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RESEARCH ARTICLE

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Vestibular brain changes within 70 days of head down bed rest

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Abstract

Head-down-tilt bed rest (HDBR) is frequently utilized as a spaceflight analog research environment to study the effects of axial body unloading and fluid shifts that are associated with spaceflight in the absence of gravitational modifications. HDBR has been shown to result in balance changes, presumably due to sensory reweighting and adaptation processes. Here, we examined whether HDBR results in changes in the neural correlates of vestibular processing. Thirteen men participated in a 70-day HDBR intervention; we measured balance, functional mobility, and functional brain activity in response to vestibular stimulation at 7 time points before, during, and after HDBR. Vestibular stimulation was administered by means of skull taps, resulting in activation of the vestibular cortex and deactivation of the cerebellar, motor, and somatosensory cortices. Activation in the bilateral insular cortex, part of the vestibular network, gradually increased across the course of HDBR, suggesting an upregulation of vestibular inputs in response to the reduced somatosensory inputs experienced during bed rest. Furthermore, greater increase of activation in multiple frontal, parietal, and occipital regions in response to vestibular stimulation during HDBR was associated with greater decrements in balance and mobility from before to after HDBR, suggesting reduced neural efficiency. These findings shed light on neuroplastic changes occurring with conditions of altered sensory inputs, and reveal the potential for central vestibular-somatosensory convergence and reweighting with bed rest.

KEYWORDS
bed rest, fMRI, sensory, spaceflight analog, vestibular cortex

1 | INTRODUCTION

Previous studies have documented a range of physiological and behavioral changes that are related to long-term microgravity exposure. These include reductions in bone density, muscle mass, cardiovascular function, sensorimotor function, and cognitive performance (Buckey, 2006; Cohen, Kimball, Mulavara, Bloomberg, & Paloski, 2012; Manzey & Lorenz, 1998; Mulavara et al., 2010; Nicogossian, Huntoon, & Pool, 1994; Strangman, Sipes, & Beven, 2014; Wood, Paloski, & Clark, 2015). Understanding these spaceflight-associated changes will facilitate future space travel and produce new knowledge about adaptive plasticity of human systems.

Head-down bed rest (HDBR) has been widely used as an analog of microgravity in studying the effects of fluid shifts and axial body unloading. When a person has been in a head-down-tilt supine position for a long time, body fluids are shifted toward the head, similar to what occurs with microgravity (Caprihan, Sanders, Cheng, & Loeppky, 1999; Pavy-Le Traon et al., 2007). Moreover, axial body unloading occurs with HDBR, simulating the reduced somatosensory inputs in microgravity.

Declines in locomotor function and balance performance have been reported after spaceflight (Cohen et al., 2012; Mulavara et al., 2010; Wood et al., 2015). Central reinterpretation of afferent sensory input appropriate for motor control in a microgravity environment is thought to contribute to these spaceflight-induced effects (Clément & Reschke, 2008; Young, Oman, Watt, Money, & Lichtenberg, 1984). In a recent case study using resting-state fMRI, researchers reported decreased connectivity in the vestibular cortex after a 169-day spaceflight, suggesting spaceflight may cause reorganization of vestibular cortex (Demertzi et al., 2016). Changes also occur at the peripheral level. For example, hypersensitivity of the utricular afferents to translational accelerations after return from spaceflight has been observed in animal studies (Boyle et al., 2001).

It is typically thought that HDBR acts as an exclusionary analog for spaceflight-induced sensorimotor changes because although the gravitational vector is reoriented, it is still present. Although there are no gravitational input changes and hence no changes to vestibular signaling mechanisms during HDBR, the axial unloading during HDBR could cause changes in sensory inputs and lead to sensory reweighting. Consequently, the interpretation of vestibular input would change during HDBR. It is this sensory reweighting that may affect brain vestibular processing even though the vestibular system is not directly affected by HDBR. We have recently shown that HDBR is associated with increases in resting state connectivity strength in a network consisting of the right lateralized vestibular cortex and cerebellar regions (Cassady et al., 2016). Behavioral experiments also suggest that vestibular function is altered with HDBR, possibly because of the sensory reweighting that occurs in this analog environment. For example, a 30-day HDBR study was reported to decrease balance stability, and the balance loss could be partially counteracted by lower body negative pressure (LBNP) during HDBR (Macaulay et al., 2016). It was proposed that the HDBR-related declines in balance performance could be due to sensorimotor changes (Dupui, Montoya, Costes-Salon, Severac, & Guell, 1992). Therefore, changes in vestibular functions such as orientation and balance could be affected by sensorimotor changes, indicating sensory reweighting during HDBR. The loss of pressure to the foot soles could induce changes in weighting of sensory inputs.

In this study, we used fMRI to evaluate whether cortical responses to vestibular stimulation are altered as a result of a 70-day HDBR exposure relative to a longitudinal control group. We used a skull tap method to activate the vestibular system in the MRI scanner. We have recently shown that this approach is well tolerated by subjects, it activates vestibular cortical regions, it results in vestibular evoked myogenic potentials in eye muscles, and it does not evoke excessive head motion (Noohi et al., 2017). We also found that pneumatically powered skull taps elicited overlapping activation with auditory tone bursts in the vestibular networks (Noohi et al., 2017). Thus, the skull tap is a validated method for studying vestibular brain activity in the MRI context. In this study, we hypothesized that functional vestibular brain activity would exhibit neuroplasticity in the HDBR subjects relative to control subjects, and that such changes would correlate with HDBR-induced declines in postural control. We have also reported that brain activity during cognitive-motor dual tasking increased with HDBR in the prefrontal cortices, possibly because of reduced neural efficiency during adaptation to the HDBR environment (Yuan et al., 2016). Thus, we hypothesized here that brain activation in response to vestibular stimulation would increase due to upregulation of sensory input during HDBR relative to control subjects, and that additional brain regions may be recruited in compensation.

