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Bed rest impairs the vestibular control of balance

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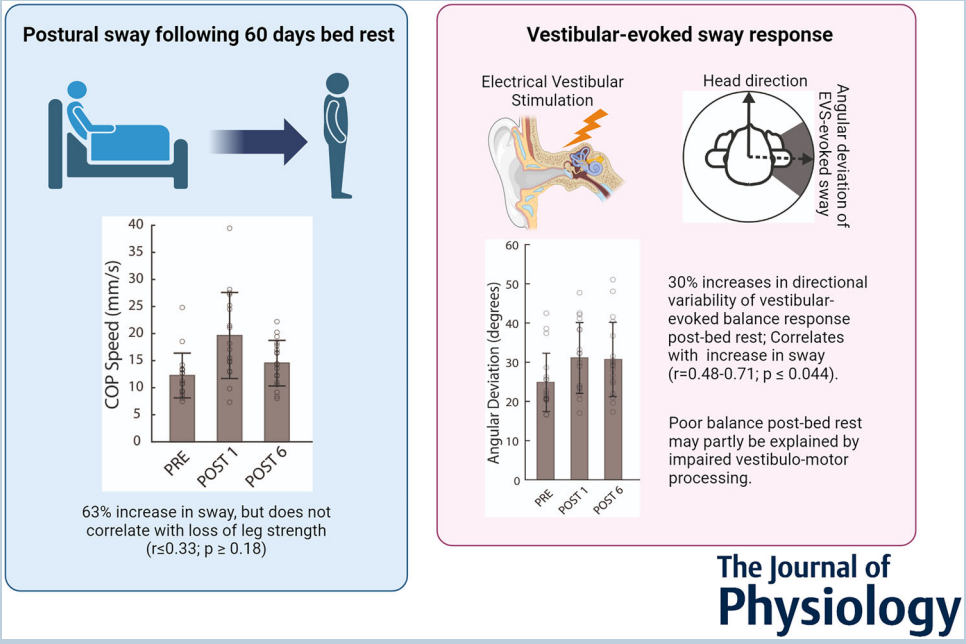

Abstract Prolonged bed rest impairs standing balance but the underlying mechanisms are uncertain. Previous research suggests strength loss is not the cause, leaving impaired sensorimotor control as an alternative. Here we examine vestibular control of posture in 18 male volunteers before and after 60 days of bed rest. Stochastic vestibular stimulation (SVS) was used to evoke sway responses before, 1 and 6 days after bed rest under different head yaw orientations. The directional accuracy and precision of these responses were calculated from ground reaction force vectors. Bed rest caused up to 63% increases in spontaneous standing sway and 31% reductions in leg strength, changes which were uncorrelated. The increase in sway was exacerbated when the eyes were closed. Mean directions of SVS-evoked sway responses were unaffected, being directed

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towards the anodal ear and rotating in line with head orientation in the same way before and after bed rest. However, individual trial analysis revealed 25%–30% increases in directional variability, which were significantly correlated with the increase in spontaneous sway ($r = 0.48$–0.71; $P \leq 0.044$) and were still elevated on day 6 post-bed rest. This reveals that individual sway responses may be inappropriately oriented, a finding masked by the averaging process. Our results confirm that impaired balance following prolonged bedrest is not related to loss of strength. Rather, they demonstrate that the sensorimotor transformation process which converts vestibular feedback into appropriately directed balance responses is impaired.

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Abstract figure legend Here we investigated impaired balance following prolonged bed rest. After spending 60 days undergoing 6 degrees head-down bed rest, volunteers exhibited a 63% increase in Centre of Pressure speed when subsequently attempting to stand still. This change in postural sway did not correlate with loss of leg muscle strength. However, when we used Electrical Vestibular Stimulation to evoke sway responses, we found increased variability in the direction of the evoked response following bed rest. Furthermore, this increase was significantly correlated with the increase in postural sway. These findings suggest the effect of bed rest upon postural control may partially be accounted for by impaired vestibulo-motor transformations for balance.

Key points

- Prolonged inactivity impairs balance but previous research suggests this is not caused by loss of strength.
- Here we investigated vestibular control of balance before and after 60 days of bed rest using electrical vestibular stimulation (EVS) to evoke sway responses.
- Spontaneous sway significantly increased and muscle strength reduced following bed rest, but, in keeping with previous research, these two effects were not correlated.
- While the overall accuracy of EVS-evoked sway responses was unaffected, their directional variability significantly increased following bed rest, and this was correlated with the increases in spontaneous sway.
- We have shown that the ability to transform head-centred vestibular feedback into an appropriately directed body sway response is negatively affected by prolonged inactivity; this may contribute to the impaired balance commonly observed following bed rest.

Introduction

Bed rest studies shed light on the physiological consequences of prolonged physical inactivity. They provide a model for the effects of microgravity upon astronauts (Hargens & Vico, 2016) and are useful for understanding the consequences of inactivity due to prolonged hospital stays (Brower, 2009). Perhaps most importantly for today's increasingly sedentary societies, they may help us understand the deleterious consequences of sustained inactivity in erstwhile healthy people. Numerous consequences of bed rest have been described, including loss of strength and muscle volume (Marusic et al., 2021), metabolic changes (Bergouignan et al., 2011), impaired cardiovascular function (Pavy-Le Traon et al., 2007), as well as impaired sensorimotor and cognitive function (Lipnicki et al., 2009).

Following cessation of bed rest, volunteers also exhibit poor balance (Haines, 1974). However, the increase in postural sway does not correlate with loss of leg strength (Sarabon & Rosker, 2013). Furthermore, resistance training countermeasures which successfully maintain lower limb strength do not influence balance or postural sway (Haines, 1974; Kouzaki et al., 2007). Conversely, stimuli aimed at improving sensory function may offer benefits (Muir et al., 2011). Hence, it seems unlikely that impaired balance following bedrest can be attributed to a loss of strength *per se*, which suggests altered sensorimotor function may play a role.

Vestibular information provides important sensory feedback for balance. Loss of vestibular input causes

increased postural sway and elevates the risk of falling (Kristinsdottir et al., 1997, 2001). It is therefore important to know if changes in vestibular function may partly underlie the postural consequences of bed rest. Attenuated vestibular–ocular reflexes have been observed immediately following 7 days' bed rest (Burgeat et al., 1981). However, research using head taps to activate the vestibular system has demonstrated *enhanced* brain responses (Yuan et al., 2018). It is an open question as to whether vestibular control of balance is affected by bed rest. Here we address this by studying vestibular-evoked balance responses before and after 60 days of bed rest.

Electrical vestibular stimulation (EVS) offers a repeatable and precise method for evoking sway responses in standing subjects (Mackenzie & Reynolds, 2018; Osler et al., 2013; Reynolds, 2010; Reynolds & Osler, 2012; Smith et al., 2017). EVS involves small currents applied to the mastoid process. It modulates vestibular nerve activity (Goldberg et al., 1984), resulting in a net signal of head roll towards the cathode electrode (Day & Fitzpatrick, 2005a,b; Fitzpatrick & Day, 2004). When standing, this evokes a compensatory sway response towards the anode electrode. This response is craniocentric, meaning that the direction of evoked sway rotates in line with head orientation (Lund & Broberg, 1983). Hence, EVS offers a unique method for investigating the efficacy with which the sensorimotor system can transform a specific pattern of vestibular feedback into an appropriately directed balance response.

