angles were feasible within the WHIP facemask (<3°).

Experimental Protocol

Subjects were pre-screened, and excluded from the study if they had a self-reported history of vestibular dysfunction, or scored in the 0th or above the 90th percentile on the Motion Sickness Susceptibility Questionnaire (Reason, 1968; Reason & Brand, 1975) as this may indicate an undiagnosed vestibular dysfunction. Subjects were assigned to one of three groups: WHIP subjects (head restrained with a facemask during exposure), Control subjects (head unrestrained during exposure) and Baseline subjects (no exposure; general population task performance). Assignments were made based upon the needs of the study prior to subject recruitment. The Control group performed an identical experimental protocol, but did not have their heads restrained in a facemask during the exposure phase of the protocol (details below). This allowed for subjects to perform coupled head tilts relative to gravity, as desired, and experience the tonic loading of gravity in each axis, while controlling for laying down for an extended duration and using the wheelchair device to navigate in a novel body orientation. As some of the functional metrics adopted from previous spaceflight studies were modified for the needs of the paradigm, or experiment, we tested the Baseline group that does not perform any exposure phase (unmonitored daily activity) to quantify variability in the general population.

The experimental protocol consisted of four phases: training, pre-tests, exposure (for WHIP and Control groups), and post-tests. Training occurred at least 24-hours prior to the start of the exposure to allow the thermoplastic facemasks to fully cure, but no more than 5 days in advance to avoid receding of task-learning. The break between training and pre-test also ensured pre-test performance was not artificially inflated from having recently practiced the tasks, as compared to post-tests in which tasks were not just recently practiced due to the exposure. During training subjects were required to practice all functional tasks, with at least as many repetitions as trials of the task, and until both the experimenters and subjects subjectively determined they had adopted and honed their personal sensorimotor strategy for completing the task. WHIP subjects then had a custom facemask molded (Civco Medical Solutions, MTAPU standard MRI uni-frame mask). The pre- and post-test were performed identically, and were used to evaluate neurovestibular adaptation to the exposure protocol by means of functional sensorimotor performance. The pre-test was conducted within 12 hours of the start of the exposure window (i.e., evening prior to when post-tests would occur, or morning of exposure day) depending on subject availability. The exposure window was nominally 12 hours due to laboratory and staff constraints. Post-tests began immediately following the conclusion of the exposure (i.e., within 15 seconds). In the case of Baseline subjects, post-tests were performed approximately 12 or 24 hours following pre-tests based upon subject availability.

During the exposure, WHIP and Control subjects were required to periodically drive the WHIP device around a large space to stimulate the vestibular system; for the WHIP subjects this stimulated *uncoupled* otolith and SCC cues. Subjects were required to drive for at least 25% of the total exposure time with at least three distinct driving sessions defined by a continuous period of activity greater than 15 minutes, but were not limited to how much they could drive. While driving, subjects were instructed to explore all possible motions (i.e., left and right rotations, fore and aft translations, and combinations of rotations and translations) at varying magnitudes based on joystick deflection and the wheelchair power setting. We encouraged multiple styles of driving that was supported by the layout of the rooms, and temporary placement of cones as a form of obstacle around which they would need to maneuver. Other activities (watching movies, using a smartphone or iPad, or sleeping) were unmonitored, however, additional attention during resting periods was given to Control subjects to ensure they maintained a fully recumbent head position.

Pre- and Post-Test Metrics

Four well-established balance and locomotion tests – that mimic those used to assess astronauts – were used to quantify sensorimotor performance. The presentation of the tasks was ordered from those that required the least head and body movement to the most (detailed in sequence below), in effort to minimize the impact of readaptation during post-testing. Further, the spatial layout of task equipment was constructed such that there was little-to-no movement required to transition between tasks. Tests began with subjects laying on their sides, and with WHIP subjects in the facemask. The experimenter reiterated to the subject to "*Please keep your eyes closed, and make as little head movement as possible unless instructed otherwise for the task.*" Immediately upon conclusion of the exposure window (for WHIP and Control groups), subjects were assisted to a seated position, making a slow transition to upright to minimize effects from fluid shifts or cardiovascular loading.

Spatial Orientation Perception during Static and Dynamic (Active) Head Tilts

In the first task, we had WHIP and Control subjects verbally report their spatial orientation perceptions in response to first static and then dynamic head tilts (Baseline subjects only performed the subsequent functional performance tasks). While keeping their eyes closed, they were asked to make a static head tilt forward (pitch, nose down ~20˚) and maintain the head tilt while answering a series of questions (details below). They were then asked to make dynamic head tilts, ±20˚ at 0.33 Hz with the aid of a metronome, while the same questions were asked. The subject was instructed to stop making head tilts, and continue answering the questions once 4-6 head tilt cycles were made, based on their ability to clearly describe sensations. The number of head tilts was kept to as few as needed to describe the sensation while limiting stimuli that might induce readaptation.

Before the task was performed, the subject was instructed to: "*describe any sensations you might have to the best of your ability, in any verbiage you can and/or feel is most appropriate. Feel free to provide as much detail as you'd like.*" For each series of questions, a prompt question was asked first that determines whether subsequent questions followed. The structure of the series was as follows:

- "*Did you have any unusual perceptions of motion?*"
    - If answered "yes":
        1. *"Please describe it to the best of your ability."*
        2. *"Did the sense of moving oscillate?"*
        3. *"Was the sensation sustained or transient?"*
        4. *"What direction was the sensation?"*
        5. *"Do you have any additional comments?"*
    - If answered "no":
        - Do not ask further questions to avoid biasing later subject responses

After the subject finished responding to the questions, they were asked to open their eyes and were assisted off the wheelchair bed into a standing position to immediately begin the next task. However, a follow-up question session occurred at the conclusion of post-testing, which we describe here. Follow-up questions did not have a rigid structure, as it was tuned to individual subject reports, but broadly were aimed to: 1) disambiguate previous verbal reports that were unclear; 2) discover distinct differences of possible sensations or conscious motor control employed pre- versus post-test; 3) determine if illusory sensations were analogous in any way to past experiences; and; 4) attempt to chart the timeline of readaptation via decay of illusory perceptions (e.g., if/when during the post-test protocol were illusory sensations unperceivable).

Audio from subject reports was recorded, transcribed, and analyzed after testing. To capture patterns in subjects' motion perception reports, we recorded the number of subjects (in WHIP vs. Control) that reported any illusory sensation, whether they were sustained, the directions of those sensations (e.g., coronal/roll tilt, and only clockwise), and whether the sensations were static perceptions of a rotation angle/translation distance or dynamic perception of constant spin/translation (see Tables 1 and 2).

Modified Romberg Standing Balance Test

The Modified Romberg Standing Balance test (Agrawal et al., 2011; Bermúdez Rey et al., 2016) involves standing both on the ground and on a medium density foam pad (to make kinesthetic cues unreliable), with eyes open and closed (conditions 1-4). As is standard, each condition 1-4 was performed for 30 seconds or until failure. If failed, the subject was given a second opportunity. Tests were presented in the typical order of increasing difficulty (1: eyes open, on ground; 2: eyes closed, on ground; 3: eyes open, on foam; 4: eyes closed, on foam). Following these tests, we added a fifth condition called “4 Modified”, or “4M”, involving ±20˚ head tilts at 0.33Hz while standing on the foam pad (16”x18”x3” with slip covers, Sunmate from Dynamic Systems Inc.) with eyes closed. This condition was inspired by condition 5M added to the Sensory Organization Test (SOT) for computerized dynamic posturography previously used as a sensitive measure of balance function in returning astronauts (Jain et al., 2010; Wood et al., 2015), and is also similar to Trial 3 of the sharpened Clinical Test of Sensory Interaction on Balance (Cohen et al., 2019). The experimental setup used for those spaceflight experiments, however, had hardware to measure body sway which was used to calculate an equilibrium score metric. Without the ability to measure body sway and calculate the same metric, we introduced a new failure criteria for our condition 4M associated with the secondary task of performing head tilts. In addition to the standard failure criteria of the Modified Romberg test – the subject moving their feet, uncrossing their arms, opening their eyes, or falling (caught by the experimenters) – a trial was considered a failure if the subject could not maintain performing head tilts for more than 3 seconds. This new condition 4M was repeated for eight trials, each lasting up to 15 seconds or until a failure, as it was anticipated to be a relatively sensitive metric based on post-spaceflight tests (Wood et al., 2015). All eight trials of Condition 4M are performed by the subject regardless of their performance on Conditions 1-4 or previous trials of Condition 4M. This and the following two performance tasks were initially graded in real-time, but were also video recorded for detailed review and validation.