2 | METHODS

2.1 | Participants

Eighteen healthy male subjects participated in a 70-day, 6°-HDBR campaign. Functional images of vestibular cortex activation were collected with the same technique from 13 of these subjects. The 13 subjects were all right-handed and aged 28.8 ± 3.3 years at the time of admission (range: 25.7–35.6 years). Subjects were admitted to the University of Texas, Medical Branch (UTMB) at Galveston flight analog facility 13–23 days before the start of HDBR and released 14 days after HDBR. During the 70-days of bed rest, participants remained in the head-down-tilt position all the time with their heads tilted 6° below their feet, except for 30 min at each meal, when they were allowed to support their head with their hand. All subjects received financial compensation for their participation. Eleven of these 13 subjects participated in an exercise protocol (Koppelmans et al., 2015; Ploutz-Snyder et al., 2014), which started 20 days before HDBR and kept on until HDBR ended, 6 days per week. The other 2 HDBR subjects did not exercise aside from stretching and physiotherapy. In this study, all HDBR participants' data were analyzed as one group and exercise was not included as a factor because the majority of HDBR participants exercised.

Another 12 healthy men participated as control participants who did not undergo bed rest. They were recruited by the Human Test subject facility at NASA-Johnson Space Center. These ground-based control subjects were aged 41.4 ± 9.9 years at the time of admission (range: 26.2–59.7 years). All the HDBR and control subjects passed an Air Force Class III equivalent physical examination. Both studies—HDBR and control—were approved by the institutional review boards of the University of Michigan, UTMB, and NASA-Johnson Space Center. Written informed consent was obtained from all participants.

2.2 | Vestibular stimulation and sensorimotor tests

Functional MR images were collected at 7 sessions for HDBR subjects: 15.1 ± 4.0 days and 8.2 ± 2.3 days before the start of HDBR; 8.4 ± 1.2 days, 50.5 ± 0.7 days, and 66.8 ± 1.8 days after the onset of HDBR; and 6.6 ± 0.9 days and 11.3 ± 1.5 days after completion of HDBR. For control subjects, the functional images were collected four times at days 0, 12.6 ± 9.7, 50.2 ± 12.8, and 84.8 ± 14.0. All the HDBR and control subjects performed a series of cognitive and sensorimotor tests. The effects of HDBR on cognitive and sensorimotor performance have been previously published from this sample (Koppelmans et al., 2015). In this study, we were particularly interested in the Functional Mobility Test (FMT) and Sensory Organization Test 5 (SOT-5 and SOT-5M) as

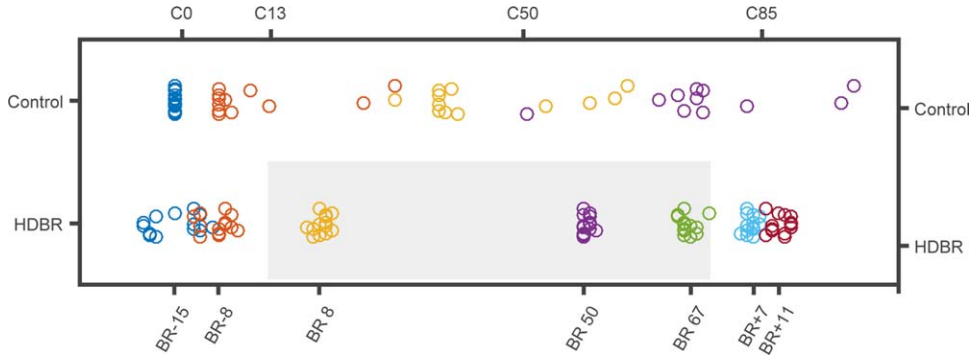

FIGURE 1 Testing timeline for HDBR subjects and normative control subjects. Color of the circles represents different testing session; each circle represents the session time of an individual participant. For HDBR subjects, the shading represents the duration of HDBR. BR-15 and BR-8 are pre-HDBR sessions; BR 8, BR 50, and BR 67 are during HDBR sessions; BR + 7 and BR + 11 are post-HDBR sessions [Color figure can be viewed at wileyonlinelibrary.com]

potential correlates of vestibular brain activity (tests described below). FMT, SOT-5, and SOT-5M were performed before and after HDBR by HDBR subjects and at all four sessions by the control subjects. The timeline is depicted in Figure 1.

2.2.1 | Vestibular stimulation

Subjects received skull taps via a pneumatic tactile pulse system (MR-compatible Pn Tactile Pulse System (PnTPS), Engineering Acoustics Inc.) that was placed over the lateral cheekbones (see Noohi et al., 2017). The skull tapper used compressed air (50–55 psi) to power a small piston that delivered low-force taps (0.6 kg) to the left or right cheekbone. The taps were delivered at 1 Hz, and each tapping block contained 24 taps. There were two fMRI runs. The first run consisted of five 24-s blocks of taps on the left cheekbone, and the second run included five 24-s blocks of taps on the right cheekbone. Each tapping block was preceded and followed by 20-s rest periods, constituting fMRI runs of 240 s. The force of the taps was sufficiently low that they did not induce large head motion: there were only 4 fMRI runs involving 3 control subjects and an additional one fMRI run in an HDBR subject showing head motions that were larger than 3 mm; these runs constituted 3.6% of the fMRI data, and were omitted from analyses. This is not a greater frequency than in our other experiments.

