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Upper body balance control strategy during continuous 3D postural perturbation in young adults

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ABSTRACT

We explored how changes in vision and perturbation frequency impacted upright postural control in healthy adults exposed to continuous multiaxial support-surface perturbation. Ten subjects were asked to maintain equilibrium in standing stance with eyes open (EO) and eyes closed (EC) during sinusoidal 3D rotations at 0.25 (L) and 0.50 Hz (H). We measured upper-body kinematics – head, trunk, and pelvis – and analyzed differences in horizontal displacements and roll, pitch, and yaw sways. The presence of vision significantly decreased upper-body displacements in the horizontal plane, especially at the head level, while in EC the head was the most unstable segment. H trials produced a greater segment stabilization compared to L ones in EO and EC. Analysis of sways showed that in EO participants stabilized their posture by reducing the variability of trunk angles; in H trials a sway decrease for the examined segments was observed in the yaw plane and, for the pelvis only, in the pitch plane. Our results suggest that, during continuous multiaxial perturbations, visual information induced: (i) in L condition, a compensation for the ongoing perturbation. These findings were not confirmed in EC where the same strategy – that is, the use of the pelvis as a reference frame for the body balance was adopted both in L and H.

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1. Introduction

Posturography is used to assess balance control deterioration due to age, trauma and disease [1]. It is generally believed that the maintenance of an upright stance during the imposition of an induced external perturbation, that is dynamic posturography, is one of the more complex equilibrium tasks for the Central Nervous System (CNS) to manage [2]. The usefulness of dynamic posturography was also explored from a rehabilitative perspective [3,4].

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http://dx.doi.org/10.1016/j.gaitpost.2014.08.003 0966-6362/© 2014 Elsevier B.V. All rights reserved. A common method for inducing standing balance perturbation is to use a motorized platform. In the majority of studies, subjects were perturbed with antero/posterior translations [5–7] or rotations only in the pitch [8,9], roll [10] or yaw [11] angles. Previous investigations have described the effect of experimental conditions on posture stabilization and they can be broadly grouped as: those in which visual cues are present [5–11] and those in which perturbation frequency is varied [5–9,11].

The main limitation inherent in the above-mentioned studies is their reliance on postural responses elicited via uniaxial perturbations. Researchers then administered either a combination of abrupt roll-pitch rotations delivered randomly [12–16] or a sequence of unexpected and continuous perturbations [17]. The main finding was that passive and active synergies are triggered and shaped by the CNS eliciting two directionally specific postural responses: one induced by pitch perturbations and the other by a combination of roll and pitch. It was also demonstrated that visual and vestibular information play a relevant role in the control of trunk and head posture [7,18,19].

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Furthermore, real-life situations typically involve continuous periodical multi-directional perturbations such as those that are self-induced by walking. Actually, the ability to manage roll, pitch and yaw combination is necessary to prevent falls, which are common in populations that manifest immature or compromised motor control [3,20–22]. Thus, it can be hypothesized that a more profound examination of postural response could be reached by imposing 3D continuous periodical perturbations, which are generated by a combination of rotations along the roll–pitch–yaw axes. In addition 3D perturbation could represent a potentially innovative approach for the rehabilitative assessment and treatment of posture.

In the present study we decided: (i) to use an in-house developed 3D robotic device [23–28], which could continuously change the rotation direction and which could be set at different amplitudes and frequencies; and (ii) to conduct quantitative assessments of upper body kinematics. In our first working hypothesis we sought to confirm that the presence of visual information, when healthy adults were subjected to continuous 3D perturbation, would induce a greater upper-body stabilization than that occurring when vision is absent. The second working hypothesis was that different perturbation frequencies and the continuous change in perturbation direction would elicit in healthy adult subjects dissimilar compensation strategies of the upper-body.

2. Methods

2.1. Subjects

Ten healthy adult subjects (six men and four women, age 23.7 \pm 0.7 years; height 165 \pm 12 cm, and mass 64 \pm 12 kg) volunteered

for the present study. Participants met the following inclusion criteria: absence of neurological or musculoskeletal disorders, vestibular diseases, dizziness, long term medications, and bone lesions or joint pathologies of the lower limbs in the year prior to the study; it was also ensured that they had normal vision, with or without glasses. All subjects were naïve to the experimental procedures.