Here we use a variant of EVS called stochastic vestibular stimulation (SVS). SVS involves a continuously time-varying current, randomised in both amplitude and direction. Response direction is measured by cross-correlating stimulus (SVS) and response (shear force) (Mian & Day, 2009). We have demonstrated that SVS can be used to study both the precision and the accuracy of vestibular-evoked sway responses (Mackenzie & Reynolds, 2018). Accuracy is determined by analysing the mean direction of the evoked sway response over a prolonged period of stimulation. Precision is determined by analysing the *variability* of response direction between separate shorter duration trials. Analysing precision is important from a functional perspective. This is because any transient error in transforming vestibular feedback into a balance response could potentially cause a loss of balance. But such error may be masked by the averaging process and may not be apparent in the overall accuracy of the response. Indeed, we have shown that changes in accuracy and precision are dissociable (Mackenzie & Reynolds, 2018). Here we use SVS to determine the precision and accuracy of vestibular control of balance before and after prolonged bed rest. We also determine whether these changes are related to postural stability and muscle strength.

Methods

Ethical approval

This research was conducted in accordance with the *Declaration of Helsinki*, except for registration in a database. All experiments were approved by the local ethics committee (CPP Sud-Ouest et Outre-Mer I, France, RCB: 2016-A00401-50). All participants gave written informed consent.

Participants

The study was conducted at The French Institute for Space Medicine and Physiology (MEDES) in Toulouse, France. Eighteen male participants aged 20–45 years (34 ± 9 years; mean ± SD) with no known neurological or vestibular disorders were included in the study. Participants were non-smokers with no alcohol or drug dependencies and were receiving no current medical treatment. Two participants were removed from an original cohort of 20, one due to poor adherence to the bed rest protocol, and one due an inability to stand to perform the experimental task following bed rest.

Apparatus

A Kistler 9281B force plate (Kistler Instrumente AG, Winterthur, Switzerland) was used to sample ground reaction forces at 1 kHz using an NI-PCI6229 data acquisition card (National Instruments, Austin, TX, USA). A Polhemus Fastrak sensor (Polhemus Inc., Colchester, VT, USA) attached to a welding helmet frame was used to sample head orientation at 50 Hz via the serial port. Any offset in yaw or roll angles between sensor and head orientation was measured using a second sensor attached to a stereotactic frame, and subsequently subtracted.

A Digitimer DS5 constant-current stimulator was used to deliver vestibular stimulation (Digitimer Ltd, Welwyn Garden City, UK) using carbon rubber electrodes (46 × 37 mm) in a bipolar binaural configuration. Electrodes were coated in conductive gel and secured to the mastoid processes using adhesive tape. The stochastic vestibular stimulus was generated by passing white noise through a low-pass filter (5 Hz; sixth order Butterworth) and then scaled to give a root-mean-square value of 0.6 mA, and a peak amplitude of ±2 mA. We selected a bandwidth of 0–5 Hz since the transfer of SVS signal power to force is clearest below 5 Hz (Dakin et al., 2007). An RMS amplitude of 0.6 mA was chosen to ensure a clear SVS–force cross-correlation for the calculation of response direction (Mian & Day, 2009), whilst not being uncomfortable for participants after the prolonged bed rest period.

All signals were sampled, output and synchronised using Simulink Desktop Real-Time software (The MathWorks, Natick, MA, USA).

Protocol

Bed rest intervention. Participants underwent 60 days of anti-orthostatic bed rest in a 6 degree head-down orientation. The European Space Agency (ESA) bed rest protocol was followed, where one shoulder had to be in contact with the bed at all times and no torso flexion or exercise was permitted. Immediately following bed rest participants were required to remain out of bed for 7 h per day, although this time could be seated. The measurements for the experiment reported here were performed at three time points: 9 days before commencement of bed rest (PRE), 24 h following the end of bed rest (POST-1), and 6 days following the end of bed rest (POST-6). For reference, the morning of day zero (POST-0) is when participants are first permitted to sit upright, stand and walk.

As part of the standard bed rest study procedure, half the participants ($n = 9$) underwent a 'counter-measure' intervention. This involved ingesting a cocktail of nutritional supplements consisting of the natural anti-oxidants XXS-2A (2 tablets 3 times a day, total 741 mg) alongside vitamin E and selenium (1 tablet a day; 180 mg vitamin E; 80 μg of selenium) in addition to omega-3 (1 tablet 3 times a day: 1.1 g eicosapentaenoic acid and 1 g docosahexaenoic acid). The supplementation was found to have no effect upon any of the parameters measured in the study reported here: spontaneous sway speed ($F_{(1,8)} = 0.39$, $P = 0.848$), spontaneous sway area ($F_{(1,8)} = 2.42$, $P = 0.158$), response precision ($F_{(1,8)} < 0.01$, $P = 0.991$), response gain ($F_{(1,8)} < 0.01$, $P = 0.972$), response accuracy ($F_{(1,8)} = 1.15$, $P = 0.315$), isometric knee torque ($F_{(1,8)} = 2.99$, $P = 0.122$) or isometric ankle torque ($F_{(1,8)} = 0.16$, $P = 0.702$). Therefore, all 18 participants from both cohorts (supplement and control) were combined for all analysis reported here.

Maximum voluntary contraction strength. As part of the overall MEDES bed rest protocol, maximal isometric voluntary contraction (MVC) was recorded for knee and ankle extensors and flexors using a Cybex dynamometer (Cybex, Ronkonkoma, NY, USA). This was performed before bed rest (PRE) and on the day of getting out of bed (POST-0). The dominant limb was tested with the participants in a seated position for knee MVC and prone for the ankle MVC, following Cybex user protocols. Participants performed a maximum extension contraction that lasted 5–7 s, followed by 30 s rest, then a flexion contraction. Three repeats of each contraction were completed. The mean of the three peak isometric joint torque values (in N m) was taken as the MVC.

Spontaneous sway and vestibular-evoked postural responses. Participants stood in the centre of a force plate, unshod, with feet parallel and placed 4 cm apart (instep to instep) with the hands held clasped together in front of them for the duration of each 40 s recording period.

The orientation of SVS-evoked sway responses is known to rotate in line with head orientation, demonstrating that head-centred vestibular information is transformed into body-centred coordinates for postural control (Lund & Broberg, 1983; Mian & Day, 2009). The purpose of our study was to determine if bed rest affects this transformation process. We therefore asked participants to adopt one of three head orientations during stimulation trials, facing visual targets oriented at −45, 0 and +45 degrees, all located at eye level at a distance of 1 m. At the beginning of each trial participants adopted the required head orientation with their eyes open. They were guided by the experimenter who could see head yaw angle in real time. A slight head-up pitch position was maintained throughout each trial to ensure that Reid's plane (the line between inferior orbit and external auditory meatus) was ∼15–20 degrees above horizontal. This ensured that the SVS-evoked rotation vector was approximately horizontal (Day & Fitzpatrick, 2005b; Osler & Reynolds, 2012), ensuring the largest postural response. Once the correct head orientation was achieved, the eyes were then kept open for half the trials and closed for the other half. This resulted in six stimulation conditions (3 head orientations × 2 visual conditions). To measure spontaneous sway, participants stood facing forward, with the eyes either open or closed, in the absence of vestibular stimulation (2 conditions). Spontaneous sway and vestibular stimulation trials were interspersed, leading to a total of eight conditions. Each condition was repeated 5 times leading to a total of 40 trials. Trial order was randomised and participants were allowed seated rest between trials.