2.2.2 | Functional mobility test (FMT)

In the FMT, subjects walked through an obstacle course that consisted of two parts. The first part was set up on a hard floor and the second part was set up on a base of medium-density foam to increase postural challenge. The course consisted of a series of obstacles such as hurdles, pylons, and bars (Koppelmans et al., 2013; Mulavara et al., 2010; Reschke et al., 2009). Participants were asked to walk through the course without touching the obstacles as quickly and safely as possible. We used the time to complete the first part, the time to complete the second part, and the total completion time as performance measures. The FMT was repeated 10 times at each session; however, only the completion times for the first trial of each session were analyzed here because they were considered the most sensitive to change.

2.2.3 | Sensory organization tests (SOT)

We used the SOTs to measure subjects' balance ability. SOTs were conducted with the EquiTest System platform (NeuroCom, Clackamas, OR). During the tests, subjects were instructed to keep a stable upright position for 20-s trials with their eyes closed, arms folded across the chest, and feet placed shoulder width apart. The support surface, that is, the force platform, swayed during all the trials, and the eyes were closed so as to disrupt somatosensory and visual feedback; therefore, the role of vestibular input for balance control was emphasized (SOT-5). A second-order low-pass Butterworth filter (cutoff 0.85 Hz) was applied to the center of pressure to estimate center of mass (COM). The subject's sway angle was then derived from the COM that was assumed to be above the support surface at ~55% of total height. The anterior–posterior peak-to-peak sway angle was used to calculate a continuous equilibrium score that was scaled relative to 12.5° and normalized based on the percentage of the trial completed (Wood, Reschke, & Black, 2012). Each subject completed three trials with the head erect (referred to as SOT-5) and three trials with approximately ±20° head pitch movements at 0.33 Hz (referred to as SOT-5M). For both SOT-5 and SOT-5M, the median score of three trials was used to prevent the influence of outliers.

2.3 | Image acquisition and processing

The fMRI scans for HDBR subjects were collected on a 3 T Siemens Magnetom Verio MRI scanner, and the fMRIs for control subjects were collected on a 3 T Siemens Magnetom Skyra MRI scanner. A gradient echo T2*-weighted echo-planar imaging (EPI) sequence was used to collect the fMRI scans with an identical protocol for all subjects: TR = 3,660 ms, TE = 39 ms, flip angle = 90°, FOV = 240 × 240 mm, slice thickness = 4 mm, slice gap = 1 mm, matrix = 94 × 94, voxel size = 2.55 × 2.55 × 5.0 mm, 36 axial slices. A T1-weighted gradient-echo pulse sequence was also collected. For HDBR subjects, the following parameters were used: TR = 1,900 ms, TE = 2.49 ms, flip angle = 9°, FOV = 270 × 270 mm, slice thickness = 0.9 mm; matrix = 288 × 288, voxel size = 0.94 × 0.94 mm, 192 slices; duration = ~4 min. For the control subjects, we used the following

parameters: TR = 1,900 ms, TE = 2.32 ms, flip angle = 9°, FOV = 250 × 250 mm, slice thickness = 0.9 mm, 192 slices; matrix = 512 × 512, voxel size = 0.49 × 0.49 mm, 3D T1 axial overlay; duration = ~4 min.

The functional images were corrected for slice timing and head motion using SPM8 software (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/). Then the Artifact Detection Tool (ART, www.nitrc.org/projects/artifact_detect/) was used to quantify head motion and detect outliers of head motion and global brain signal, which were used as nuisance variables in the first level analyses in addition to the head motion parameters. Next, the images were normalized to MNI space using multiple steps: First, the T1 images were corrected for field inhomogeneity using N4ITK within an intracranial mask obtained from FSL's brain extraction tool (BET) (Tustison et al., 2010). Second, skull stripping was applied on the field bias corrected image using FSL's BET, with robust brain center estimation and a fractional intensity threshold of 0.1. Third, the skull stripped T1 images were co-registered to the mean fMRI EPI using SPM8. Fourth, the co-registered images were normalized to MNI152 common space using advanced normalization tools (ANTs) (Avants et al., 2011). Then the warped images were spatially smoothed with an 8-mm full-width half-maximum three-dimensional Gaussian kernel. In addition to the whole-brain normalization, a spatially unbiased atlas template of the cerebellum and brainstem (SUIT) (Diedrichsen, 2006) was used for cerebellar normalization. fMRI runs with large head motion (>3 mm) were omitted.

The functional images were analyzed using SPM8. In the first-level analyses, we calculated brain activity for each participant on a voxel-by-voxel basis for left tapping versus rest, right tapping versus rest, and the averaged BOLD signal change for left and right tapping.

In the second-level analyses, we compared activation changes between HDBR subjects and control subjects. As illustrated in Figure 1, assessment time points and intervals differed between control and HDBR subjects. To be able to directly compare HDBR subjects with control subjects we calculated the regression slope and intercept for HDBR subjects (from pre-HDBR to the last day in HDBR) and for control subjects (over all 4 time points). For HDBR subjects, the last image collected before HDBR was treated as 0 days, assuming that pre-HDBR activation was stable. Intercept images between groups were tested using a two-sample *t* test to see if there were any between group offsets at baseline. Subsequently, we tested between group differences in the slope images using a two-sample *t* test. For both intercept and slope testing, we used nonparametric permutation tests for inference (Randomize as part of FMRIB Software Library (FSL v5.0.1) (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). All these analyses were conducted running 15,000 random permutations, adjusted for age and family-wise error (FWE) corrected ($p < .05$).