All procedures of the present study were approved by the Research Ethics Board of the "Bambino Gesù" Children's Hospital in Rome.

2.2. Equipment

Dynamic posturography was performed using an electrically actuated robotic device, the RotoBit^{3D}, which permits arbitrary rotations – in terms of roll, pitch and yaw directions – around a fixed point. In brief, RotoBit^{3D} [23–28] is characterized by: a workspace of about $\pm 10^{\circ}$ for roll and pitch when yaw is in the range $\pm 15^{\circ}$, a phase delay of 1°, and an amplitude error $\leq 1.5\%$. The RotoBit^{3D} was installed in the middle of a 10-m walkway of the laboratory. A photograph of the RotoBit^{3D} is shown in Fig. 1.

Kinematics was recorded by the VICON system (MX 8camera-workstation, Nexus 1.7 software, 200 Hz, PlugInGait marker set based on the Davis protocol [29]). A total of 13 reflective markers (Fig. 2) were placed on the head (2 anterior and 2 posterior), thorax (2 on the upper and lower extremities of the sternum; 1 on the 7th cervical vertebra; 1 on the 10th dorsal vertebra; and an asymmetric one on the left side), and pelvis (2 on the anterior superior iliac spine and 2 on the posterior iliac spine). We decided to study the kinematics of the upper body and to postpone until the ongoing research phase the analysis of how arm movement contributes to balance recovery [30]. A



Fig. 1. Photograph of the in-house developed electrically actuated 3D robotic device, the RotoBit^{3D}. The platform includes the following components: (a) a moving metal plate that supports the subject; (b) three fixed length floating arms that connect the support plate with the motors by means of spherical joints; and (c) three linear electrical actuators. The robot is concealed in the floor, but in the picture the protective layers have been removed for the viewer's convenience.

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Fig. 2. Front (A) and back view (B) of the experimental setup: moving base, equipped with four retro-reflective markers, and the standing subject, equipped in accordance to the PlugInGait marker set.

further set of 4 markers was used for recording the platform movements.

2.3. Procedure

All subjects wore tight-fitting shorts and female subjects also wore an upper body garment that allowed for the placement of reflective markers. Participants stood barefoot on the platform in their preferred standing position, with arms hanging comfortably at their sides and feet placed symmetrically at the center of rotation of the circular moving base (Fig. 2). Foot position was marked on the platform to assure a consistent position of participants within and across trial blocks. In the eyes open trials (EO), subjects were instructed to look straight ahead and to not gaze at any specific target. In eyes closed trials (EC), the visual feedback was denied to the subjects by having them don eye masks; participants were also instructed to face forward as if looking straight ahead.

Subjects were instructed to maintain equilibrium, restricting their response strategy to a feet-in-place response, unless a fall was imminent; consequently, participants were free to move body segments to compensate for their instability. In order to reduce the risk of falls and to minimize interference from external support, a trainer stayed close to the participant from behind. The trial did not start until the participants indicated they were ready to begin, then a verbal warning was given about five seconds before the platform started moving. Each trial consisted of a spherical perturbation, lasting 20 s, obtained through the combination of roll–pitch–yaw rotations. The amplitude was set at 6° for roll and pitch rotations, and 10° for yaw rotation; the selected combination of rotations was used for every trial and for every subject.

Two frequency levels were selected: low (L, 0.25 Hz) and high (H, 0.50 Hz). The perturbation frequencies were chosen on the basis of preliminary dry-tests carried out with three healthy adults, who did not participate in the present study. A set of perturbations in the range of 0.2–0.6 Hz was presented to the subjects. A frequency of 0.25 Hz was selected because it was the minimum perceived perturbation, while 0.50 Hz was the highest frequency managed by the participants without stepping or falling. In addition, L and H perturbations. In ongoing research, the selected frequencies will represent the target frequency range for testing and training subjects with postural disorders.

The experimental session consisted of four trial conditions obtained by different combinations of the two visual conditions (EO and EC) and two frequency conditions (L and H). The four conditions were randomly repeated three times with a timeinterval of at least 30 s between trials, during which participants were free to move on the still platform in the horizontal pose. The session per subject lasted approximately 20 min.

The initial unpracticed trials for the four conditions were excluded from the sample because they could have produced significantly different reactions from those exhibited during

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Mean values \pm SDs of the 95% confidence ellipse area (CEA) for the head (h_{CEA}), trunk (t_{CEA}) and pelvis (p_{CEA}) in the four experimental conditions.