Data analysis

Ground reaction force data were used to calculate centre of pressure (CoP), from which mean CoP speed and CoP area were derived. Area was calculated by fitting a 95% confidence ellipse to CoP data.

Directional analysis of SVS-evoked sway responses was performed using a method adapted from and previously described in Mian and Day (2009). Our method is based upon the cross-correlation (CC) function, which tracks the relationship between two time-series as a function of the delay between them. The larger the similarity between two signals, the greater the CC value. Here we performed raw non-normalised CCs between SVS stimuli and shear forces using the 'xcorr' function in MATLAB (see Fig. 4 for example).

The SVS–force CC was calculated separately for each shear force vector corresponding to every degree of a circle (±180). Each rotated force vector ($F_{ROT\Theta}$) was calculated from lateral (F_x) and anterio-posterior (F_y) forces as follows:

$$F_{ROT\theta}\ (s) = F_x\ (s) \times \cos\theta + F_y\,(s) \times \sin\theta$$

SVS-evoked force responses consist of a small early and brief response, termed the short-latency (SL) response, followed by a larger, longer response in the opposite direction, termed the medium-latency (ML) response. The ML response is primarily responsible for the evoked body sway. To determine response direction we measured the peak absolute value of the CC ML response within the range 225–500 ms. The force vector resulting in the largest peak CC value determined the response direction in force platform coordinates. Mean angular direction was referenced to head orientation for each trial, prior to calculating mean direction and angular deviation. This was done by subtracting the mean head angle for that trial. For example, if the head was oriented leftward by 30 degrees, then a sway response direction of −90 degrees in force platform coordinates would become −120 in head coordinates. Referencing to head orientation in this way prevented any trial-by-trial variability in head orientation producing spurious changes in response direction precision. Precision was measured using angular deviation, which is the equivalent of standard deviation for circular data. Each 40 s recording period was split into two 20 s segments, providing a total of 10 segments per condition for each subject. This provided 10 values of response direction from which a variability could be calculated. Angular deviation and mean angular direction were calculated using the circular statistics toolbox for MATLAB (Berens, 2009).

To determine the gain of the vestibular-evoked sway response we calculated the transfer function between the SVS signal and the force vector which corresponded to the response direction. This was done using the 'tfestimate' function in MATLAB, which calculates the ratio between the SVS–force cross-power spectral density and the SVS autospectrum, using Welch's periodogram method. The mean absolute value of the transfer function was then calculated between 0 and 5 Hz to provide a measure of gain.

Response latencies were measured as the time of the peak CC responses between 0 and 225 ms for SL responses, and 225–500 ms for ML responses.

To determine the extent of any head position drift throughout the course of each 40 s trial, we applied a linear fit to the head yaw angle time series and calculated the difference between the beginning and end of each trial. Signed and unsigned drift was then recorded, to determine directional and absolute drift, respectively.

Repeated-measures ANOVA was used to test for effects of vision (eyes open, EO; eyes closed, EC), head orientation (−45, 0 and +45) and time point (PRE, POST-1, POST-6). Following a significant main effect or interaction, pairwise tests were performed using the Tukey correction for multiple comparisons. To examine relationships between variables we used Pearson's correlation, except where data were not normally distributed in which case we applied Spearman's rank correlation. $P \leq 0.05$ was considered significant for all tests. All error bars displayed in graphs represent ±1 standard deviation.

Results

Strength

Bed rest produced considerable reductions in leg strength, which were more pronounced for the extensor muscles. Maximum voluntary contraction torque is shown in Fig. 1. For both knee and ankle MVC there were significant main effects of time point (PRE *vs.* POST-0; $F_{(1,17)} \geq 87$,

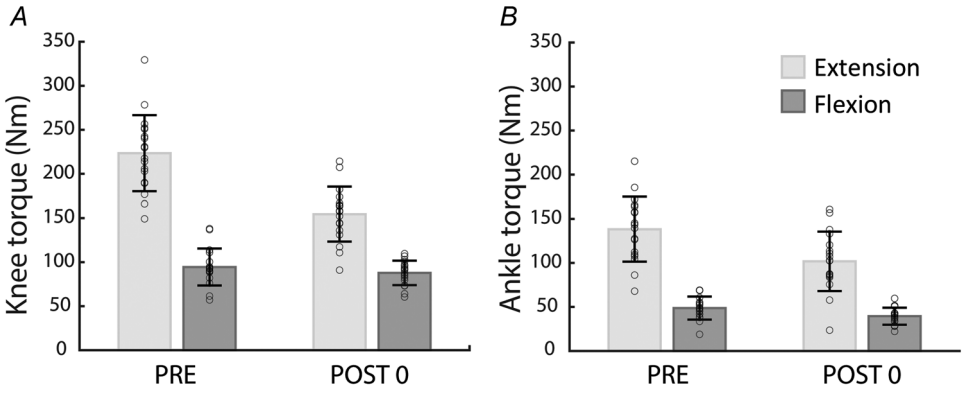

Figure 1. Strength
Maximum isometric voluntary contractile force for the knee (*A*) and ankle (*B*), measured 11 days prior to bed rest (PRE) and on the day of getting out of bed (POST-0). $n = 18$.

$P < 0.001$) and contraction type (flexion *vs.* extension; $F_{(1,17)} \geq 121$, $P < 0.001$), as well as significant interactions between these two factors ($F_{(1,17)} \geq 48$, $P < 0.001$). *Post hoc* comparisons reveal a significant reduction in knee extensor torque between PRE and POST-0 (30.5% reduction; $P < 0.001$), but no difference in flexor torque ($P = 0.225$). For the ankle, both extensor and flexor torque exhibited a significant reduction between PRE and POST-0 (27.0% and 16.0% reduction, respectively; $P < 0.001$ for both comparisons).

Spontaneous sway

Bed rest resulted in significant increases in postural sway in the absence of vestibular stimulation, an effect which was exacerbated by closing the eyes. CoP speed is depicted in Fig. 2*A*. There was a significant interaction between visual condition and time point due to a greater effect of bed rest with the eyes closed ($F_{(2,34)} = 18.8$, $P < 0.001$). There were also significant main effects of both vision ($F_{(1,17)} = 74.4$, $P < 0.001$) and time point ($F_{(2,34)} = 19.4$, $P < 0.001$). Pairwise comparisons revealed that CoP speed increased between PRE and POST-1 for both eyes-open (EO) and eyes-closed (EC) conditions (increase of 63.1% EC and 49.8% EO; $P \leq 0.004$; Tukey *post hoc* comparison). By POST-6, CoP speed was not significantly different from PRE, for either EC or EO ($P = 0.0862$).