Furthermore, we also used flexible factorial (SPM's mixed model equivalent) analysis to determine HDBR-associated brain activity changes and subsequent recovery across post HDBR sessions for the HDBR group. Several contrast vectors were set to test the hypothesized relative level of brain activation in each session. For the HDBR subjects, we identified brain areas with two types of HDBR-related activity change: immediate change and cumulative change (Yuan et al., 2016). The immediate change was presumed to be sensitive to HDBR status, and was hypothesized to take place shortly after the beginning of HDBR, to maintain during HDBR, and to recover shortly after the finish of HDBR. The cumulative change was assumed to increase progressively with the length in HDBR, peaking at the end of HDBR, and to restore gradually after HDBR. We tested for both increases and decreases in activation with bed rest using these two contrast shapes. The first measurement session was regarded as a practice session, and therefore was excluded from analyses. For HDBR subjects, we assessed the brain activation levels in the later six sessions (second to seventh) using contrast vectors as weights, and using the regions showing significant slope difference between HDBR and control subjects as an inclusive mask. For the control subjects, linear increases and decreases in activation across the second, third, and fourth sessions were estimated. To better detect the within-subject changes, the alpha level was set at 0.001 (uncorrected for multiple comparisons), and the extent threshold was 10 voxels.

In addition, for the HDBR subjects, we also computed the brain activation difference between the baseline (second session) and the end of HDBR (fifth session), to identify brain areas in which brain changes were associated with behavioral changes (e.g., SOT-5, SOT-5M, and FMT, which were measured only pre and post HDBR given the requirement of stance). For these correlation analyses, the alpha level was set at 0.001 (uncorrected for multiple comparisons), and the extent threshold was 10 voxels.

3 | RESULTS

3.1 | Behavioral declines with HDBR

HDBR-related declines in FMT and SOT have been documented in our previous publication in a larger sample (Koppelmans et al., 2015). Functional mobility and standing balance performance declined following HDBR, in comparison with the pre-HDBR level, as has been reported in previous studies (Mulder et al., 2014; Reschke et al., 2009). In the subsample of this study, the effects of HDBR on FMT completion time and SOT scores were also significant: $p < .01$ for all the *t* tests comparing pre-HDBR and post-HDBR performance.

3.2 | fMRI results

3.2.1 | Group vestibular activation and deactivation patterns across sessions

The averaged BOLD signal changes for left and right vestibular stimulation across sessions 2–7 in the HDBR group are shown in Figure 2 to illustrate activation associated with the skull tap technique. All the reported voxels are significant at $p < .001$. We observed brain activation in the bilateral insula, superior temporal, and supramarginal cortices while subjects were receiving vestibular stimulation, and deactivation in cerebellar, somatosensory and motor cortices versus rest; these findings are consistent with our previous work using this mode of vestibular stimulation (Noohi et al., 2017).

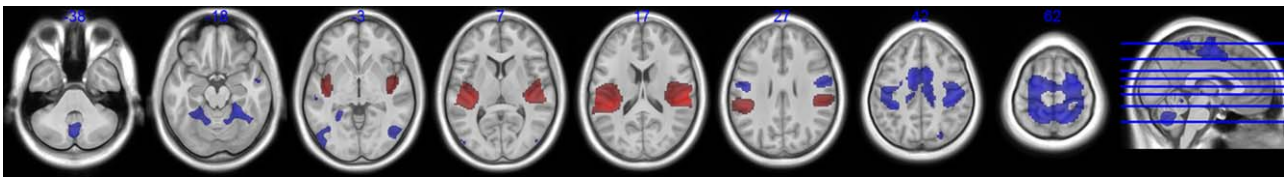

FIGURE 2 Group-level activation (red) and deactivation (blue) in response to vestibular stimulation across all time points. $p < .001$, uncorrected [Color figure can be viewed at wileyonlinelibrary.com]

3.2.2 | Comparison of activation changes between HDBR versus control subjects

There were no significant differences in intercept between groups. However, group differences in the slopes of activation change were observed in many cerebral areas, including frontal, parietal, temporal, occipital, and insular cortices (Figure 3 and Table 1). In these regions, the slopes of between-session change in activation for vestibular stimulation were larger in HDBR subjects than in control subjects, that is, activation for vestibular stimulation in these brain areas increased more in the HDBR group than in the control group. These effects were all significant at $p < .05$, FWE corrected.

3.2.3 | HDBR-related changes in vestibular brain activity

We investigated HDBR-related changes in brain activation and deactivation. For the HDBR subjects, several clusters in the parietal, frontal, and insula cortices exhibited HDBR-related cumulative increases for left and right vestibular stimulation (Figure 4 and Table 2). Three of these clusters were within the regions showing group differences in the slope of between-session change in vestibular activation. The vestibular activation in right angular gyrus, right precentral gyrus, and left insula increased faster during HDBR than in control subjects, and this HDBR-associated activation increase subsequently recovered. These changes could reflect increases of activation, decreases in deactivation, or brain activity changes outside the regions which on average, across all sessions, exhibited significant activation and deactivation. However, no HDBR-related cumulative decreases or immediate changes were found in functional vestibular brain activity. As shown in Table 2, the patterns reveal both cumulative increases in vestibular activation and HDBR-related changes in regions that are not activated or deactivated. All the reported results are significant at $p < .001$, uncorrected for multiple comparisons.