Tandem Walk (Heel-to-Toe Walking) Task

Next, a standard Tandem Walk task was assessed (Cohen et al., 2012b) that had subjects walk forward with arms crossed for 10 steps, with the heel touching the toe of the other foot on each step. Subjects did this in two conditions, first with eyes open and then with eyes closed. An error in a step included having a space between the heel and toe (small gaps, ~< 1 inch, were allowable), the foot touching the ground while bringing it forward (side stepping), not taking a step for more than 3 seconds, or opening eyes when they were supposed to be closed (Mulavara et al., 2018). This procedure and failure criteria were selected to match those used to assess returning astronauts in the laboratory setting (Mulavara et al., 2018), as well as in the Field Test (Tomilovskaya et al., 2014) with our addition of the eyes open condition. By reviewing video recordings, a naïve judge graded each step and represents the data presented in the Results section. For WHIP subjects, three additional blinded judges scored the videos, and the results were highly correlated ($r^2 = 0.833; 0.884; 0.868$).

Modified Functional Mobility Test

The final task had WHIP and Control subjects perform eight trials of a complex obstacle course (Figure 2), at a self-selected pace (based on laboratory constraints, Baseline subjects did not perform this task). The course is set up on a base of medium-density foam. This task is modeled after the Functional Mobility Test (FMT) used at NASA Johnson Space Center to assess functional mobility of ISS crewmembers returning from spaceflight (Cohen et al., 2012a; Mulavara et al., 2010). Our course included identical or analogous obstacles tuned to require movement primarily in the relevant, sagittal (pitch) plane, which we term the modified FMT (mFMT).

FIGURE 2 PLACEMENT (modified FMT)

The subjects began and ended each trial seated in a chair (left side of Figure 2). Floor obstacles (requiring subjects to 'hurdle/step-over') were 0.5 meters tall, and hanging obstacles (requiring subjects to 'duck') were adjusted to the subject's shoulder height at the start of training. At their discretion, they began each trial by standing up out of the chair and were timed for how long it took to complete the out-and-back course, and sit back down. To encourage subjects to avoid the obstacles, they were told each contact counted as a five second penalty.

Pre- and post-tests were streamlined, such that one of the sessions was completed within 15-20 minutes: ~1-2 minutes for orientation perception reports, 4-5 minutes for modified Romberg tests including eight trials of condition 4M, 2-3 minutes for Tandem Walk tests with eyes open and then closed, 4-6 minutes for eight trials of the mFMT, with ~1 minute between tasks to refresh instructions (though subjects could request a brief rest, typically only used during the more fatiguing mFMT trials).

Subject Pool

The protocol was approved by the University of Colorado Institutional Review Board, and all subjects signed a written informed consent form. Ten subjects were assigned to the WHIP exposure group, one of whom voluntarily dropped out of the study and is not further considered (8M/1F; ages 19-26 years). Eight of nine subjects were exposed to the full 12-hour duration and one subject was exposed for 10 hours. This subject is shown as an orange square in the WHIP panels of the figures below, but did not have noticeably different responses and was pooled with the other WHIP subjects for analysis. We also enrolled and tested 6 Control subjects (6M; ages 21-26), all of whom completed the full 12-hour exposure window. All subjects performed at least 3 hours of wheelchair driving and completed the post-tests.

Subjects were aware of the high-level project goal from the informed consent (i.e., development of a new analog for spaceflight deconditioning), but were left naïve to the general purpose of the protocol and study, potential effects of WHIP-exposure, and the different subject groups (e.g., Control subjects were unaware of the head-restrained WHIP group).

Statistical Tests

To analyze the effects on sensorimotor performance of the Exposure group (WHIP, Control, or Baseline) at pre-test and post-test time points (PrePost), we fit a linear mixed model (Equation 1). This model was fit twice, first with the Performance metric as the number of successful trials on Romberg balance condition 4M, and then again with the number of correct tandem walk steps with eyes closed. We acknowledge that these data are not strictly ratio data (i.e., successful balance trials and correct steps can only be integers between zero and eight or ten, respectively).

$$Performance = \beta_0 + \rho_i + Exposure + PrePost + PrePost * Exposure + \varepsilon_{ij} \qquad (1)$$

The model included an intercept (β_0) and random effects for each subject (ρ_i). The Exposure and Pre vs. Post time points were applied as dummy variables. The base condition in which all dummy variables were null was set as the pre-test in the Baseline group. This approach was taken as it causes 1) the Exposure coefficients to represent a difference in pre-test performance for the Baseline group vs. the Control (or Baseline vs. WHIP), 2) the PrePost coefficient to be a difference from pre- to post-test performance in the Baseline group, and 3) the PrePost*Exposure cross-effects to represent differences in pre vs. post-test performance in Baseline vs. Control (or Baseline vs. WHIP). As will be seen in the Results, the Exposure effects and the PrePost effect were not significant, as expected. However, the PrePost*Exposure cross-effect was significant for the WHIP group, corresponding to the pre-test vs. post-test performance differing for the WHIP group compared to that for the Baseline group.

To further investigate this cross-effect, we performed paired comparison tests between pre-test and post-test performance for the WHIP group. In each comparison, Shapiro-Wilks and Anderson-Darling tests were used to verify the assumption of normality prior to performing paired t-tests. We used one-tailed tests as we *a priori* hypothesized that the WHIP-subjects with head-restrained exposure would have significant sensorimotor decrements as compared to their pre-test baseline performance. All statistical tests were performed using MATLAB (v.2019a) and R/RStudio (v.1.0.153, 2017).

RESULTS

Before presenting the results for each task, in summary, WHIP subjects systematically reported illusory orientation perceptions and had substantial functional performance decrements post WHIP-exposure. Control subjects tended to not have sensorimotor decrements, nor reported similar illusory perceptions of motion post-test. Particularly, on the locomotion and balance tasks that involved having eyes closed and/or active head tilts, WHIP subjects showed substantial sensorimotor impairment, as well as perceived increased difficulty in these tasks post-test.

Spatial Orientation Perception during Static and Dynamic (Active) Head Tilts

As expected, no subjects reported illusory perceptions of motion pre-test, so Table 1 only presents post-test sensations. As subjects tended to report similar sensations during the initial static head tilt as during the subsequent dynamic head tilts, no distinction was made based upon this.

TABLE 1 PLACEMENT (Orientation perception)

All 9 WHIP subjects experienced illusory perceptions of tilt and/or rotation post-exposure. These illusory perceptions were always sustained, but spanned all three directionalities (Table 2) with some subjects reporting static and others reporting dynamic perceptions (specified in brackets in Table 1). In contrast, only 2 of 6 control subjects experienced sensations of tilt and/or translation. These two both only had transient, static perceptions of left-ear-down tilt, which was also commonly reported by WHIP subjects (though WHIP subjects reported this sensation to be sustained). This may be an artifact of the exposure orientation, in which we had subjects always laying and driving on their left sides (see Discussion for elaboration on potential underlying mechanisms). Three of 9 WHIP subjects also experienced sustained translation perception, predominately in the coronal plane (left-right) with one subject not able to articulate a directionality. Only 1 of 6 Control subjects reported any illusory translation, noting a "*slight heave, up and down*".

TABLE 2 PLACEMENT

In the follow-up question session, some subjects provided colorful analogies to specific past experiences which are detailed elsewhere (Dixon & Clark, 2018). When asked whether the illusory sensations were similar to a "head rush", 7 of 9 of WHIP subjects reported it did not (i.e., that it was something more than just a head rush), one said it did, and the last reported "*I don't know*". In contrast, only 1 of 6 Control subjects reported their sensation did not feel similar to "head rush" noting that it was "*definitely more than that*" without further elaboration. Additionally, all 9 WHIP subjects reported that they perceived performing eyes-closed tasks notably more difficult post-test, particularly recovering from body sway using common phrases such as: "*there's kind of a lag*", "*overcompensated*", and "*recognized too late*". Six of 9 WHIP subjects also explicitly addressed the increased difficulty in performing and maintaining head tilts, calling them "*sluggish*" and that they "*couldn't feel [their] accelerations*" with respect to starting and stopping head tilts on the metronome beat, "*as if there [was] noise over it*". No Control subjects reported perceived differences with respect to difficulty or motor strategy from pre- to post-test. Finally, all subjects reported that illusory perceptions decayed fairly quickly throughout the post-tests, but 6 of 9 WHIP subjects reported their noticeable perceptions persisted at least through the modified Romberg test (> 8-10 minutes).