Confidence ellipse areas (cm ²)	Eyes open (EO)		Eyes closed (EC)	
	Low frequency (L) 0.25 Hz	High frequency (H) 0.50 Hz	Low frequency (L) 0.25 Hz	High frequency (H) 0.50 Hz
$h_{\text{CEA}}^{\mathbf{v} \times \mathbf{f}, \mathbf{v}, \mathbf{f}}$ t_{CEA}	$\begin{array}{c} 80\pm 36\\ 82\pm 40 \end{array}$	$\begin{array}{c} 48\pm24\\ 48\pm26 \end{array}$	$\begin{array}{c} 248 \pm 148 \\ 203 \pm 100 \end{array}$	$\begin{array}{c} 165\pm71 \\ 138\pm54 \end{array}$
p _{CEA}	86 ± 41	53 ± 23	138 ± 46	102 ± 36

^{v × f} Significant visual × frequency interaction effect, α = 0.05.

^v Significant visual simple effect or main effect, $\alpha = 0.025$ or $\alpha = 0.05$, respectively.

^f Significant frequency simple effect or main effect, $\alpha = 0.025$ or $\alpha = 0.05$, respectively.

subsequent trials [31,32]. The unpracticed trials also allowed subjects to familiarize themselves with the equipment and testing procedure prior to the data collection.

2.4. Data analysis

To study the upper-body behaviour – i.e., head, trunk and pelvis (h, t, p) – we processed the kinematic data of the segment centers so as to determine their horizontal displacements and sways in terms of roll-pitch-yaw angles. A centered time window of 10 s in each trial was considered for data analysis to exclude the initial acceleration phase and the final deceleration phase; the transition periods permit the participants to accustom themselves to the perturbation.

We have selected the following indices: (i) the 95% confidence ellipse areas (CEA) of the trajectories in the horizontal plane [33]; (ii) the absolute sways; and (iii) the relative sways between proximal body-segments.

The confidence ellipse areas – evaluated for head, trunk, and pelvis (h_{CEA} , t_{CEA} , p_{CEA}) – were averaged across the four experimental conditions and expressed as means and SDs.

The time course of absolute angles relative to each body segment was categorized into roll–pitch–yaw angles ($h_{r,p,y}$, $t_{r,p,y}$, and $p_{r,p,y}$), and after which we calculated the standard deviations ($\delta_{-}h_{r,p,y}$, $\delta_{-}t_{r,p,y}$, and $\delta_{-}p_{r,p,y}$). Considering also the time course of the moving platform ($pt_{r,p,y}$), we determined the standard deviations of relative angles: head vs. trunk ($\delta_{-}h/t_{r,p,y}$); trunk vs. pelvis ($\delta_{-}t/p_{r,p,y}$); and pelvis vs. platform ($\delta_{-}p/pt_{r,p,y}$). Absolute and relative sways were normalized to 6°, i.e., the selected amplitude of the platform rotation for roll and pitch axes. Finally, absolute and relative sways were averaged across the four experimental conditions and expressed as means and SDs.

A multifactorial analysis of variance considering interactions was used. Two-way ANOVA was used to study the main effects of visual conditions (2 groups: EO and EC), frequency conditions (2 groups: L and H), and their interactions. The significance level was set at α = 0.05.

Visual × frequency interactions, if significant, were further studied, as described in the following. All data were grouped by frequency and a 1-way ANOVA, between EO and EC, was computed for both L and H, respectively, to study the simple effect of the visual condition. The equivalent procedure was implemented to study the simple effect of the frequency condition for EO and EC, respectively. The significance level was set at α = 0.025, for the four previously mentioned 1-way ANOVAs, in order to take into account the type I error.

The software package SPSS (IBM-SPSS Inc., USA) was used.

3. Results

Our results support the expectation that the visual and frequency conditions influence postural behavior; in fact, a significant visual \times frequency interaction effect and simple effects for both the vision and frequency conditions were observed.

3.1. Confidence ellipse areas of horizontal displacements

A significant visual \times frequency interaction (p = 0.039), Table 1, was observed for confidence ellipse areas at the head level, h_{CEA} . The interaction graph (Fig. 3) reveals

that the interaction was ordinal; the maximum and the minimum values of h_{CEA} were observed in EC–L and EO–H, respectively. The 1-way ANOVA test conducted on head values showed that there were significant simple effects in both the visual (p = 0.004) and frequency (p = 0.003) conditions.