CoP area is depicted in Fig. 2*B*. There was a significant interaction between visual condition and time point ($F_{(2,34)} = 6.45$, $P = 0.004$) as well as significant main effects of both vision ($F_{(1,17)} = 41.9$, $P < 0.001$) and time point ($F_{(2,34)} = 3.8$, $P = 0.0322$). Pairwise comparisons reveal that EC CoP area significantly increased from PRE to POST-1 by 53% ($P = 0.0116$). By POST-6 it was not significantly different from PRE ($P = 0.710$). For the EO condition there were no significant changes associated with bed rest ($P \approx 1$ for all comparisons).

Head position

Mean head yaw angles can be seen in Fig. 3. As expected, there was a significant effect of requested head orientation upon *actual* head orientation ($F_{1,17} = 2497$; $P < 0.001$). Actual head angles slightly undershot the 45 degree targets (mean ± SD: Left: 38.0 ± 3.6°; Forward: 0.12 ± 2.4°; Right: −37.0 ± 4.2°). There was no effect of time point, indicating that bed rest did not influence mean head position ($F_{2,34} = 2.2$; $P = 0.125$). There was, however, a significant effect of vision, caused by a very slight leftward bias with the eyes open (overall mean with eyes open: 1.1 ± 2.4°; eyes closed: −0.036 ± 2.6°; $F_{1,17} = 14.3$; $P = 0.001$).

In addition to mean head angle, we assessed the degree of head drift across the duration of each trial. This revealed a slight tendency for the head to drift back towards the forward position during both head-left and head-right conditions by up to 2° over 40 s (main effect of head position upon signed drift: $F_{(2,34)} = 8.0$; $P = 0.001$). This effect was greater with the eyes closed (vision–head interaction: $F_{(2,34)} = 3.3$; $P = 0.0496$). There was no effect of time point upon signed head drift, indicating that bed rest did not cause any directional bias in the extent of head drift ($F_{(2,34)} = 0.25$; $P = 0.765$).

Absolute (unsigned) drift was 1.92 ± 0.66° (mean of all conditions). It was greater with the eyes closed (EC: 2.45 ± 0.95°; EO: 1.52 ± 0.56°; main effect of vision: $F_{(1,17)} = 23.6$; $P < 0.001$), and with the head left or right (Left: 2.50 ± 1.0°; Forward: 1.22 ± 0.46°; Right: 2.23 ± 1.0°; main effect of head position: $F_{(1,17)} = 16.4$; $P < 0.001$). There was also a significant effect of time point ($F_{(2,34)} = 6.0$; $P = 0.00466$), due to an increased absolute drift following bed rest by up to 1.12° (PRE *vs.* POST-1). This increase was significantly less with the eyes open (vision–time point interaction: $F_{(2,34)} = 3.5$; $P = 0.0419$). For example, during the head-forward, eyes open condition, there was effectively no additional drift associated with bed rest (0.02° difference between PRE and POST-1)

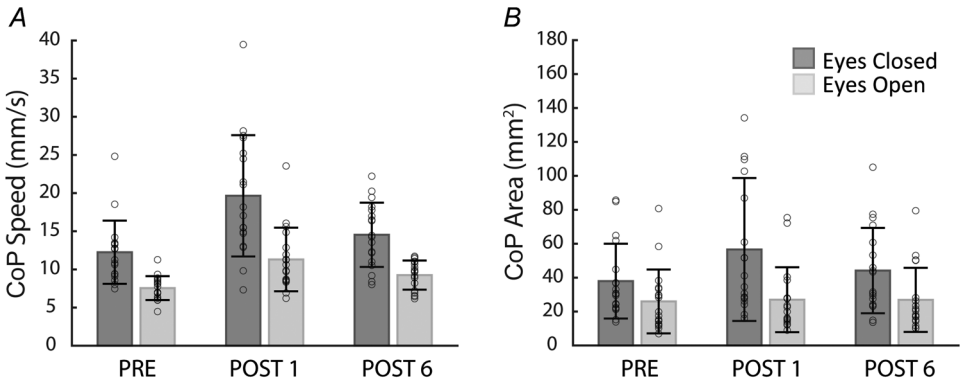

Figure 2. Effect of bed rest upon spontaneous sway
A, centre of pressure speed. *B*, sway area, as determined by the area of a fitted ellipse encompassing 95% of CoP position data. $n = 18$.

Overall, therefore, bed rest very slightly increased the tendency for the head to drift, especially with the eyes closed and with the head left or right, but not in a specific direction.

Vestibular-evoked postural responses

Figure 4 shows representative cross-correlations between the SVS stimulus and shear force, for a trial with the head facing forward during the PRE condition. The response is oriented predominantly in the medio-lateral direction and is approximately double with the eyes closed compared to open.

The direction of the evoked sway response was determined by finding the direction of the force vector which exhibited the greatest cross-correlation with the SVS stimulus (Mian & Day, 2009). The effect of head orientation on the direction of the evoked response is depicted in Fig. 3. For all conditions, the mean force response (dashed arrow) is directed approximately 90 degrees to head orientation (solid arrow). Rotation of the head resulted in the rotation of the force vector by a similar amount, producing a craniocentric response pattern. The direction of the mean force response was used to determine response accuracy, while the analysis of individual 20 s segment directions was used to calculate response precision. This variability is depicted by the shaded region in Fig. 3, which shows angular deviation (the equivalent of standard deviation for circular data).

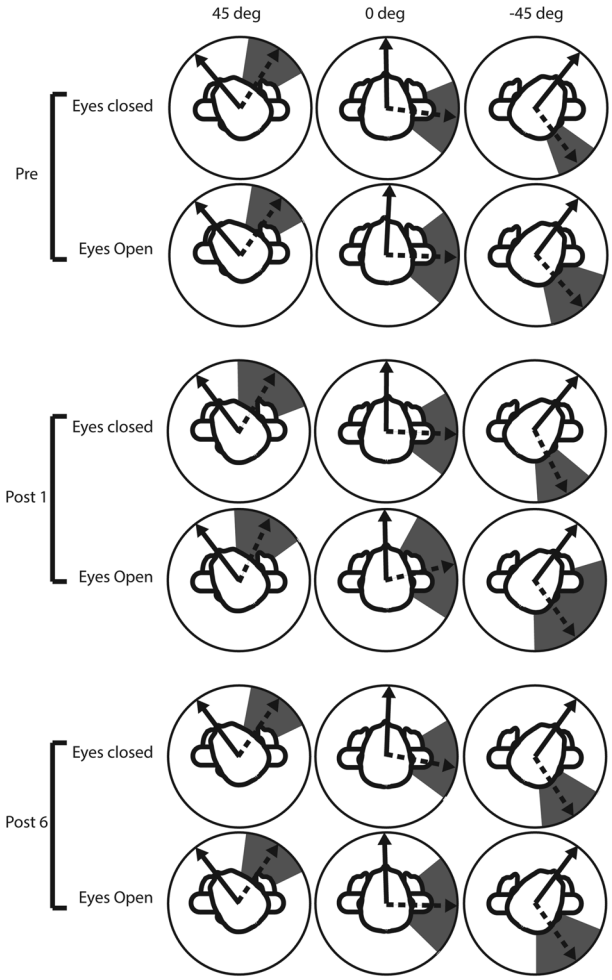

Figure 3. Direction of SVS-evoked force vectors
Group mean head orientation and evoked force directions are shown by the continuous and dashed arrows, respectively. This response rotated in line with head orientation. The average within-subject variability is represented by the grey shaded region showing ±1 angular deviation. n = 18.