FIGURE 3 PLACEMENT (Romberg condition 4M)

Functional Balance and Locomotion Tests

As previously noted, tasks requiring eyes to be closed and/or those involving head tilts resulted in substantial performance decrements for the WHIP group post-exposure. WHIP subjects decreased from a mean of 7.0/8 successful trials pre-test to 4.6/8 post-test on Romberg condition 4M that involved both eyes closed and head tilts while standing on the foam pad (Figure 3). Additionally, a performance decrement was seen on the eyes-closed condition of the Tandem Walk task for WHIP subjects (Figure 4) who made an average of 7.7/10 correct steps pre-test, but only 5.9/10 correct steps post-test. These performance decrements were not observed in the Control (head unrestrained) or Baseline (unmonitored activity) groups (Figures 3 and 4 B, C).

To statistically assess these effects, we fit the linear mixed model in Equation 1, first to the number of successfully completed trials in the modified Romberg balance test condition 4M (3). With 9 subjects in the WHIP group, 6 in Control, and 8 in Baseline, each performing pre and post-tests (46 observations), and six fixed-effects (shown in Table 3), there remained 40 degrees of freedom in the model.

TABLE 3 PLACEMENT (Linear model for Romberg 4M)

As the null condition for the dummy variables was set to be the Baseline subject's pre-test performance, the value of β_0 (7.34) corresponds to the number of successful balance trials out of eight in that condition (i.e., while challenging, subjects were nominally successful in completing the Romberg balance condition 4M trials). The main effects for Exposure were not significant for either Control ($p = 0.29$) or WHIP ($p = 0.70$), corresponding to the pre-test performance not differing between groups, as expected. Also as expected, the main effect of PrePost was not significant ($p = 0.58$) as the Baseline subjects performance did not differ between pre-test and post-test. However, the PrePost*Exposure cross-effect was significant for the WHIP group (coeff = -3.07, $t(40) = -3.80$, $p < 0.0005$). This corresponds to the pre-test vs. post-test performance differing between the WHIP vs. Baseline groups. As the Baseline group did not have a significant difference between pre and post-tests, the difference in WHIP corresponds to a performance decrement (negative coefficient). To further investigate this, in WHIP subjects we performed a paired t-test between pre-test vs. post-test number of successful balance trials (condition 4M) and found a significant decrement (difference = -2.6 trials of 8, $t(8) = -2.98$, $p = 0.0087$). In addition, to investigate the pre- vs. post-test changes in performance between groups, we performed a one-tailed t-test, hypothesizing larger decrements in the WHIP group than the Control group. Indeed, we found the WHIP group successfully completed fewer Romberg 4M balance trials post vs. pre, as compared to the Control group (t-test, $t(13) = 2.1$, $p = 0.03$).

We also fit the linear mixed model in Equation 1 with the Performance dependent variable as the number of correct steps in the tandem walk test with eyes closed (Table 4).

TABLE 4 PLACEMENT (Linear model for Tandem Gait eyes closed)

The model fit to the tandem walk with eyes closed performance reached identical conclusions as that for the modified Romberg 4M data. Neither of the Exposure or PrePost main effects were significant, as expected. The PrePost*Exposure cross-effect was significant for the WHIP group ($p = 0.025$). This corresponds to the change in performance from pre to post-test being different in the WHIP group as compared to the Baseline subjects (in which there was not a significant difference between pre and post-tests). To further evaluate this, we performed a paired t-test on the WHIP subjects' pre vs. post-test performance. We found the number of corrects steps in tandem walk with eyes closed to significantly decrease (difference = -1.8 steps out of 10, $t(8) = -2.10$, $p = 0.034$).

In contrast with WHIP subjects, Control subjects did not have comparable performance decrements, in either the Modified Romberg Standing Balance test condition 4M (Figure 3B) or the Tandem Walk test with eyes closed (Figure 4B). We also hypothesized the pre- vs. post-test decrement in performance to be greater in the WHIP group than the Control group for the tandem walk with eyes closed. However, this did not reach statistical significance (t-test, $t(13) = 0.9$, $p = 0.19$). Thus, while the WHIP group had a significant decrement and the Control group did not, the difference in the two groups' decrements was not significantly different. Similarly the Baseline subjects who did not have any exposure, but instead just unmonitored daily activities between pre- and post-test, did not tend to have any change in performance (Figures 3B and 4B).

FIGURE 4 PLACEMENT (Tandem Walk)

During tasks where subjects had their eyes open or were not making dynamic head tilts, however, there was no evidence of performance decrements following WHIP as compared to the pre-test baselines. All subjects in all conditions completed conditions 1 through 4 on the Modified

Romberg Standing Balance test (thus pre- vs. post-: p>0.05). Similarly, all subjects scored perfectly on the eyes open condition of the Tandem Walk task both pre- and post-test, except for six subjects (3 WHIP, 2 Control and 1 Baseline) that scored 9/10 correct steps on *either* pre- or post-test (p>0.05). The average time to complete the mFMT across eight repetitions was not significantly different for pre- vs. post-test, for WHIP subjects (pre-test mean ± SD: 11.3±4.0 seconds, post-test: 11.1±3.0, p>0.05) and Controls (pre-test: 10.6±2.3, post-test: 11.9±4.8, p>0.05). These conclusions were the same if time penalties for contacting obstacles mentioned in the instructions were integrated into the scores. We also explored pre- vs. post- differences only considering the first mFMT trial or the first four trials (hypothesizing a decrement might decay in later trials), but did not find any significant differences. Figure 5 shows the results of the mFMT for the WHIP and Control subjects, not including time penalties to be consistent with previous published FMT data (Cohen et al., 2012a; Mulavara et al., 2010)

FIGURE 5 PLACEMENT (modified Functional Mobility Test)

Finally, we note one interesting observation; one WHIP subject reported feeling motion sickness part way through post-tests (during mFMT trials, the final performance test). This included moderate nausea (no vomiting) and after a brief break (~1 minute) did not prevent the subject from completing the remaining mFMT trials. Motion sickness symptoms subsided shortly following the post-tests (~30 minutes after the end of WHIP exposure). No other subjects, WHIP, Control, or Baseline, reported motion sickness during exposure, while performing post-tests, or in debrief, though it was not explicitly questioned.

DISCUSSION

Here we propose a novel ground-based analog aimed at replicating the neurovestibular cues experienced by astronauts in microgravity. We demonstrated its feasibility for up to 12 hours (9/10 subjects completed the head-restrained testing, 8 for the full 12 hours, 1 for 10 hours). As our primary finding, this duration of WHIP exposure (head-restrained exposure) led to systematically altered orientation perception and significant decrements in sensorimotor functional tasks that are most sensitive to vestibular function (e.g., eyes closed and/or making head tilts).

While sensorimotor decrements were significant across the WHIP group for both Romberg 4M and Tandem Gait with eyes closed tasks, it is worth noting some subjects did not appear to have much or any change in performance. However, all 9 subjects had substantial impairment in at least one of these two tasks (Figure 3A & 4A): The WHIP subject (blue triangle) that had slightly improved performance pre- to post-test from 3/8 to 4/8 successful Romberg 4M trials decreased from 8/10 to 5/10 correct steps in Tandem Walk with eyes closed. Similarly, the two subjects with slightly better performance post-WHIP (blue circle and orange square) and the one that was unaffected (green diamond) on Tandem Walk with eyes closed, all had decrements in Romberg 4M post-WHIP (decreases of 4, 3, and 1 of 8 correct steps, respectively). Thus while there was substantial inter-individual variability (as might be expected), all 9 WHIP subjects demonstrated sensorimotor impairment on at least one of our two most sensitive functional tests.

These effects appear to be specifically due to the altered neurovestibular cues experienced in WHIP, as they were not observed in the Control condition, which replicated aspects of the exposure other than the head-restraint, or the Baseline condition in which there was unmonitored activity. This is highlighted by the linear mixed model results in Equation 1 and Tables 3 and 4. In each case there was not a significant main effect of Exposure, indicating WHIP, Control, and Baseline subjects all had similar performance pre-test, as expected. Further, there was a not a significant main effect of PrePost, which corresponds to no difference pre to post-test in the Baseline subjects, again as expected. Finally, there was not a significant cross-effect of

PrePost*Exposure: Control, indicating the difference pre vs. post-test in Control subjects was similar to the insignificant effect of the Baseline subjects. It is briefly worth mentioning that while not significant, there were slight trends of performance decrements in the Control subjects (<1 fewer successful balance trial (Table 3); ~1 fewer correct tandem walk steps (Table 4)). Additional control conditions with alternative WHIP-exposures will likely help differentiate the specific effects of altered neurovestibular cues (WHIP subjects) versus sustained recumbent posture with unnatural motion (Control subjects), in the context of sensorimotor performance.