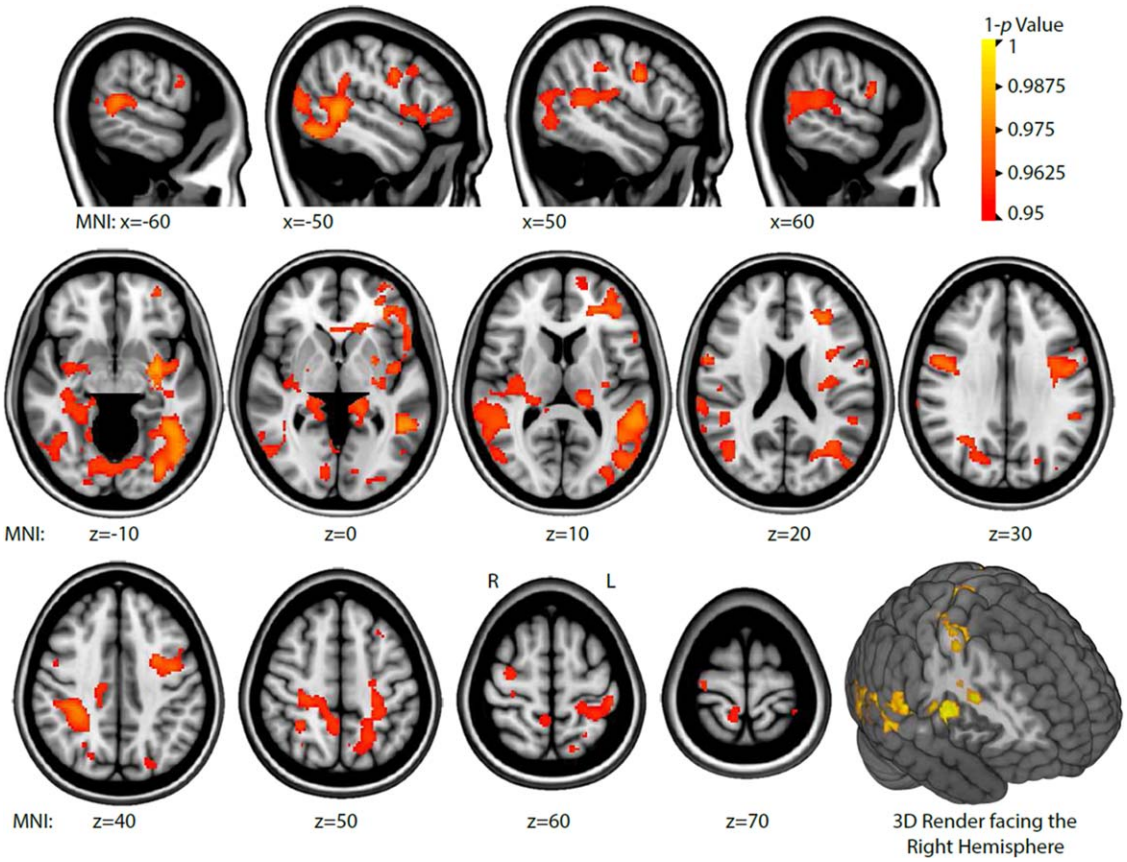

FIGURE 3 Regions showing steeper slope of activation change in HDBR subjects than control subjects. $p < .05$, corrected for FWE [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Regions showing steeper slope of activation change in HDBR subjects than control subjects

Region	*k*	Peak *T*	Peak *p*	*x*, *y*, *z* (mm)		
L middle temporal	10,198	4.634	0.021	−50	−48	4
L insula	4,308	6.445	0.017	−32	−2	−12
L postcentral	1,154	4.720	0.038	−40	−38	64
R precentral	428	5.371	0.028	52	0	30
L superior frontal	106	3.418	0.048	−14	62	12
L middle frontal	32	3.909	0.049	−32	20	46

Note. Region: the brain region with peak *T* value; *k*: cluster size; peak *T*: *t* value at the peak voxel; peak *p*: *p* value at the peak voxel; *x*, *y*, *z*: MNI coordinates of the peak voxel.

TABLE 2 Regions showing HDBR-related cumulative increases in activation for bilateral vestibular stimulation

Region	*k*	Peak *T*	Peak *p*	*x*, *y*, *z* (mm)		
R angular gyrus[a]	20	4.215	4E-05	34	−56	34
R Rolandic operculum	68	4.004	8E-05	32	−14	30
R insula[b]	29	3.585	3E-04	34	−26	16
L insula[a,b]	17	3.553	4E-04	−30	−18	18
R precentral gyrus[a]	15	3.511	4E-04	54	0	36

Note. Region: the brain region with peak *T* value; *k*: cluster size; peak *T*: *t* value at the peak voxel; peak *p*: *p* value at the peak voxel; *x*, *y*, *z*: MNI coordinates of the peak voxel.
[a]Cluster within the regions showing group difference in the slope of between-session change in vestibular activation.
[b]Cluster within the regions showing brain activation for vestibular stimulation.

In the control subjects, no increases in activation for vestibular stimulation were found across the second session to the fourth. Several clusters (Figure 5 and Table 3) exhibited decreased activation for vestibular stimulation from the second session to the fourth in control subjects, suggesting some habituation to the stimulation over time.

3.2.4 | Brain–behavioral correlations

The pre-to-post-HDBR difference in FMT total completion time was positively associated with pre-to-post-HDBR changes of vestibular functional brain activity in the frontal, parietal, temporal, occipital, and insula areas (Figure 6 and Table 4). That is, greater slowing in FMT with HDBR was associated with greater activation increases with vestibular stimulation in these regions.

Similarly, the pre-to-post-HDBR differences in SOT scores were negatively correlated with HDBR-associated changes of functional vestibular brain activity in frontal, cingulate, and supplementary motor areas (Figure 7 and Table 5). Greater deterioration in SOT-5 and SOT-5M was associated with larger increases in vestibular activation in these areas. All the reported results were significant at $p < .001$.

4 | DISCUSSION

We investigated the effects of long-term HDBR on functional vestibular brain activity that was induced by the skull tap method (Iwasaki et al., 2008; Noohi et al., 2017; Wackym et al., 2012). The insula, frontal, and parietal areas exhibited cumulative increases in activation for vestibular stimulation during the course of HDBR, indicating that more neural resources were required to process vestibular information during HDBR, or that vestibular system sensitivity was upregulated in response to decreased somatosensory input experienced during bed rest. Greater increases were associated with larger declines in locomotor and postural control from pre- to post-bed rest.