Accuracy. The relationship between head orientation and sway response direction was similar for all conditions, as shown in Fig. 5. For graphical purposes 90 degrees has been added to all sway direction values in this figure only. This means that if the sway response is perfectly orthogonal to head orientation, it should conform to the line of unity (long dashed line). However, with the head left or right, response direction rotated by approximately 20 degrees more than head orientation.

To analyse the data further we referenced sway direction to head orientation (instead of laboratory orientation). Head-referenced data are presented in Fig. 6 and exhibit a significant effect of head orientation (see Fig. 6*A*; $F_{2,34} = 65.2$; $P < 0.001$). This confirms that sway direction does not rotate perfectly in line with the head but slightly overshoots head orientation by 21 ± 14 and 17 ± 11 degrees when the head is oriented leftward or rightward, respectively. There was also a significant effect of vision due to a slight leftward bias with the eyes open ($F_{2,34} = 5.5$; $P = 0.0314$). However, there was no significant effect of time point, indicating that bed rest had no effect upon response accuracy ($F_{2,34} = 1.6$; $P = 0.214$).

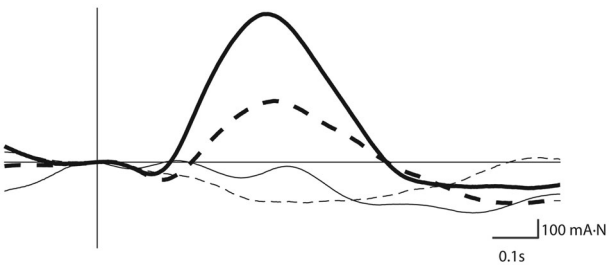

Figure 4. Postural responses to vestibular stimulation
Traces depict cross-correlations between stochastic vestibular stimuli and shear forces for individual trials with the head facing forwards. Conditions depicted are: eyes open (dashed) and eyes closed (continuous); anterior–posterior force (thin) and medio-lateral force (thick). Mean head angles during these trials were 0.72 degrees (EC) and −2.5 degrees (EO). The vertical line depicts a lag of zero. n = 1.

Precision. Unlike accuracy, bed rest significantly affected the precision of vestibular-evoked sway responses. Angular deviation (AD) reflects variability and therefore precision of the sway response to SVS. AD was larger with the eyes open, *versus* closed (Fig. 7; main effect of vision: $F_{(1,17)} = 35.7$, $P < 0.001$). AD was also larger when facing forwards, compared to head-left or right (main effect of head orientation: $F_{(2,34)} = 16.3$, $P < 0.001$). There was an interaction between vision and head orientation, due to a larger effect of head orientation with the eyes open ($F_{(2,34)} = 6.65$, $P = 0.004$). There was also a main effect of time, indicating that bed rest had a significant effect ($F_{(2,34)} = 4.23$, $P = 0.0228$). *Post hoc* corrected tests revealed a significant increase in AD between PRE and POST-1 ($P = 0.0498$), of 25% and 30% for eyes open and closed, respectively. There was no significant change between POST-1 and POST-6 ($P = 0.700$).

Since we observed a significant effect of bed rest upon absolute head drift, it is possible that this could be causally related to the changes in angular deviation. We therefore calculated the percentage change in both parameters between PRE and POST-1, and then calculated the Pearson correlation between these two percentage changes. This revealed no significant correlation (EO: $r = 0.14$; $P = 0.586$; EC: $r = -0.27$; $P = 0.275$), suggesting that the changes in angular deviation are not associated with changes in head drift.

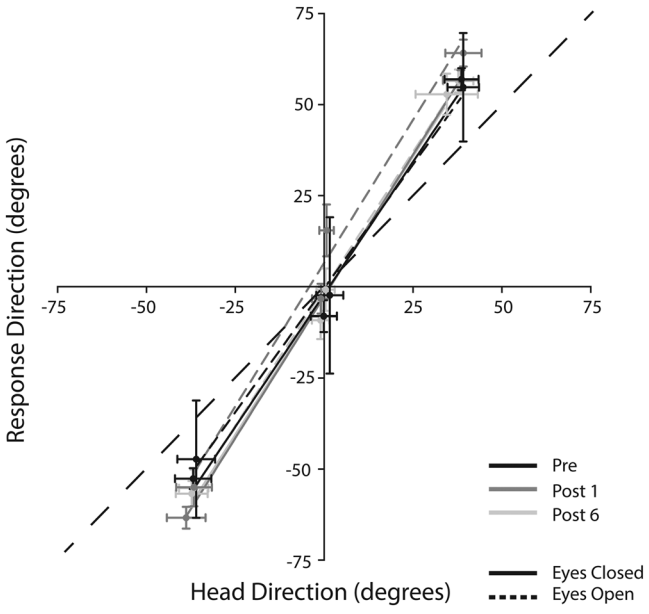

Figure 5. Relationship between head and sway response direction
Mean head orientation is plotted against the direction of the mean evoked force vector for all time points and visual conditions. For graphical purposes only, 90 degrees has been added to all response direction values. This means that if head and sway direction are perfectly orthogonal the data should conform to the line of unity (long-dashed line). n = 18.

Gain. Mean SVS–force gain calculated between 0 and 5 Hz is presented in Fig. 8. Gain was significantly lower when the eyes were open *versus* closed (main effect of vision: $F_{(1,17)} = 69.1$, $P < 0.001$). It was also smaller with the head forwards, compared to head left or right (main effect of head orientation: $F_{(2,34)} = 6.16$, $P = 0.00521$). There was a significant effect of time ($F_{(2,34)} = 13.66$, $P < 0.001$). *Post hoc* comparisons revealed that gain increased from PRE to POST-1 (50% and 53% increase for eyes open and closed, respectively; $P = 0.00394$) and reduced from POST-1 to POST-6 ($P = 0.00430$).

Latency. Overall mean SVS–force CC response latencies were 137 ± 12 ms and 354 ± 42 ms for short- and medium-latency responses, respectively (mean ± 1 SD). There was no significant main effect of time point ($F_{(2,34)} = 2.4$, $P = 0.106$), nor any interaction ($F_{(2,34)} \leq 1.6$, $P \geq 0.219$) indicating that response latencies were not influenced by bed rest. There was, however, a significant main effect of vision ($F_{(2,34)} = 19.53$, $P < 0.001$) due to peak responses occurring slightly later with the eyes open (SL – EC: 133 ± 10 ms, SL – EO: 142 ± 16 ms; ML – EC: 341 ± 36 ms, ML – EO: 367 ± 50 ms).