Comparison to post-spaceflight perceptual reports

In a recent study (Reschke & Clément, 2018a), 10 of 13 Space Shuttle crewmembers reported that head movements made during reentry and immediately after return resulted in increased sensations of self-motion as well as a lag in motion perception after the movement stopped. This mirrors the verbal reports from WHIP subjects, all of whom reported illusory sensations of rotation/tilt, with specific descriptions of "*there's kind of a lag*", "*recognized too late*", and head tilts feeling "*sluggish*". During passive, whole-body tilts in the dark, post-spaceflight astronauts overestimate the amount of tilt (Clément, 1998; Clément & Wood, 2013, 2014) and often feel an illusory sensation of translation (Clément & Wood, 2014; Parker et al., 1985; Reschke & Parker, 1987; Young et al., 1984). Following WHIP, pitch head tilts might be expected to yield an overestimation of pitch (ROTTR hypothesis) or translation in the sagittal plane (OTTR and ROTTR hypotheses). While some WHIP subjects did experience illusory fore-aft translation and/or pitch tilt (Table 2), this was not pervasive. Instead, an illusory roll tilt or coronal (y-axis) translation sensation were more common reports post-WHIP. Among other explanations (see Limitations section for potential mechanisms), we note the methodological difference of active, head tilts vs. passive, whole-body tilts (Carriot et al., 2013). Nonetheless, WHIP subjects systematically reported sustained illusory orientation perceptions that either did not occur or were not sustained for our Control subjects, suggesting WHIP head-restrained motion drives a relevant central reinterpretation of neurovestibular stimuli.

In the same recent study (Reschke & Clément, 2018a), 11 of 14 crewmembers also reported difficulties standing or walking immediately after Shuttle wheel-stop. Subjective reports from our WHIP subjects were similar to these provided by returning astronauts. In particular our WHIP subjects tended to notice or perceive effects of the illusory sensations primarily in the presence of multisensory deprivation (e.g., eyes closed, standing on foam pad).

Comparison to post-spaceflight functional performance

Wood et al. (2015, 2011) assessed balance performance in crewmembers returning from the International Space Station (ISS) using the SOT, finding the added condition 5M (eyes closed, unstable support, dynamic pitch head tilts +/- 20˚ at 0.33 Hz) was the most sensitive. Pre-flight, condition 5M was challenging, but feasible, resulting in an average 'continuous Equilibrium Score' (cEQ) of 62.3 (Wood et al., 2015), on a 0 to 100 scale (100 being perfect balance with no sway). However, post-spaceflight, the task was essentially infeasible, either not being attempted or leading to a fall, corresponding to a score of zero. Another study performing the identical task (Mulavara et al., 2018), also with crewmembers from long-duration ISS flights, showed the cEQ significantly decreased from a median of approximately 75 to 45. Additionally, SOT data collected from short-duration returning Shuttle crewmembers and matched controls (Jain et al., 2010; Ozdemir et al., 2018), showed astronauts post-spaceflight had 20/22 falls during condition 5M while controls only had 2/22 falls. Similarly, condition 4M of the modified Romberg test which is analogous to condition 5M of the SOT – but using a foam pad rather than sway referenced platform

– was the most sensitive functional performance metric collected in WHIP subjects, with the proportion of completed trials decreasing by an average of 34%.

To date, results from the post-spaceflight Field Test including the Tandem Walk task have not been formally published. In a presentation given at the 2016 NASA HRP Investigator's Workshop (Rosenberg et al., 2016), however, preliminary results from 18 crewmembers showed significantly worse performance on the Tandem Walk task (eyes closed) for at least 24 hours after flight (subsequent HRP presentations reached similar conclusions (Reschke et al., 2017a, 2017b, 2019; Rosenberg et al., 2018)). In fact, the Tandem Walk was the most challenging of 12 tasks assessed in the Field Test (computerized dynamic posturography for the SOT is not feasible in the field). One day after returning from the ISS, the median percent correct steps was significantly reduced to 45% from 75% pre-flight (Mulavara et al., 2018). In the identical test, WHIP subjects show a similar tendency of having significantly worse performance post-test (based on mean proportion of correct steps reducing from 7.7/10 to 5.9/10). This was further supported through our informal review of the video recordings (i.e., decreased ground contact stability, increased number of falls leading to missteps, time to correct after misstep). Future tests will aim to quantify these additional metrics by incorporating an IMU system to measure body sway, and pressure plate insoles to measure mediolateral center of pressure.

Returning astronauts often experience motion sickness ("Earth sickness"), presumably due to the unexpected graviceptor cues after having adapted to the microgravity environment (Lackner & DiZio, 2006; Paloski et al., 2008). It is worth noting that one of our WHIP subjects reported motion sickness during post-tests (this was 1 of the 8 WHIP subjects that completed the full 12 hours of exposure). This could have been due to extraneous causes, such as feeling light headed from returning to an upright posture after being lateral-recumbent during exposure or the subject choosing to not eat as much during exposure. However, we speculate the motion sickness was due to WHIP-induced neurovestibular reinterpretations, since: i) the WHIP subject reported motion sickness between performing mFMT trials (the most active task) after having completed head tilts, the modified Romberg balance task, and the heel-to-toe walking task, and; ii) no Control subjects reported motion sickness. This one WHIP subject may have been particularly susceptible to neurovestibular reinterpretations within the 12 hour time period, to motion sickness when exposed to unexpected sensory cues, or simply more willing to offer unsolicited comments during testing. As we did not initially anticipate motion sickness to occur following only 12 hours of WHIP exposure (based upon pilot testing), we did not specifically ask subjects to report symptoms. Longer duration exposures should include measures of motion sickness.

Eyes-open tasks and readaptation during post-tests

WHIP subjects had no significant or observable differences pre- to post-test in task conditions that allowed eyes to be open (modified Romberg balance conditions 1 and 3, Tandem Walk with eyes open, and the mFMT). Visual cues provide a strong orientation reference to estimate vertical (Karmali et al., 2014) and can dominate over vestibular influence. One interpretation is that tasks which did not isolate vestibular cues were less sensitive to capturing post-WHIP decrements as visual and other cues could still be used effectively. This is subjectively supported by the fact that some WHIP subjects reported their illusory sensations were still present during eyes-open tasks, but that they were not "*noticeably distracting*".

We also found time to complete the mFMT post-WHIP was not significantly different from baseline values (11.3 seconds pre-WHIP vs. 11.1 post-WHIP). Following long duration spaceflight (average of 185 days on the ISS), a substantial increase in time to complete the traditional FMT was observed (Mulavara et al., 2010). The lack of a performance decrement following WHIP on our mFMT could be attributed to a number of factors: it was an eyes-open task following a relatively short exposure duration (12 hours vs. 185 days), *re*adaptation may be occurring during the post-tests prior to performing mFMT, since head movements tend to drive readaptation to a gravity environment (Reschke & Clément, 2018a), and subjects often adopted a strategy where the head was maintained level, which may make the mFMT less sensitive to quantifying post-WHIP performance decrements. Future work should aim to assess the impact of WHIP on an alternate complex, functional task that may be more sensitive. We suggest a task that includes required pitch head tilts (e.g, bending over or reaching up high to grab a small item that cannot be accomplished while keeping the head level) and/or limited visual cues to emphasize dependence upon vestibular alterations (e.g., a reduced field of view similar to a space suit helmet or reduced/altered lighting like the challenging lighting conditions on the moon (Oravetz et al., 2009)). Finally, this task might be performed first, immediately post-WHIP to minimize the influence of readaptation, but at the risk of impacting the sensitivity of other functional performance metrics.