Vestibular stimulation resulted in brain activation in the bilateral insula, superior temporal, and supramarginal cortices. Meanwhile, relative to rest, deactivation was found in the cerebellum, cingulate, superior frontal, superior parietal, precuneus, paracentral, somatosensory, and motor cortices. These results are consistent with the existing literature (Noohi et al., 2017; Schlindwein et al., 2008), including activation of the vestibular cortex (Lopez, Blanke, & Mast, 2012; zu Eulenburg, Caspers, Roski, & Eickhoff, 2012). Declines in visual and somatosensory activation during vestibular stimulation versus rest likely reflect increased attention to, or weighting of, vestibular inputs (Schlindwein et al., 2008).

The observed HDBR-related activation increase parallels our recent findings of dual tasking brain activity during HDBR (Yuan et al., 2016). We found HDBR-related immediate increases and cumulative increases in brain activation when participants simultaneously performed a motor and cognitive task. These findings suggest that long-term HDBR could lead to reduced neural efficiency, which then recovered after HDBR. Such a reduction in neural efficiency could result from adaptation to the bed rest environment. When participants are in a head-down tilt supine position for a long period, the extravascular

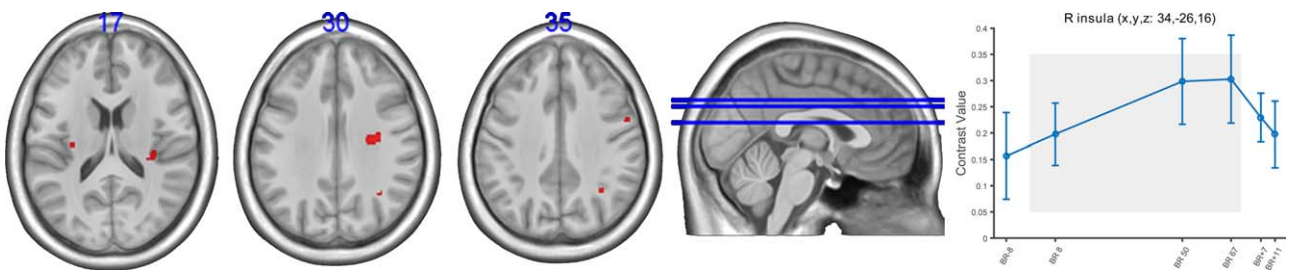

FIGURE 4 (a) Regions showing HDBR-related cumulative increases in activation for bilateral vestibular stimulation. $p < .001$, uncorrected. (b) Example of brain activation change across sessions in right insula [Color figure can be viewed at wileyonlinelibrary.com]

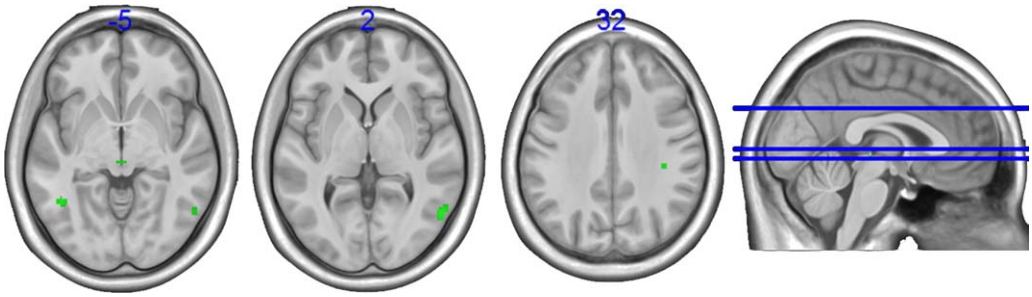

FIGURE 5 Regions showing decreased activation for vestibular stimulation in control subjects. $p < .001$, uncorrected [Color figure can be viewed at wileyonlinelibrary.com]

and intravascular fluids are shifted toward the upper body, and the brain shifts into a new position toward the posterior skull, resulting in gray matter volume change (Koppelmans et al., 2017; Roberts et al., 2015).

The HDBR-associated vestibular activation increase also parallels changes in sensory sensitivity following return from spaceflight. For example, Boyle et al. (2001) reported increased firing rate of the utricular afferents in oyster toadfish after spaceflight. In astronauts, increased perception threshold, or decreased skin sensitivity for vibration on the foot sole after spaceflight is documented (Lowrey et al., 2014; Strzalkowski et al., 2015). Lowrey et al. attribute this effect to reweighting of sensory inputs for the unreliable vestibular input in microgravity. We have recently reported increases in resting state connectivity with HDBR in a right lateralized network consisting of vestibular cortical and cerebellar regions (Cassady et al., 2016), further supporting increased sensitivity to vestibular stimulation with HDBR. It may be that both adaptation-induced declines in neural resource availability and upweighting of vestibular inputs contribute to the observed increase in vestibular activation during HDBR. In a previous study, we investigated how locomotor control adaptively responds after a period of body unloading (Mulavara et al., 2012). Subjects walked for 30 min on a treadmill at 5.4 km/h with 40% support of body weight. Head–trunk coordination measures were obtained before and after the body unloaded walking adaptation period. Subjects showed adaptive modification in vestibularly mediated compensatory head control supporting the notion that changes in body load-sensing somatosensory input centrally modulate vestibular input.