Relationship between spontaneous sway and other parameters affected by bed rest

Bed rest caused a significant worsening of balance as shown by the increase in CoP speed and CoP area described above. We sought to determine if these increases were associated with changes in other parameters which also exhibited significant changes due to bed rest. We therefore calculated the percentage change in CoP speed and area between PRE and POST-1, and compared this to both strength changes and changes in SVS response parameters, as well as absolute head drift (Table 1).

There were no significant correlations between changes in strength and CoP speed ($P \geq 0.178$). In contrast, changes in SVS–force gain were strongly positively correlated with CoP speed changes ($P < 0.001$). SVS angular deviation values were also significantly positively correlated with CoP speed and area changes ($P \leq 0.0445$), except for CoP area with eyes open ($P = 0.509$).

Discussion

The directional variability of vestibular-evoked balance responses significantly increased following 60 days of bed rest. Vestibulo-spinal reflexes are intended to produce corrective sway responses in the event of an unintended loss of balance. This requires a sensorimotor transformation process in which head-centred sensory information is transformed into body-centred balance responses. Our results suggest that this transformation

process has been compromised by a prolonged period of inactivity. This may partially explain the loss of balance following bed rest.

In addition to changes in vestibular-evoked sway, bed rest caused significant increases in spontaneous sway. This effect was exacerbated by closing the eyes, with bed rest causing a 50% and 63% increase in CoP speed with the eyes open and closed, respectively. CoP area showed no significant change with the eyes open but increased by 53% with the eyes closed. Hence, the negative influence of prolonged inactivity on spontaneous sway is greater when relying upon non-visual sensory feedback for balance. This suggests bed rest primarily affects proprioceptive and/or vestibular control mechanisms. Research in older adults shows the effect of eye closure upon sway is disproportionately greater in subjects who are physically weaker (Butler et al., 2008). This suggests proprioceptive control of standing is compromised by loss of muscle strength. We observed a significant reduction in leg muscle strength primarily affecting the extensor muscles, as reported by others (Marusic et al., 2021; Sarabon & Rosker, 2013). However, we observed no correlation between changes in strength and changes in postural sway, with or without vision. This lack of relationship tallies with the findings of Sarabon and Rosker (2013) who found no correlation between loss of ankle strength and changes in RMS CoP following 14 days bed rest in males aged 55–65. In a countermeasure study, Kouzaki et al. (2007) studied 12 young men before and after 20 days' bed rest. Half of them underwent strength training exercises during the bed rest period, which successfully maintained their lower leg strength and muscle volume. Despite this, both the trained and untrained groups exhibited the same increase in postural sway after bed rest. Taken in the context of previous research, our data confirm that the increase in spontaneous sway following bed rest is not primarily caused by a loss of strength. This suggests sensorimotor control mechanisms are affected instead.

There were no changes in the overall accuracy of the vestibular-evoked balance response due to bed rest. Before and after the 60-day period, sway responses were oriented approximately along the inter-aural axis (see Fig. 3). This is consistent with the known effects of EVS, which activates all afferents (Goldberg et al., 1984) to cause a net signal of head roll towards the cathodal ear and a compensatory sway response towards the anodal ear (Day & Fitzpatrick, 2005b; Fitzpatrick & Day, 2004; Lund & Broberg, 1983). We did observe that when the head was turned left or right, the sway response did not rotate quite by the same amount, overshooting by ∼20 degrees (see Figs 5 and 6). This phenomenon has been previously described as a consequence of non-zero

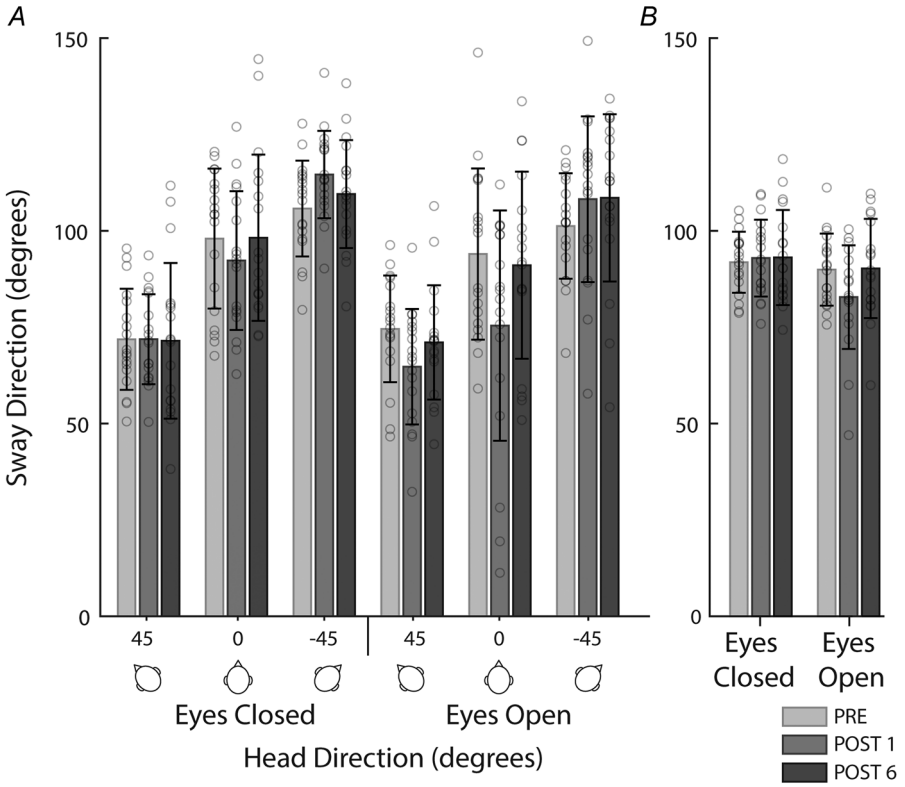

Figure 6. Head-referenced sway response direction
A, mean SVS-evoked sway direction. *B*, the same data averaged across head directions. n = 18.

stance widths producing differing levels of spontaneous postural sway along different directions (Mian & Day, 2014). The 4 cm stance width adopted here would explain this non-linearity, since it preferentially reduces sway in the medio-lateral direction (compared to feet together). Nevertheless, the absence of any time-dependent changes in response accuracy confirms that bed rest did not introduce any directional bias into the vestibulo-motor transformation process. All subjects were still capable of transforming vestibular feedback into an appropriately directed balance response, at least in terms of the *average* direction recorded over multiple trials.