Sensorimotor Analogs of Spaceflight

As a primary objective, we aimed to assess WHIP as an analog for spaceflight-induced neurovestibular adaptations. However, other analogs have been proposed and used to investigate sensorimotor changes, such as head down tilt bed rest (Koppelmans et al., 2013; Lee et al., 2019; Mulavara et al., 2018). Bed rest prevents subjects from performing balance and locomotion tasks otherwise experienced in Earth-bound ambulatory life, which mimics the reduction in these activities experienced by astronauts on orbit (though treadmill and exercise with elastic resistance allow for some activity). Extended bed rest (weeks to months) also induces muscle weakening (Akima et al., 2005) and elevated heart rates to maintain blood pressure (Mulavara et al., 2018), which may at least partially contribute to performance decrements in balance and locomotion tasks following long duration (70 day) bed rest (Mulavara et al., 2018). However, in bedrest paradigms subjects' heads are unrestrained such that the vestibular sensory stimulation patterns are generally unaltered compared to normal ambulatory life. The consistent supine orientation and lack of ambulation obviously differs from typical experiences, which may lead to the neuroplasticity observed in previous studies (Yuan et al., 2018), but the coupling of graviceptor (otolith) and rotational (semicircular canal) cues is maintained during bed rest, such as when rolling to one's side or pitching the head up. With the unaltered vestibular stimulation, shorter duration bed rest (5 days) does not induce balance and locomotion decrements, including in a task with head tilts, eyes closed, on a foam pad (Clément et al., 2015). Yet Shuttle flights of comparable microgravity exposure duration (11-13 days) do significantly impair balance, particularly when head tilts are performed (Jain et al., 2010; Ozdemir et al., 2018; Paloski et al., 2006). Taken together these results suggest the sensorimotor functional impairments observed after long-duration bed rest are impacted by motor disuse and atrophy, rather than neurovestibular adaptations which occur over the shorter timescale in microgravity degrading post-spaceflight sensorimotor performance.

As an alternative, WHIP specifically aims to partially replicate the vestibular sensory cues experienced in microgravity and capture the neurovestibular-induced functional impairment. While 12-hours of WHIP exposure and 70-days of bed rest both impair balance and locomotion function analogous to post-spaceflight, WHIP more meaningfully replicates the neurovestibular contribution to sensorimotor impairment. To our knowledge, illusory perceptions of self-motion are not reported post-bed rest, such as those reported by all 9 of our WHIP subjects. We note that the lateral recumbent posture of WHIP also replicates the motor disuse of bed rest (if not the precise 6° head down configuration for fluid shifts). If it were feasible to sustain for long enough durations (e.g., weeks to months), extended exposure to WHIP could serve as a comprehensive analog for spaceflight neurovestibular/sensorimotor alterations.

While WHIP was initially conceived as a potential ground-based analog for spaceflight-induced sensorimotor impairment, it may have other uses from a basic science and clinical perspective. While other paradigms (e.g., prism reversing glasses (Welch, 1974), altered gravity on a centrifuge (Galvan-Garza et al., 2018), galvanic vestibular stimulation (Dilda et al., 2014)) may be used to explore how the brain reinterprets sensory information when exposed to a novel environment, WHIP allows us to explore changes when reinforcing sensory information (i.e., coupling of otolith and canal cues during head tilts) is systematically removed. Specifically, WHIP may be used to investigate how internal models for orientation perception degrade without sensory reinforcement and how that impacts sensorimotor performance, such as has been explored in motor learning (Cohen et al., 2004) for alterations to the vestibulo-ocular reflex gain once reinforcement has been removed. Further, by studying the degradation of internal models, it may be possible to better understand how internal models are developed, maintained, and optimized. In addition to the basic science implications, this may be important for clinical populations where acute damage (e.g., unilateral dysfunction) or gradual changes (e.g., hair cell loss with aging (Karmali et al., 2018)) require maintenance of internal models for orientation perception.

Limitations and Future Work

As an analog for replicating the neurovestibular stimulation patterns of spaceflight, WHIP has some limitations. First, WHIP does not remove gravity; it simply fixes the direction of gravity out of the pitch/sagittal plane. (Of course, microgravity on orbit also does not "remove" gravity either, but effectively counters it by continual free fall around the Earth.) If the CNS processes sensory cues holistically, it may continue to track the direction of gravity during WHIP, despite it being fixed in the y-axis (inter-aural). Nonetheless, this paradigm prevents normal, coupled rotation and tilt stimulation and removes the typical tonic loading of gravity in the z-axis (rostrocaudal) for an extended period of time, similar to microgravity exposure.

As the altered stimulation patterns were in the pitch plane, we anticipated altered responses primarily within this plane. Unexpectedly, several WHIP subjects reported illusory perceptions in roll tilt and/or y-axis translation. One explanation is that the precisely 1G sustained stimulation in the +y-axis when laying on their left side led to an unexpected sensory response as the fixed GIA was removed when sitting upright post-WHIP. This aspect of reinterpretation is not relevant for microgravity where there is no fixed GIA stimulation, but may contribute to post-WHIP functional impairment as subjects could fall/misstep in any direction. A potential control condition is to configure WHIP subjects with right side down, instead of on their left. If the fixed GIA stimulation from gravity was critical, one might hypothesize the direction of illusory y-axis motion and falls/missteps post-WHIP would differ between groups with right versus left-side down.

Second, while the inertial orientation cues mimicked those in microgravity, other orientation cues were largely unchanged during WHIP. For example, visual verticality cues (doorways and the ceiling and floor in our testing room) still aligned with gravitational vertical. Similarly, while the memory foam mattress comfortably distributed tactile cues, the subject's weight was still felt on their left side in the gravitational direction. As WHIP was proposed as a neurovestibular-specific analog, these non-vestibular cues failing to mimic microgravity may be acceptable. However, if desired, future work could aim to provide altered visual cues using virtual reality (VR). A VR headset worn throughout WHIP exposure could provide visual motion cues without vertical indicators, for example consisting of a dot pattern that provides visual flow of angular rotation and linear translation. To mimic microgravity space stations, where visual vertical cues may exist, but are not consistent (e.g. working with a piece of hardware on the "ceiling"), the VR environment could have virtual tunnels (no verticality cues) that connect to virtual rooms with specific, but differing verticality cues. We hypothesize combining WHIP with VR-altered visual orientation cues would accelerate the adaptation process by reinforcing the ambiguity of vestibular information.

Third, in our initial WHIP assessment, angular rotation and linear translation were actuated actively (Figure 1), which we hoped would more effectively induce neurovestibular reinterpretations (Carriot et al., 2015; Welch et al., 1998), even if produced indirectly using a joystick. While it may not be feasible to enable natural active control (e.g., walking) with WHIP head-restraint, future work could explore the criticality of joystick active control. We envision control groups with either i) no motion at all (wheelchair turned off) or ii) passive control (wheelchair drives itself without the subject using the joystick). We note simply actively driving the wheelchair with the joystick head-unrestrained is unlikely to account for the post-WHIP sensorimotor decrements, as Control subjects had this experience but were not impaired.

Further, the wheelchair-produced translation and rotation were likely different in character than those typically experienced in spaceflight. The precise magnitudes, frequencies, and characteristics of astronaut motions likely depend upon the activity being performed (e.g., EVA vs. floating down a hallway vs. pushing off a wall). However, our prototype WHIP device was likely unable to produce large enough stimuli. For example, quickly shaking one's head "no" reaches peak angular velocities of at least 360 °/s (Grossman et al., 1988), while the wheelchair peaked at ~100 °/s. Similarly, pushing off a wall could briefly yield >1G of acceleration, but the wheelchair was more limited. The frequency content of motions also likely differed. Finally, very slight head tilts (<3°) were feasible within the custom-modeled facemask. Nonetheless, the wheelchair reproduced decoupled translations and rotations, without substantial head tilts, similar to microgravity.

Finally, WHIP exposure was limited to 12 hours in our initial validation effort. This duration was selected as a compromise between what we anticipated would be tolerable for most subjects (based upon pilot tests) versus being long enough to expect quantifiable sensorimotor changes post-WHIP (loosely based upon most astronauts "adapting" to microgravity within 0-3 days (Shelhamer, 2015)). While early spaceflight missions were fairly short (e.g., Mercury: 15 minutes, hours, and then a day+), in the last 40 years most missions have been approximately 1-2 weeks (Shuttle, now termed "short duration") or 3-6 months (ISS, termed "long duration") and future missions may be even longer (Mars: 1-2 years). Yet, neurovestibular reinterpretations appear to occur in response to gravity *transitions*, not necessarily extended exposure within an altered gravity environment. Thus WHIP may be leveraged to better understand the underlying mechanisms and temporal dynamics of central reinterpretation occurring in astronauts during gravity transitions, even if longer durations may cause altered internal models to be more engrained and lead to motor/balance disuse and musculoskeletal deconditioning.