3.2. Absolute and relative sways

The results for absolute and relative sways, Tables 2 and 3, are clustered in rollpitch-yaw angles.

For the roll angle, a significant main effect of vision emerged only for the trunk (p = 0.002) and pelvis sways (p = 0.003) and the values were significantly higher in eyes closed condition than in eyes open one. No significant frequency main effect or significant visual \times frequency interaction effect was observed in the roll plane.

For the pitch angle, a significant main effect of the visual condition emerged only on the absolute sway for the trunk (p = 0.040), the relative sways of head vs. trunk (p = 0.042) and trunk vs. pelvis (p = 0.040), at levels that were higher in EC than in EO. There was also a significant main effect of frequency on the absolute sway of the pelvis (p = 0.002) and relative sway of the pelvis vs. platform (p = 0.000). Specifically, absolute sway $\delta_{-}p_p$ assumed higher values in low frequency trials than in high frequency ones, while relative sway $\delta_{-}p/ptp$ values were lower in L compared with H. No significant visual × frequency interaction effects were observed in pitch sways.

Finally, in the yaw angles there was a significant main effect of the visual condition on the absolute sway for the head (p = 0.001), trunk (p = 0.048), and pelvis (p = 0.008); in particular, higher values of absolute sways were observed in the EC condition than in the EO condition. Focusing on the absolute sway values, a significant main effect of the frequency condition was observed for the head (p = 0.032), trunk (p = 0.033) and pelvis (p = 0.007), δ_{-fy} . As regards the relative sways, a significant main effect of the frequency condition was observed for trunk vs. pelvis (p = 0.004) and pelvis vs. platform (p = 0.005). More specifically, results show that while the previously mentioned absolute sway values were higher in L than in H, the opposite emerged for the relative sways in the yaw plane.

While not planned for in the original experimental design, and therefore not supported by an *ad-hoc* statistical analysis, some further qualitative findings



Fig. 3. Confidence ellipse area of the horizontal displacements (CEA) relative to the head: visual \times frequency interaction graph.

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Table 1

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Table 2

Mean values \pm SDs of the absolute sways in the roll, pitch and yaw angles for the head ($\delta_{-}h_{r,p,y}$), trunk ($\delta_{-}t_{r,p,y}$) and pelvis ($\delta_{-}p_{r,p,y}$) in the four experimental conditions.

Absolute sways [%]	Eyes open (EO)	Eyes open (EO)		Eyes closed (EC)	
	Low frequency (L) Hz	High frequency (H) Hz	Low frequency (L) Hz	High frequency (H) Hz	
Roll					
δ_h_r	47 ± 30	45 ± 23	45 ± 15	50 ± 17	
$\delta_t_r^{v}$	29 ± 7	30 ± 8	51 ± 30	51 ± 24	
$\delta_p_r^{\vee}$	34 ± 9	33 ± 8	46 ± 21	41 ± 15	
Pitch					
δ_h_p	39 ± 18	42 ± 22	36 ± 14	37 ± 20	
$\delta_t_p^v$	27 ± 7	27 ± 8	40 ± 15	35 ± 10	
$\delta_p_p^f$	46 ± 15	39 ± 12	48 ± 17	42 ± 11	
Yaw					
$\delta_h_y^{v,f}$	75 ± 28	68 ± 34	90 ± 35	76 ± 33	
$\delta_t y^{v,f}$	91 ± 21	87 ± 29	101 ± 31	91 ± 29	
$\delta_p y^{v,f}$	92 ± 19	$84\!\pm\!25$	101 ± 24	91 ± 22	

^{v × f} Significant visual × frequency interaction effect, α = 0.05.

^v Significant visual simple effect or main effect, $\alpha = 0.025$ or $\alpha = 0.05$, respectively.

^f Significant frequency simple effect or main effect, $\alpha = 0.025$ or $\alpha = 0.05$, respectively.

emerged from a comparative examination of the body segment data in the same trial condition.

When the visual cue was denied and the moving platform was set to 0.25 Hz, the means of CEA's were generally higher at the head than at the trunk and pelvis, and higher at the trunk than pelvis. In the same visual condition and by increasing the perturbation frequency to 0.50 Hz, the mean value of CEA at the head level was higher than that of trunk, and that at the trunk was higher than that of pelvis.