In contrast to accuracy, bed rest reduced the precision of vestibular-evoked balance responses, as shown by an increase in directional variability. To measure variability, we analysed response directions obtained from separate 20 s segments and calculated the angular deviation (AD) of these multiple values. AD increased by up to 30% between PRE and POST-1. We have previously demonstrated that removing vision has no effect upon the directional accuracy of SVS responses but does paradoxically increase their precision (Mackenzie & Reynolds, 2018). Here we show a dissociation between accuracy and precision caused by bed rest, but in the opposite direction. These changes in variability are functionally important for balance. The vestibular apparatus signals the direction of head motion. This information must first be transformed into body coordinates if an appropriate balance response is to be generated, and a fall prevented. This requires a good sense of head orientation. For example, depending upon whether the head is facing forwards or turned, the same pattern of vestibular feedback will require a compensatory sway response in a different direction. Any error in this vestibulo-motor coordinate transformation process will lead to an inappropriate sway response, potentially threatening balance (Dalton et al., 2016; Gurfinkel et al., 1989; Reynolds, 2017). An accurately directed response *on average* is of little consolation if an inappropriately directed response at any given instant results in a fall. Therefore the increased directional variability caused by bed rest may have functionally important consequences for balance. Indeed, we observed a significant correlation between the bed rest-induced increases in spontaneous sway and the increase in SVS response variability. Although this does not prove causality, it is consistent with changes in vestibular control of posture being responsible for impaired balance following prolonged inactivity.

Participants exhibited a greater tendency for head position to drift after bed rest. This did not occur in any specific direction and mean head orientation was unaffected. Nevertheless, this additional drift could potentially explain the increased response angular

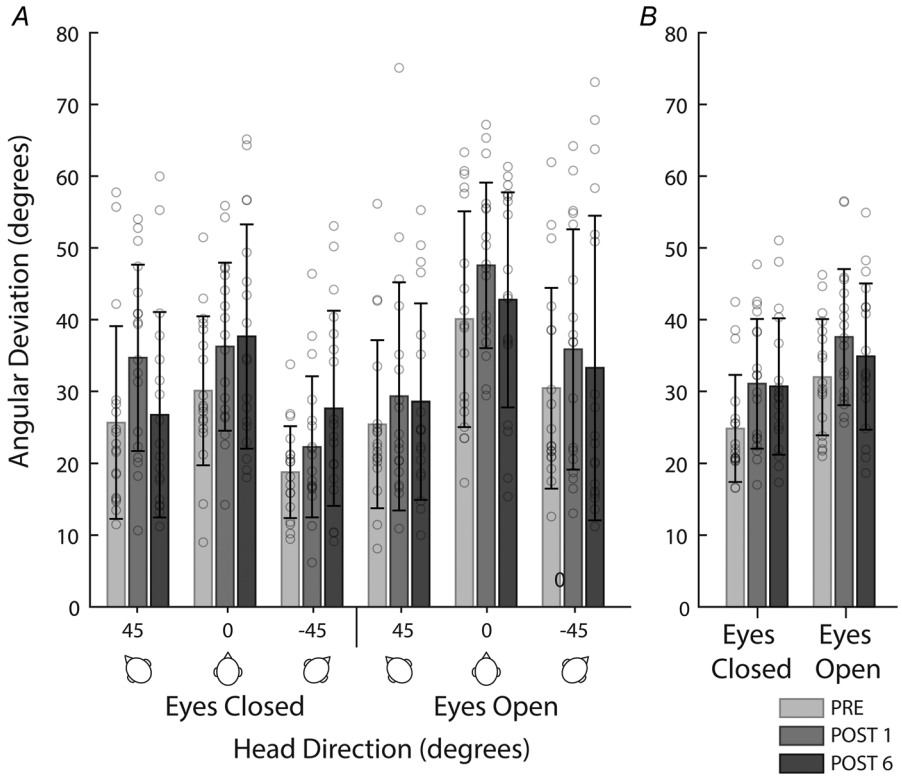

Figure 7. Sway response precision
A, the angular deviation of SVS-evoked sway responses (equivalent to standard deviation), representing the variability of response direction. *B*, the same data averaged across head directions. n = 18.

deviation after bed rest. This seems unlikely for the following reasons. Firstly, the increase in drift was small (∼1°). Secondly, all sway and angular deviation values were referenced to head angle for each trial. Third, during the condition when the eyes were open and the head faced forwards there was no change in drift, and yet angular deviation did increase. Lastly and crucially, we found no correlation between percentage changes in head drift and changes in angular deviation before and after bed rest.

We found a 42%–63% increase in SVS response gain following bed rest which was strongly correlated to changes in spontaneous sway (r = 0.57–0.97). Scaling of vestibular-evoked balance responses with spontaneous sway has previously been reported, whereby the amplitude of an EVS-evoked sway response is proportional to the amplitude of body sway recorded immediately before the stimulus (Day et al., 1997; Mian & Day, 2014; Pastor et al., 1993). In our case, spontaneous sway was measured at separate times from vestibular stimulation trials, confirming that the observed correlation was not confounded by simultaneous measurement. The strong correlation suggests that the increased response gain is not necessarily caused by a general increase in vestibular gain due to bed rest; previously reported reductions in vestibular–ocular reflex gain suggests bed rest may actually cause a *down*-weighting of vestibular input (Burgeat et al., 1981). Rather, the increased SVS response gain may be secondary to the increase in spontaneous sway. However, the two explanations are not mutually exclusive, i.e. changes in SVS response gain might occur independently of spontaneous sway.

Our previous research identified a relationship between the gain and precision of SVS-evoked balance responses (Mackenzie & Reynolds, 2018). We measured the directional error in each trial in terms of its difference from the mean response direction and compared this with SVS–force gain. As gain increased, error tended to reduce. In other words, response precision improved with increasing gain. This helped to explain why opening the eyes caused a paradoxical *reduction* in response precision, because it also reduced response gain. We interpreted this as a sensory weighting phenomenon; as additional veridical sensory information becomes available the relative contribution of vestibular input is reduced, causing a simultaneous reduction in both the gain and precision of the SVS response. In the current

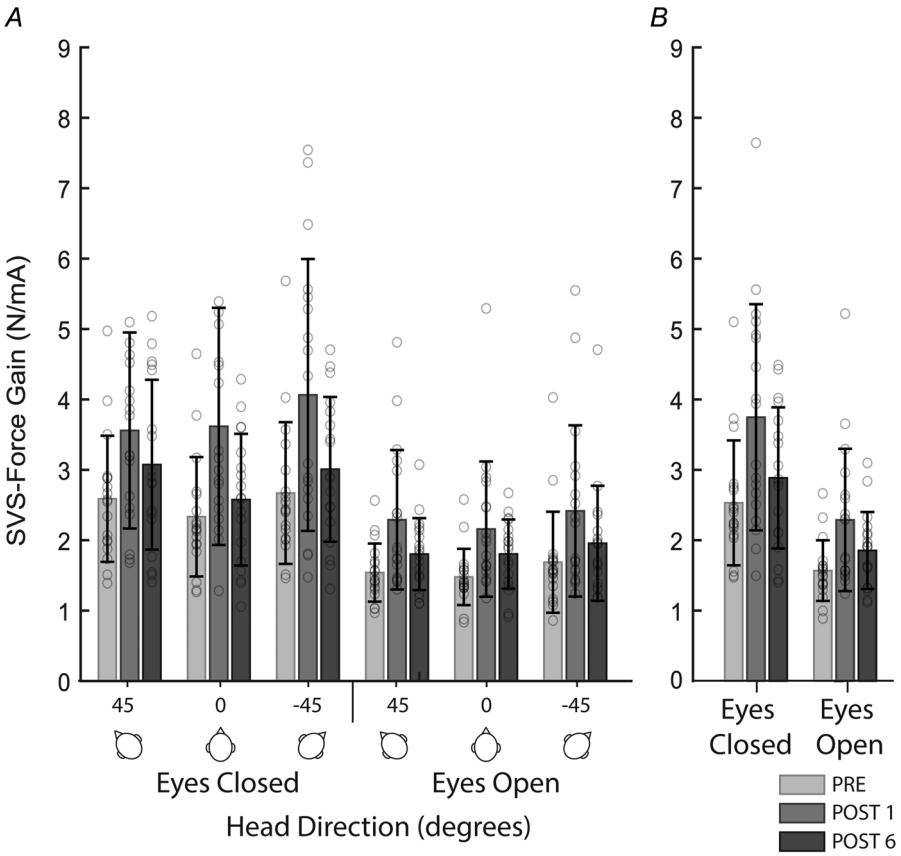

Figure 8. SVS–force gain
A, mean SVS–force gain values between 0 and 5 Hz. *B*, shows the same data averaged across head directions. n = 18.