Based upon our first-hand experience, WHIP exposure could likely be extended for more than 12 hours. First, of the 10 subjects that enrolled in the WHIP group, eight completed all 12 hours, one went for 10 hours, and one asked to stop after approximately 5 hours. While most subjects eventually noted slight discomfort from the facemask, none reported high levels of pain. A more supportive, structural custom facemask design could alleviate discomfort (with an added benefit of further limiting the magnitude of out-of-plane head tilts possible within the mask). Second, biological activities required beyond 12 hours are feasible within WHIP, including sleep (subjects often took brief naps during the 12 hours), eating/drinking (with a straw), and urination

(ONEDONE unisex bottle system). In a hospital setting, WHIP exposure on the order of several days could be feasible, but it is unlikely to be tolerable for weeks or months. However, as noted above, neurovestibular reinterpretations may be completed within a few days. If post-WHIP decrements stabilize after a few days of exposure, it would be unnecessary to extend beyond this as further decrements would likely be associated with motor/balance disuse and muscle atrophy.

Each of these limitations would be expected to reduce the efficacy of WHIP to induce neurovestibular reinterpretations. Yet, post-WHIP we found systematically altered orientation perception and significant decrements in sensorimotor tasks, not observed for Control or Baseline subjects. This suggests the impact of these limitations was sufficiently small, although we note the persistence of impairment post-WHIP was relatively brief (subjects typically reported feeling normal within 30 minutes) as compared to that observed post-spaceflight. This may have been a result of WHIP-induced central reinterpretations not being fully engrained due to a combination of the limitations listed above. We suggest the effects of WHIP not be *quantitatively* compared to those in astronauts post-spaceflight, even if the duration is matched (e.g., 4 days of WHIP compared to a 4 day Shuttle mission). Instead, WHIP might be seen as an analog that partially replicates the neurovestibular stimulation patterns of microgravity, inducing *qualitatively* similar sensorimotor impairment.

The most exciting area of future work is utilizing WHIP as an analog to investigate questions of scientific and operational interest that may be difficult in a spaceflight study. For example, WHIP could be used to assess impairment *immediately* post-exposure to better quantify readaptation and/or in response to varied exposure durations. The ability to assess effects immediately post-WHIP in a laboratory environment enables carefully controlled experiments using sophisticated equipment (in contrast to the Field Test where tasks are limited by the environment). For example, fundamental scientific questions like testing the ROTTR and OTTR hypotheses could be done using passive, whole-body motions on a computer-controlled motion device.

Experiments with WHIP exposure are difficult, but not nearly to the extent of spaceflight experiments. Thus WHIP could be used to investigate topics that require a large number of subjects, such as better quantifying, understanding, and predicting individual differences in neurovestibular adaptation. WHIP could also be used as a first step for countermeasure development. There are currently too few NASA astronauts flying (a few per year) to quickly assess and iterate countermeasure approaches as it will take years to produce a single group sample of sufficient statistical power (during which many confounding factors may be varied). Instead WHIP could be used, as head down tilt bed rest is for the musculoskeletal system, to quickly assess the efficacy of neurovestibular-specific countermeasures, and varying aspects such as intensity, personalization, etc. to optimize approaches. The most promising countermeasure prescriptions identified during WHIP testing could then move forward to full validation during operational spaceflight studies.

CONCLUSION

We propose a novel neurovestibular analog for spaceflight, termed the wheelchair head immobilization paradigm (WHIP), which aims to replicate the spatial orientation sensory cues experienced by astronauts in microgravity. Specifically, coupled head tilt stimulation is eliminated using a facemask, while decoupled linear translation and angular velocity are actuated via a joystick-controlled motorized wheelchair. A prototype WHIP device was constructed and tested in nine subjects (plus six head-unrestrained Controls) for up to 12 hours and found to be tolerable. Using similar or identical tasks as assessed with astronauts post-spaceflight, post-WHIP we found systematically altered orientation perception when making head tilts and significant decrements in balance and locomotion performance not observed in control groups. Future work should aim to use WHIP to address scientific and operational topics not easily investigated with a spaceflight study.

ACKNOWLEDGEMENTS

We would like to acknowledge the support of the University of Colorado-Boulder Research and Innovations Office SEED Grant, Discovery Learning Assistantship, Biological Sciences Initiative, and Undergraduate Research Opportunities programs. Katherine Bretl, Victoria Brazell, Azalee Rafii, David Grestle, and Alexander Kryuchkov helped construct the WHIP prototype and test subjects. Brazell, Kryuckkov, and Marissa Rosenberg blindly reviewed videos. We thank Raquel Galvan-Garza, Mark Shelhamer, Charles Oman, and Robin Dowell for insightful conversations and feedback regarding the paradigm.

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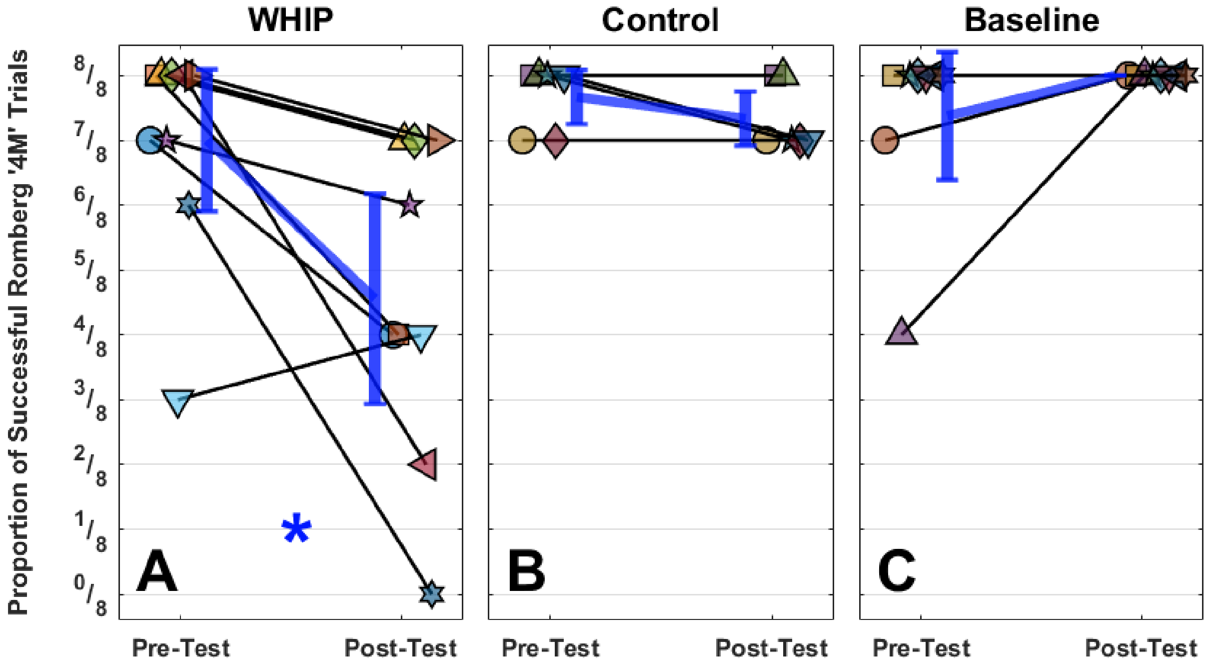
TABLES AND FIGURES

Table 1. Post-test illusory tilt/rotation and translation perception counts, sustainment, and directionalities based on subjective reports during static and dynamic head tilts (task #1) for WHIP vs. control subjects. Values in shaded sections include counts only from subjects that responded ‘Yes’ to experiencing ‘Any Illusory Sensation(s)’. Subjects’ illusory sensations could be categorized into more than one *Directionality*, but it is only possible to have one *Distinction* per colored section, per subject. If *Distinction* was unable to be extracted from verbal reports it was considered as ‘No clear direction’. Values outside of brackets indicate a static rotation/tilt angle

perception, while values inside of brackets indicate a perception of constant spin. Oscillatory sensations are inherently perceptions of constant spin, but that change direction.