The relative immobility and loss of foot sole pressure inputs could lead to reweighting of sensory information for orientation and motor control. For example, Lee and Whitt (2015) have shown that visual loss in a rodent model results in long-term potentiation (LTP)-like enhancement of auditory inputs. Yates and Miller demonstrated the integration of nonlabyrinthine and vestibular systems (Yates & Miller, 2009). Thus, while HDBR does not directly affect the vestibular system, vestibular processing appears to be affected by sensory reweighting and other features of the HDBR environment. For example, when the somatosensory input from the feet decreased during HDBR, vestibular activation increased as compensation. This sensory reweighting challenges the brain to adapt, which may limit neural resource availability and affect brain activation for vestibular processing. Therefore, our results support the notion of vestibular-somatosensory input convergence (Mulavara et al., 2012).

The bilateral insula cortices are within the regions exhibiting brain activation in response to vestibular stimulation (Lopez et al., 2012; zu Eulenburg et al., 2012). Here we found HDBR-related activation increase in these regions. The HDBR-associated activation enhancement in bilateral insula directly reflects reduced neural efficiency or increased sensitivity during HDBR. We also observed HDBR-related activation increases with vestibular stimulation in the prefrontal cortex. This finding is similar to the well-documented engagement of prefrontal cortex even for seemingly simple motor tasks in older adults (Seidler et al., 2010). This is often interpreted as functional compensation for age-related neurostructural and neurophysiological declines (Heuninckx, Wenderoth, Debaere, Peeters, & Swinnen, 2005; Heuninckx, Wenderoth, & Swinnen, 2008). In this study, recruitment of prefrontal regions during HDBR for vestibular processing suggests engagement of cognitive control mechanisms. This could arise due to enhanced demand of vestibular processing during HDBR, as the central nervous system is adapting to the altered environment and sensory inputs. According to the compensation view (Seidler et al., 2010) and Scaffolding Theory of Aging and Cognition (STAC) (Reuter-Lorenz & Park, 2014), additional brain activation serves as compensation to counteract

TABLE 3 Regions showing decreased activation for vestibular stimulation in normal subjects

Region	*k*	Peak *T*	Peak *p*	*x*, *y*, *z* (mm)		
R middle temporal gyrus	76	4.398	8E-05	56	−64	2
L inferior temporal gyrus	43	4.174	1E-04	−44	−56	−4
midbrain	10	3.947	3E-04	2	−26	−6
R supramarginal	18	3.946	3E-04	40	−28	32

Note. Region: the brain region with peak *T* value; *k*: cluster size; peak *T*: *t* value at the peak voxel; peak *p*: *p* value at the peak voxel; *x*, *y*, *z*: MNI coordinates of the peak voxel.

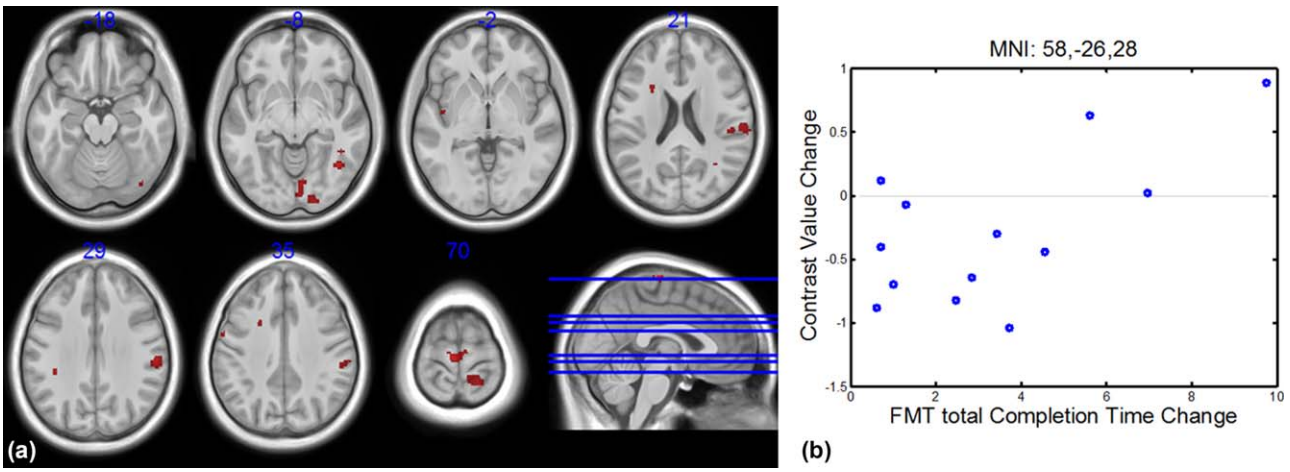

FIGURE 6 (a) Regions showing associations between pre-to-post-HDBR differences in FMT total completion time and averaged brain activation for left and right vestibular stimulation. $p < .001$, uncorrected. (b) Example of correlation between changes in brain activation and FMT performance [Color figure can be viewed at wileyonlinelibrary.com]

the adverse effects and thereby preserve performance. In this study, adverse effects include HDBR-related sensory reweighting, body unloading, and reduced neural efficiency or increased neural demand. Subjects with greater pre-to-post HDBR declines in FMT, SOT-5 and SOT-5M showed the greatest activation increases for vestibular stimulation in several areas. If the additional brain activation was not engaged during and right after HDBR, the adverse effects of HDBR would be under-ameliorated, and then the post-HDBR performance would be even worse.

Our previous publication has documented that the HDBR-induced declines in mobility can be partially mitigated by exercise (Koppelmans et al., 2015). Considering the observed association between HDBR-related changes in FMT and brain activation, we speculate that appropriate exercise would be able to alleviate HDBR-associated changes in brain activation for vestibular stimulation.