Concerning the roll angles, mean values of the absolute sway for the head were generally higher than those achieved by the trunk only in EO, whereas in EC they were lower or comparable. In EO, the trunk exhibited lower sways compared not only to the head, but also to the pelvis, whereas this trend was not observed in the EC.

Furthermore, irrespective of the visual condition, as regards the yaw angle, mean values of the absolute sway for the head were lower than those of trunk and the pelvis, while SDs increased going from the pelvis to the head.

4. Discussion

Our findings highlighted that healthy adult subjects respond differently to the administration of continuous 3D support-surface motion when the visual information and frequency perturbation are changed. The visual cues drive the selection of the body segment used as a reference frame: the head when vision is allowed, the pelvis when vision is denied. Low values of oscillation frequency induce a balance control aimed at following the perturbation, while higher frequencies elicit a behavior aimed at compensating for the perturbation. Hence, the previously mentioned findings, together with the observed postural flexibility, support the hypothesis that 3D perturbations induce healthy subjects to enrich their perception of the ongoing postural configuration and to re-weight the relative contribution of body-segment activity. Finally, the previously indicated outcomes represent a rationale for the proposal of personalized goal-driven learning and rehabilitative processes.

4.1. Confidence ellipse areas of horizontal displacements

Subjects exhibited higher values of CEA's in eyes closed EC trials than in eyes open EO ones, especially at the head level, confirming the findings of previous studies [5–7] obtained with continuous anterior/posterior translating perturbations. In fact, in our study healthy subjects: (i) use the incoming information to select a feedforward mechanism to obtain upper-body stabilization; and (ii) reweight multi-sensory information as evidenced by the differences in the results obtained in the EO trial, where visual information is dominant, with respect to the EC trials, where vestibular and proprioceptive information are prevalent.

Concerning the effect of perturbation frequency, CEA's were higher in trials carried out at low frequency condition, L, than in high frequency one, H. The observed results suggest that the L condition could be easily tolerated by the subjects who permit the perturbation to dislocate body segments in space. In trials conducted with high perturbation frequency a more complex behavior emerged; in fact, the significant reduction of CEA's indicates a strategy modification to achieve postural balance and participants preferred to compensate for the imposed perturbations. In previous

Table 3

Mean values \pm SDs of the relative sways in the roll, pitch and yaw angles for the head vs. trunk ($\delta_{-}h/t_{r,p,y}$), trunk vs. pelvis ($\delta_{-}t/p_{r,p,y}$) and pelvis vs. platform ($\delta_{-}p/pt_{r,p,y}$) in the four experimental conditions.

Relative sways [%]	Eyes open (EO)	Eyes open (EO)		Eyes closed (EC)	
	Low frequency (L) Hz	High frequency (H) Hz	Low frequency (L) Hz	High frequency (H) Hz	
Roll					
δ_h/t_r	35 ± 23	39 ± 25	34 ± 14	37 ± 17	
δ_t/p_r	54 ± 18	49 ± 14	49 ± 18	47 ± 18	
δ_p/pt_r	115 ± 11	116 ± 9	113 ± 19	113 ± 14	
Pitch					
δ_h/t_p^{v}	48 ± 31	42 ± 19	54 ± 25	53 ± 22	
δ_t/p_p^{v}	34 ± 14	37 ± 12	38 ± 15	41 ± 23	
δ_p/pt_p^f	71 ± 23	83 ± 22	69 ± 24	80 ± 19	
Yaw					
δ_h/t_y	36 ± 22	44 ± 23	35 ± 23	40 ± 17	
δ_t/p_y^f	19 ± 5	24 ± 8	20 ± 6	25 ± 58	
δ_p/pt_y^{f}	51 ± 15	68 ± 16	53 ± 17	59 ± 17	

^{v × f} Significant visual × frequency interaction effect, α = 0.05.

^v Significant visual simple effect or main effect, $\alpha = 0.025$ or $\alpha = 0.05$, respectively.

^f Significant frequency simple effect or main effect, $\alpha = 0.025$ or $\alpha = 0.05$, respectively.