Characterization	Tilt and Rotation				Translation			
	Distinction		WHIP	Control	Distinction		WHIP	Control
Any Illusory Sensation(s)	Yes		9/9	2/6	Yes		3/9	1/6
	No		0/9	4/6	No		6/9	5/6
Sustained Sensation(s)	Yes		9	0	Yes		3	1
	No		0	2	No		0	0
Directionality	Coronal / Roll Tilt [constant spin]	Clockwise (RED)	1 [1]	0	Coronal	Stationary (Left)	[1]	0
		Counterclockwise (LED)	4	2		Stationary (Right)	[1]	0
		Oscillatory	[2]	0		Oscillatory	0	0
	Sagittal / Pitch Tilt	Stationary (Fore)	0	0	Saggital	Stationary (Fore)	0	0
		Stationary (Aft)	0	0		Stationary (Aft)	0	0
		Oscillatory	[1]	0		Oscillatory	0	0
	Transverse / Yaw Rotation [constant spin]	Clockwise (Left)	[2]	0	Transverse	Stationary (Up)	0	0
		Counterclockwise (Right)	[1]	0		Stationary (Down)	0	0
		Oscillatory	0	0		Oscillatory	0	[1]
	No clear direction		0	0	No clear direction		1	0



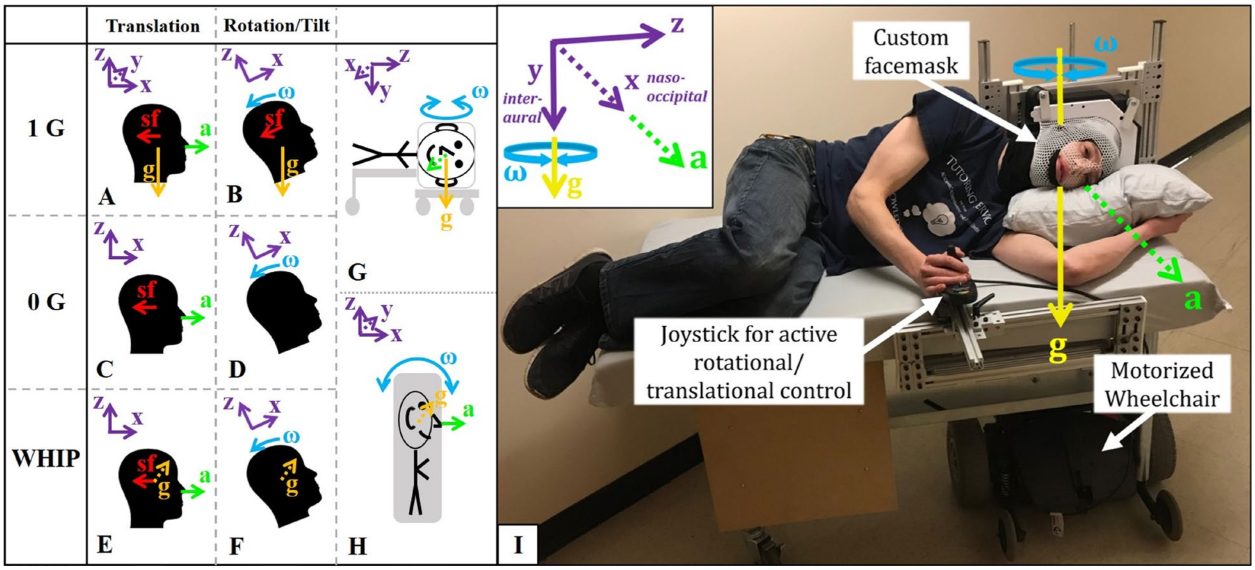


Figure 1. WHIP paradigm and device. We define a standard, right-handed, head-fixed coordinate system denoted in *purple* (x+ out nose, y+ out left ear, z+ out top of head). Otolith (*sf, red*) and semicircular canal stimuli (ω, *blue*) are shown for: translation/acceleration (*a, green*) in the leftmost column (panels A, C and E) and rotation/tilt (ω, *blue*) in the middle column (panels B, D and F) compared across 1G (panels A and B), 0G (panels C and D), and WHIP (panels E and F) environments. Gravity (*g, yellow*) present in 1G and WHIP environments is shown to elicit coupled otolith stimulation during pitch head rotations in 1G (panel B) while the same motion in WHIP does not elicit otolith stimulation (panel F). The right column and picture (panels G, H and I) shows WHIP with a subject lying on their side (lateral recumbent) with head support and the wheelchair device. The selection was arbitrary to fix gravity in the +y-axis with left-side down (panels G, H and I) to enable decoupled stimulation in the pitch plane (e.g., the subject could be supine, gravity fixed in the –x-axis, isolating the roll plane). However, the selection of pitch plane enabled the subject to navigate the wheelchair while looking out in the direction of travel. The first manufactured iteration of the WHIP device is shown on the right (panel I).

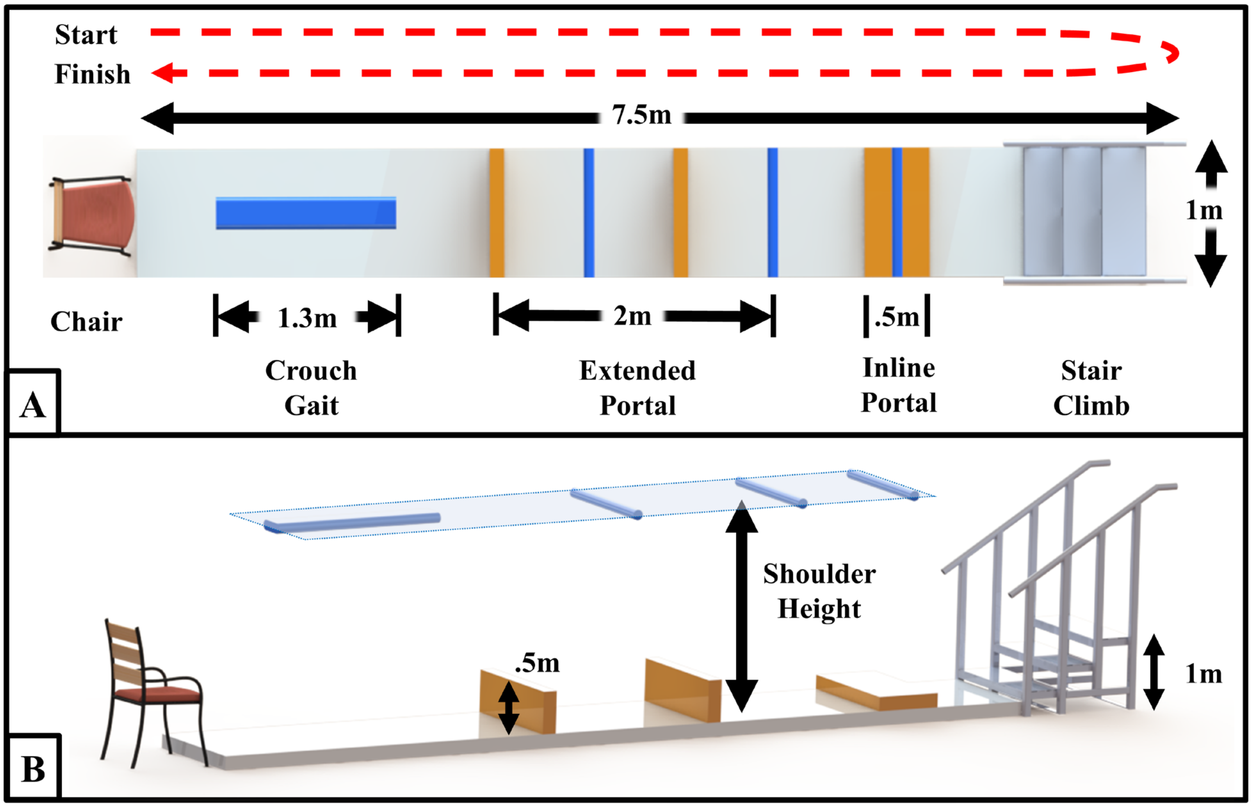


Figure 2. Modified Functional Mobility Test (mFMT) spatial layout. (A) Top-down view; (B) isometric view. Dotted *red* arrows indicate course path for each trial that starts and ends seated in the chair with each obstacle being encountered twice. *Blue* obstacles are required to be ducked under, and *orange* obstacles are required to by hurdled/stepped over.