We observed cumulative increases in brain activity, but not immediate changes, suggesting that the effect of HDBR on vestibular brain processing develops gradually. In contrast, our previously reported

TABLE 4 Regions showing associations between pre-to-post-HDBR differences in FMT total completion time and averaged brain activation for left and right vestibular stimulation

Region		*k*	Peak *T*	Peak *p*	*x*, *y*, *z* (mm)		
Frontal	R paracentral lobule	94	8.779	5E-06	−4	−22	72
	L precentral	13	5.294	2E-04	−58	0	36
	L inferior frontal	29	5.147	3E-04	−26	14	20
	L middle frontal	17	4.873	4E-04	−24	14	34
Parietal	L supramarginal	58	7.695	2E-05	−36	−32	30
	R supramarginal[a]	277	6.477	6E-05	58	−26	28
	R superior parietal[b]	104	6.384	6E-05	20	−48	68
Temporal	R inferior temporal	35	8.231	9E-06	40	−58	−6
	R inferior temporal	19	5.522	2E-04	44	−46	−10
	R middle temporal	10	5.473	2E-04	32	−58	22
Occipital	R lingual	73	5.847	1E-04	6	−76	−8
	R lingual	45	5.521	2E-04	18	−96	−6
	R inferior occipital	33	5.089	3E-04	40	−78	−18
Insula	L insula[a]	15	5.409	2E-04	−42	−8	−2

Note. Region: the brain region with peak *T* value; *k*: cluster size; peak *T*: *t* value at the peak voxel; peak *p*: *p* value at the peak voxel; *x*, *y*, *z*: MNI coordinates of the peak voxel.

[a]Cluster within the regions showing brain activation for vestibular stimulation.

[b]Cluster within the regions showing brain deactivation for vestibular stimulation.

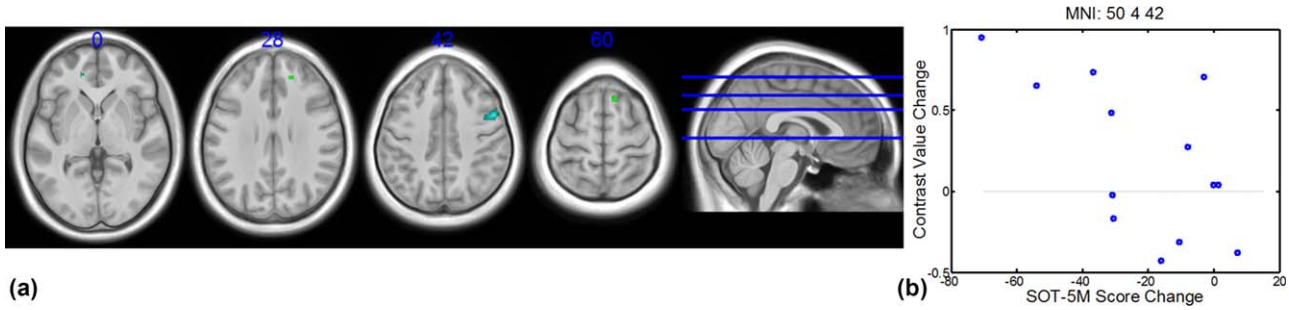

FIGURE 7 (a) Regions showing negative associations between pre-to-post-HDBR differences in SOT-5 (green), SOT-5M (blue) scores, and brain activation for vestibular stimulation. $p < .001$, uncorrected. (b) Example of correlation between changes in brain activation and SOT-5M [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 5 Regions showing negative associations between pre-to-post-HDBR differences in SOT score and brain activation for vestibular stimulation

	Region	*k*	Peak *T*	Peak *p*	*x*, *y*, *z* (mm)		
SOT-5 score	R supplementary motor area	17	5.648	2E-04	12	18	60
	R superior frontal gyrus	12	5.151	3E-04	18	40	28
SOT-5M score	R precentral gyrus	191	9.493	3E-06	50	4	42
	L anterior cingulum	11	5.378	2E-04	−16	42	0

Note. Region: the brain region with peak *T* value; *k*: cluster size; peak *T*: *t* value at the peak voxel; peak *p*: *p* value at the peak voxel; *x*, *y*, *z*: MNI coordinates of the peak voxel.

HDBR effects on brain activation for dual tasking occurred sooner, even within 7 days after the onset of HDBR. The difference in timelines of HDBR effects on different tasks suggests that HDBR has multiple time-varying effects on the brain. The exact nature of these dynamic processes remains to be determined.

In the control subjects, no brain activation increase was observed across the multiple test sessions. Instead, the brain activation for vestibular stimulation decreased with repeated measures in several regions in the control participants, implying habituation of vestibular activation. These results suggest that the HDBR-associated activation increases are even greater, because the habituation effects are leading to an underestimation of the HDBR-related increases. The between-group comparison of activation change slope revealed a greater rate of activation increase in HDBR subjects than control subjects in relatively large regions.

In this study, the HDBR group and control group were tested at different time points and using different scanners; thus the interpretations of this group comparison should be tempered by this limitation. Another limitation of this study is that only male subjects were included (the subjects in our sample served as controls for another investigator's study on testosterone supplementation). Thus generalization of the current findings to the whole population should be done with caution.

5 | CONCLUSION

In this study, we investigated the effects of 70-day HDBR on functional vestibular brain activity. We observed HDBR-associated increases in brain activation for vestibular stimulation in the insula, frontal, and parietal areas. The lack of any increases over time in the control group supports the specificity of our findings to the HDBR intervention. Our results suggest reduced neural efficiency or greater demand on the system and increased system sensitivity for processing vestibular information during HDBR. We conjecture similar neural changes may occur during environment changes that can cause body unloading and fluid shifts toward the head such as spaceflight.

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