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studies, the effect of frequency in stabilizing posture has been assessed by inducing visually simulated motion in differently structured environments, during which subjects dissociate visual and body sensorial information, centering the spatial reference on body segments [34]. Conversely, when mechanical perturbations are applied, the spatial reference frame is centered on the visual cue. In that case it was demonstrated that the exposure of healthy subjects to a moving visual environment could induce a rich variety of patterns which are dependent on the driving frequency [35]. In particular, slow visual field oscillation (\approx 0.2–0.3 Hz) almost exclusively induced absolute coordination, i.e., stimulus movement and postural response were phase-locked, while faster visual scene oscillation (>0.4 Hz) may or may not have induced coherent postural sway. Thus, their results suggest that vision was prominent at slow frequency, while at high frequency body mechanical properties are also involved in balance control; the variety of behaviors could be explained by subject dexterity based on previous experiences. The experimental paradigm based on moving the support base showed a greater effect of visual feedback in the body stabilization. Indeed, by imposing a continuous anterior/posterior translating perturbation, Buchanan et al. [5], Corna et al. [6] and Berger et al. [36] observed that, for frequencies \geq 0.5 Hz, subjects preferred to stabilize the posture with a greater damping of head and trunk, always in the anterior/posterior direction. The body damping observed in our experiment carried out at 0.5 Hz is then in accord with the findings of previous studies.

As regards the visual \times frequency interaction effects, the greater increase in head displacement observed between EC–L and EC–H with respect to the increase observed between EO-L and EO-H could be interpreted as a behavior specifically selected by participants. They preferred, due to a longer latency of the response from vestibular input compared to visual input, to increase the signals provided by the vestibular system, as described by Schieppati et al. [7]. The observed higher head displacement also determines an increased response of the receptors positioned under the feet due to the relevant contribution of the head in COP displacements. In addition, while in the eyes open condition the more perturbed segment is the pelvis, in the eyes closed condition it is the less perturbed segment, which implies that in the absence of vision, the pelvis is used as a reference frame to achieve body balance.

4.2. Absolute and relative sways

Our results show that the trunk increased the roll sway in eyes closed EC trials, whereas the visual cues did not affect the head roll and pitch sways. These results show that in EC participants did not reduce the head sways as demonstrated also by the increase of h_{CEA} ; while results on yaw angles confirm the role of visual information in compensating the upcoming perturbation [11]. Our findings highlight the role of vision in upper-body stabilization, achieved via an active rearrangement of body-segment configuration to compensate for the ongoing perturbation. Moreover, in the EC condition the reduction of the absolute pitch sway of the pelvis when perturbation with a higher frequency is imposed, the contemporaneous highest value of relative sway of the pelvis vs. platform observed in roll-pitch-yaw angles, together with the above mentioned CEA data, confirmed the hypothesis that when vision is denied the pelvis is used as a reference frame for the body to finalize balance recovery. This finding is also supported in [37], where translation frequencies < 0.6 Hz and \geq 0.6 Hz involved the ankle and hip strategy, respectively.

Furthermore, in eyes open EO trials, participants responded differently in the roll angle with respect to the pitch and yaw angles. Concerning the roll angle, sway was lower for the neck than for the lumbar joint, while the opposite was observed for pitch and yaw planes. In EO trials absolute roll sway was higher for the head than for the trunk; similar behavior was observed in the pitch but not in the yaw plane. The distinctive roll behavior was also observed in previous works where uniaxial perturbation was used [12,13]. One explanation could be that complex perturbations are compensated for by merging two main strategies: (i) by roll rotations based on hip ab/adduction; and (ii) by pitch rotations based on hip flexion-extension. It could be hypothesized that these behaviors are driven by body constraints resulting from the chosen standing position (i.e., with parallel feet) and instruction given to maintain equilibrium which determines a higher instability in the anterior/posterior than in the medio/lateral direction. Moreover, the high frequency H condition globally reduced the yaw angles of the upper-body, even though a significant difference appeared only for head and pelvis, forcing all the relative sways to increase. These findings suggest that the inter-joint flexibility was predominantly used in H to compensate for the perturbation at the pelvis and head levels. As in the findings reported in [11], our subjects chose to selectively release the degrees of freedom of the body rather than counteract the dynamic input by increasing joint stiffness.

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Conflict of interest statement

None of the authors of this manuscript has any financial or personal relationship with other people or organization that could inappropriately influence their work.

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