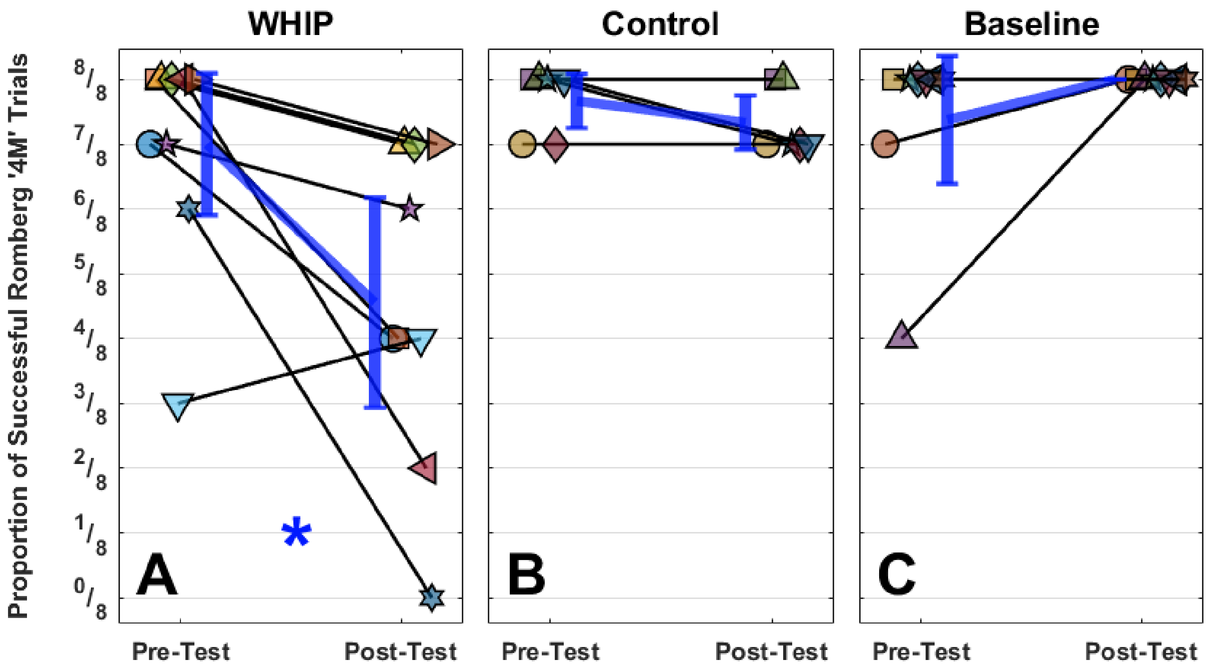


Figure 3. Proportion of successfully completed trials out of 8 for Condition '4M' of the Modified Romberg Standing Balance Test for WHIP-subjects (panel A), Control-subjects (panel B) and Baseline-subjects (panel C). *Blue* error bars represent 95% confidence intervals of the mean. Data are slightly shifted horizontally to minimize overlap of symbols. Statistically significant differences were found for the WHIP group.

Table 2. Linear Mixed Model (Equation 1) for Modified Romberg Balance Test Condition 4M.

Fixed Effect Parameters	Estimate	Standard Error	t Statistic	p-value
β_0	7.34	0.49		
Exposure: Control	0.63	0.59	1.07	0.29
Exposure: WHIP	0.29	0.74	0.39	0.70
PrePost	-0.38	0.67	-0.56	0.58
PrePost*Exposure: Control	-0.96	0.90	-1.07	0.29
PrePost*Exposure: WHIP	-3.07	0.81	-3.80	**<0.0005**

Table 3. Linear Mixed Model (Equation 1) for Tandem Walk with Eyes Closed.

Fixed Effect Parameters	Estimate	Standard Error	t Statistic	p-value
β_0	8.25	0.62		
Exposure: Control	0.50	0.71	0.70	0.49
Exposure: WHIP	-0.25	0.94	-0.27	0.79
PrePost	-0.58	0.85	-0.69	0.49

PrePost*Exposure: Control	-1.17	1.09	-1.07	0.29
PrePost*Exposure: WHIP	-2.28	0.98	-2.33	**0.025**

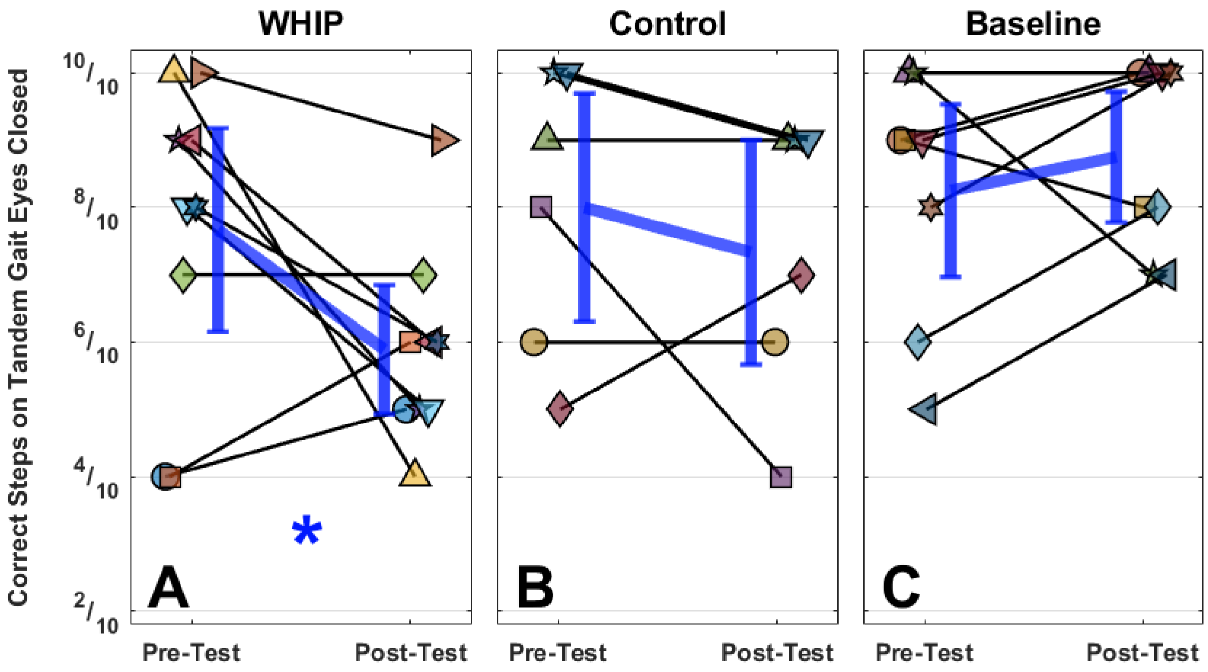


Figure 4. Number of correct steps out of ten for the Eyes-Closed condition of the Tandem Walk task for WHIP-subjects (panel A), Control-subjects (panel B) and Baseline-subjects (panel C). Blue error bars represent 95% confidence intervals of the mean. Data are slightly shifted horizontally to minimize overlap of symbols. Statistically significant differences were found for the WHIP group.

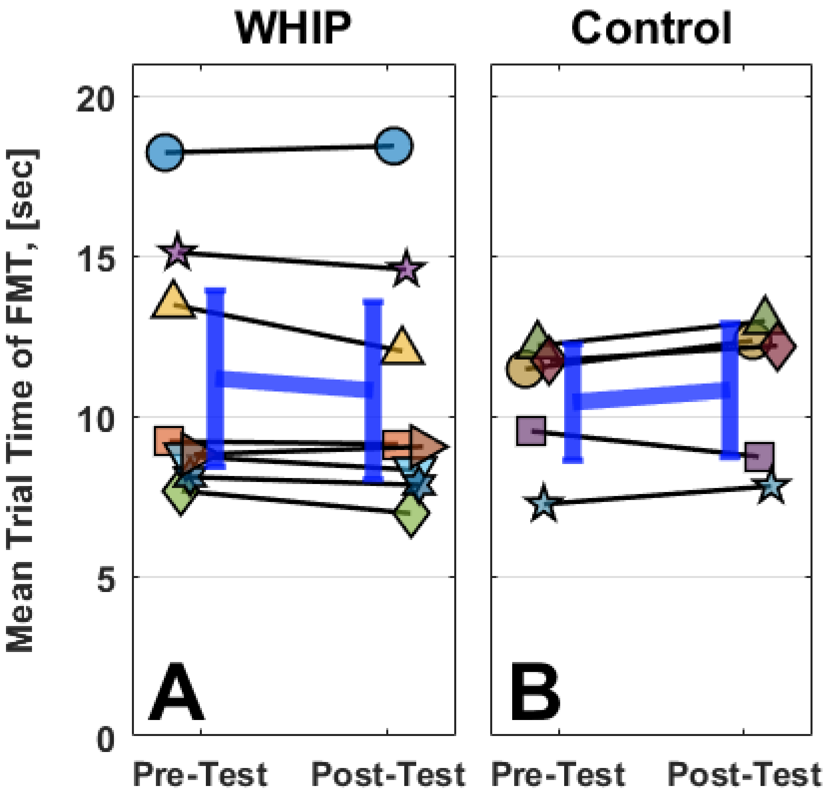


Figure 5. Mean trial times on the modified Functional Mobility Test for WHIP-subjects (panel A) and Control-subjects (panel B). Blue error bars represent 95% confidence intervals of the mean. Data are slightly shifted horizontally to minimize overlap of symbols. No significant differences were found.