Table 1. Correlations with spontaneous sway

	Eyes open		Eyes closed	
	CoP speed	CoP area	CoP speed	CoP area
MVC ankle flexors	−0.20 (0.433)	−0.16 (0.514)	−0.13 (0.623)	−0.066 (0.796)
MVC ankle extensors	−0.049 (0.848)	−0.16 (0.552)	−0.072 (0.775)	−0.029 (0.909)
MVC knee extensors	−0.33 (0.178)	−0.093 (0.713)	−0.22 (0.377)	−0.11 (0.668)
Absolute head drift	**0.52 (0.0271)**	0.38 (0.124)	0.38 (0.119)	0.39 (0.114)
SVS–force gain	**0.87 (<0.001)**	**0.57 (0.0129)**	**0.97 (<0.001)**	**0.86 (<0.001)**
Angular deviation	**0.71 (<0.001)**	0.17 (0.509)	**0.48 (0.0445)**	**0.48 (0.0421)**

Correlations were performed between percentage changes in CoP speed/area caused by bed rest (PRE *vs*. POST-1) *versus* percentage change in other parameters exhibiting significant changes after bed rest. Pearson *r* values are shown alongside *P* values in brackets. Equivalent vision conditions were compared, e.g. Angular Deviation during the eyes closed condition was correlated with CoP speed with the eyes closed. $n = 18$. Bold values denote $P \leq 0.05$. MVC, maximum voluntary contraction; SVS, stochastic vestibular stimulation.

study we observed an increase in gain between PRE and POST-1, but unlike the effect of vision reported by Mackenzie and Reynolds (2018), this was accompanied by a *reduction* in mean precision. Nevertheless, when we analysed within-subject directional error, we did observe a tendency for this to increase with response magnitude, in agreement with Mackenzie and Reynolds (2018) (significant correlation in 12 of 18 subjects). Hence, the extent of the bed rest-evoked reduction in precision may be partially masked by the increase in response gain.

What is the physiological mechanism underlying the impaired vestibular control of balance? We cannot rule out that it is secondary to orthostatic intolerance or altered cardiovascular function. A lack of brain perfusion could impair any sensorimotor process. However, given that we studied volunteers a full 24 h after they had arisen from bed, this is unlikely to have been a problem. No subject fainted or reported dizziness, and all were allowed regular seated rests in between trials (in one subject who could not stand this was due to muscle spasms). It is possible that peripheral transduction and/or central transmission of vestibular signals was noisier after bed rest. However, as discussed above, vestibular-evoked balance responses require a coordinate transformation of head-centred vestibular input into body-centred motor output. This depends not only upon vestibular transduction but also accurate proprioceptive signals. Muscle spindles are a primary source of proprioception, and the accuracy of spindle input is strongly linked to the mechanical state of the surrounding extrafusal muscle (Proske & Gandevia, 2012). Given the clear impact of bed rest upon muscle volume and strength it is therefore likely that proprioceptive signals were degraded (Bernauer et al., 1994; Weber & Proske, 2022). This would affect utilisation of vestibular input for balance even if the transduction properties of the vestibular apparatus itself were unaffected. However, if this *was* caused by a loss of proprioceptive acuity which, in turn, is related to muscle strength, then we might have expected strength changes to correlate with the SVS response precision. But we did not observe any such correlation (not reported). Nevertheless, two other observations *were* consistent with proprioceptive degradation. Firstly, participants' ability to hold their head position steadily during each trial was reduced when their eyes were closed suggesting impaired head-on-body sensation following bed rest. However, this did not correlate with changes in angular deviation, suggesting it was not primarily responsible for the observed impairment in SVS response precision. Secondly, we saw considerable increases SVS-evoked response gain. Patients with profound somatosensory loss also exhibit markedly increased vestibular-evoked postural responses (Blouin et al., 2007; Day & Cole, 2002), suggesting the observed gain change may reflect increased weighting on vestibular information when proprioception is compromised. So, in summary, it seem likely that our participants experienced some degree of proprioceptive degradation, but the extent to which this explains the changes in vestibular control of balance is uncertain.

Another possibility is that central neural processing is affected by bed rest. Previous work suggests suppression of both somatosensory signals and motor output, as well as impaired motor prediction, following limb immobilisation (Gueugneau et al., 2015; Huber et al., 2006). This suggests all aspects of the sensorimotor process may be affected by inactivity. The coordinate transformation process converting head-centred vestibular input into body-centred balance responses requires integration of vestibular and proprioceptive signals with motor output, a relatively complex process which may depend upon the cerebellum (Cullen, 2019). It is conceivable that this integration may have been compromised after a period of non-use, leading to a noisier transformation process.

One limitation of our study was waiting 24 h after volunteers arose from their beds before studying them (i.e.

day POST-1 rather than POST-0). This was a necessary compromise since we had limited access to the volunteers and, to avoid dropout, had to choose a time point when they were capable of standing unaided for minutes with minimal orthostatic intolerance. Nevertheless, during the 24 h period they were free to stand and walk as desired. Hence, a considerable amount of functional recovery likely occurred within this time window which may have masked the true extent of physiological changes.

In summary, we have shown that a prolonged period of bed rest reduces the directional precision of vestibular-evoked balance responses. The change in precision was correlated to increases in spontaneous postural sway, suggesting that changes in vestibular control of posture may contribute to the loss of balance commonly observed following bed rest.

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Additional information

Data availability statement

All data presented in this manuscript are included within the figures.

Competing interests

The authors declare no conflicts of interest.

Author contributions

R.F.R. and B.L.D. conceptualised and designed the experiments. S.W.M., C.P.S., M.F.T., R.F.R., and B.L.D. performed the experiments. S.W.M. and R.F.R. analysed the data. S.W.M., R.F.R., and B.L.D. interpreted the results of the experiments. S.W.M. and R.F.R. prepared figures and wrote the first draft of the manuscript. R.F.R. and B.L.D. revised the final version of the manuscript. All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify are listed.

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Keywords

accuracy, bed rest, electrical vestibular stimulation, precision, proprioceptive acuity

Supporting information

Additional supporting information can be found online in the Supporting Information section at the end of the HTML view of the article. Supporting information files available:

Peer Review History